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Impact of Scan Tilt on Quantitative Assessments Using Optical Coherence Tomography Angiography

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Purpose: To investigate the impact of scan tilt on quantitative assessments using swept-source optical coherence tomography angiography (SS-OCTA) in healthy participants.

Methods: Healthy participants were imaged with a SS-OCTA system (PLEX Elite 9000; Carl Zeiss Meditec, Inc, Dublin, CA). After a standard scan was obtained, tilted scans were obtained by moving the optical coherence tomography beam entrance position horizontally. The tilting angle was measured from the B-scan image, and the flattest (horizontal) and the most tilted images were selected for comparative analysis. Foveal avascular zone (FAZ) area, vessel density (VD), and vessel length density (VLD) from the superficial and deep retinal capillary plexus (SCP, DCP), and choriocapillaris flow deficits (CC FDs) were computed and compared between horizontal and tilted images.

Results: Thirteen eyes were excluded due to poor image quality or small angle difference ($<8°$) between the horizontal and tilted images. A final cohort of 27 normal eyes of 17 participants with a mean age of 39.3 ± 5.9 years was eligible for analysis. The FAZ area, VD, and VLD of both SCP and DCP were not significantly different between horizontal and tilted images. The CC FD, however, was significantly higher in horizontal images compared with tilted images ($21.65\% \pm 2.41\%$ vs. $21.06\% \pm 2.19\%$, $P = 0.005$).

Conclusions: CC FD measurements may be significantly affected by the position of the scanning beam and resultant scan tilting. These findings highlight the importance of capturing on-axis (pupil-centered) scans for quantitative OCTA analyses.

Translational Relevance: By assessing what impact a titled scan can have on OCTA measurements, this study will aid clinicians in understanding how to interpret their results in this situation.

Introduction

Optical coherence tomography angiography (OCTA) is a noninvasive imaging technique that can provide high-quality volumetric reconstructions of retinal and choroidal vascular blood flow.[1] By segmenting the cubic OCTA data into specific layers or slabs, OCTA can provide en face images of the superficial retinal plexus separately from the deep plexus, which cannot be evaluated adequately by conventional fluorescein angiography.[2] By obtaining individual retinal and deeper layer images in high contrast, OCTA can be used for quantitative analysis of microvasculature.[3] In addition to retinal vascular analysis, swept-source (SS) OCTA with high speed has recently been introduced to enable evaluation of the deeper choriocapillaris.[4] These devices use a longer wavelength (~1050 nm) with better retinal pigment epithelium penetration and thus provide more consistent evaluation of the choriocapillaris, particularly in the setting of disease.[5,6]

Previous studies on quantitative analysis using OCTA have largely used small field-of-view images (e.g., 3 × 3 mm). With the recent advances in technology, it is possible to acquire wider en face OCTA images in a single acquisition, thereby enabling quantitative analysis of retinal vessels[7,8] and the choriocapillaris[4] using widefield (e.g., 12 × 12 mm) or panoramic OCTA. However, due to the curvature of eyeball, the more peripheral regions of the retina on these images are scanned in a direction that may not be perpendicular to its surface. As the en face OCTA image is a two-dimensional projected image based on the assumption that the retina is flat, regions that are scanned somewhat obliquely (rather than perpendicularly) can produce distortions that can impact quantitative measurements.[8] In addition, the internal reflectivity of retinal tissue may be affected by the change in scan angle, which could also potentially impact measurements. For example, the reflectivity of Henle's fiber layer is directionally dependent.[9–11] Dolz-Marco and Freund[12] reported that changes in the reflectivity of Henle's fiber layer by scan tilting can affect the detection of deep capillary plexus flow imaged with OCTA.

The aim of the present study is to investigate the impact of scan tilting on quantitative analysis of the retinal capillary plexus and choriocapillaris using SS-OCTA images in healthy participants.

Methods

This was a prospective, observational, cross-sectional case series. Prior approval was obtained from the Institutional Review Board of the University of California, Los Angeles, and the procedures were conducted in accordance with the tenets of the Declaration of Helsinki and in compliance with the regulations described by the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all the participants at the time of enrollment.

Participants

Healthy participants with a normal eye exam and a normal structural OCT of the macula were enrolled. Exclusion criteria included (1) evidence or history of ocular disease, (2) history of ocular surgery, (3) refractive error >3 diopters, and/or (4) history of systemic disorders, including diabetes and hypertension.

Optical Coherence Tomography Imaging

All participants underwent OCTA imaging of the macula covering a 6 × 6–mm (1024 × 1024 pixels) area centered on the fovea using a swept-source OCT system (PLEX Elite 9000, 100 kHz; Carl Zeiss Meditec, Inc, Dublin, CA). Sufficient pupil dilation of 7 to 8 mm in size was obtained prior to imaging. Scan tilting was achieved by moving the OCT beam entrance position horizontally within the pupil as described by Lujan et al.[9] The scan was first acquired at the center of the pupil, and then scans were repeated with the beam positioned at both the nasal and temporal edge of the pupil. The images were taken twice at each position. From the B-scan images, the flattest (horizontal) and the most tilted images were selected, and the corresponding en face OCTA images were used for quantitative analysis (Fig. 1). If a signal strength less than 7 was observed for any scan or if the foveal center was decentered, the scan was repeated and the lower quality or decentered scan was not used for further analysis.

En face images of the superficial retinal capillary plexus (SCP) and deep retinal capillary plexus (DCP) layers were obtained using the device's default automated segmentation boundaries. For generation of en face image of the choriocapillaris (CC), en face slabs were obtained at the default CC setting: a 20-µm thick slab from 29 to 49 µm under the automatically segmented retinal pigment epithelium (RPE) band (which falls approximately at the center of this band). All B-scans were scrutinized for segmentation errors that were manually corrected if present. The projection removal function provided by the device was applied to all DCP and CC images.

Quantitative Measurements

The en face images were exported and analyzed using ImageJ software V.1.52 (National Institutes of Health, Bethesda, MD). The tilting angle was measured and defined as the slope of the line passing through both ends of the center of the RPE band on the B-scan image (Fig. 1). If the angle of difference between the horizontal and titled scans was less than 8°, the scans were not used in the analysis. The foveal avascular zone (FAZ) area was measured by two trained graders (YSJ and IB) using the SCP en face image. FAZ area was calculated in mm^2 using the following formula: [(pixels of FAZ) × (6/1024)^2].

The vessel density (VD) and vessel length density (VLD) were measured in both the SCP and DCP, and the CC flow deficit (FD) was also measured for comparison between horizontal and tilted images. The SCP and DCP images were binarized using a modified version of the previously reported method.[3] Briefly, the image was duplicated and a second, different binarization method was used for each image. One image was processed first by a Hessian filter, and then

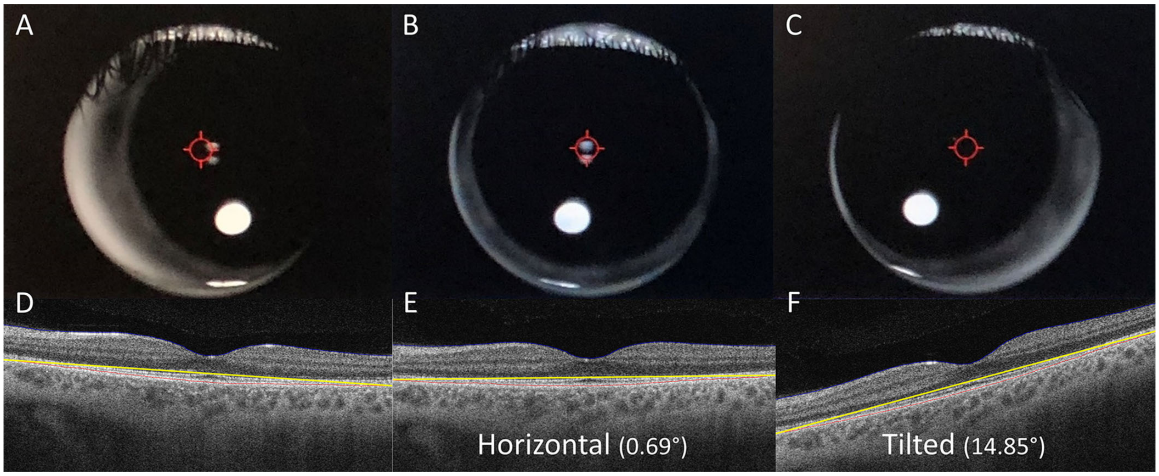

Figure 1. Scan tilting was achieved by moving the OCT beam entrance position horizontally within the pupil. The scan was first acquired at the center of the pupil (B), then moved to the nasal and temporal edge of the pupil (A, C). From the B-scan images (D–F), the flattest (horizontal) and the most tilted images were selected. The tilting angle was defined as the slope of the line (*yellow line*) passing through both ends of the center of the RPE band.

global thresholding was applied using Huang's fuzzy thresholding method. The other (duplicate) image was binarized using median local thresholding. Finally, the two different binarized images were combined to create the final binarized image, containing only pixels that coexisted on both binarized images. The choriocapillaris image was binarized using the Phansalkar method (radius, 8 pixels or 46.88 microns), as previously described (Fig. 2).[13–15]

For analysis of the DCP and CC, although the projection artifact removal tool was applied, the areas under the larger superficial retinal vessels were excluded from the calculation to avoid potential confounding effects related to residual projection artifact or other inadvertent errors introduced by the projection artifact removal.[15–17] As previously described, this large retinal vessel mask was obtained from the SCP image. MaxEntropy threshold was applied to isolate only the larger superficial retinal vessels. Then this mask image was merged with the binarized DCP and CC images (Fig. 2). The VD was assessed on the final binarized image and was defined as the ratio of blood vessels to the total area. After skeletonization of the binarized image, VLD, which represents the vessel length per unit area, was computed as described previously.[18,19] The extent of the CC FD was computed as a percentage of each analyzed area.

Statistical Analysis

All values were expressed as the mean ± standard deviation. A paired t test was used to compare tilting angle, FAZ, VD, VLD, and CC FD between horizontal and tilted scans. To detect differences in signal strength, an independent t test was applied to compare signal strengths of scans obtained with the two different tilts. Interscan repeatability between two repeated scans at the same position of OCT beam entrance was evaluated by calculating the intraclass correlation coefficients (ICCs). All analyses were performed using SPSS Statistics version 23 (IBM, Armonk, NY). A P value $\leq$0.05 was considered statistically significant.

Results

A total of 20 healthy participants (40 eyes) were enrolled in this study. Five eyes were excluded due to poor image quality or decentration of the fovea and 8 eyes that had a small angle difference (<8°) between horizontal and tilted scans were excluded. Thus, 27 eyes of 17 total participants (11 males and 6 females) were eligible and included in the analysis. The mean age of the participants was 39.3 ± 5.9 years (range, 26–52 years). There was no difference in signal strength between horizontal and tilted scans (9.26 ± 0.71 vs. 9.15 ± 0.66, $P = 0.555$). Table summarizes the measurement results. The mean angle of tilt was 1.73° ± 1.16° and 13.10° ± 2.42° for the horizontal and tilted scans, respectively ($P < 0.001$). The mean difference in the angle of tilt between horizontal and tilted scans was 11.37° ± 2.53° (range, 8.53°–19.83°). The FAZ area was numerically higher in horizontal images than in

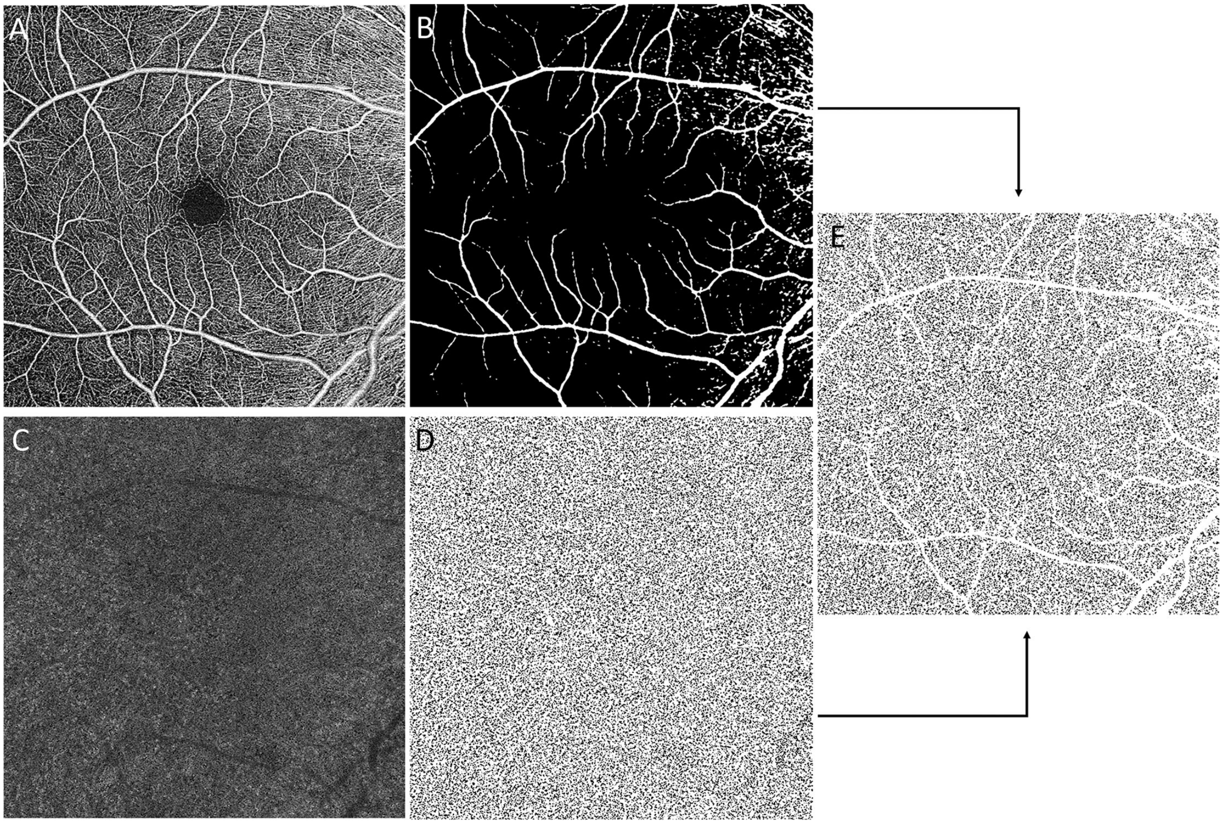

Figure 2. From the superficial capillary plexus image (A), the large retinal vessel mask (B) was obtained by applying MaxEntropy threshold. (C, D) The CC en face OCTA image was binarized using the Phansalkar method (radius, 8 pixels or 46.88 microns). (E) The superficial retinal vessels were masked from the binarized CC image.

Table. Differences in Parameters Measured in Horizontal and Tilted OCTA En Face Images

Characteristic	Horizontal	Tilted	|Δ|	*P* Value
Tilting angle (°)	1.73 ± 1.16 (0–3.73)	13.10 ± 2.42 (9.60–19.87)	11.37 ± 2.53 (8.53–19.83)	<0.001
FAZ (mm^2)	0.274 ± 0.090 (0.124–0.464)	0.269 ± 0.094 (0.128–0.472)	0.011 ± 0.010 (0.001–0.048)	0.068
SCP, %				
Vessel density	37.83 ± 0.97 (35.26–39.14)	38.07 ± 0.97 (36.13–39.63)	0.84 ± 0.73 (0.05-2.93)	0.262
Vessel length density	11.52 ± 0.29 (10.84–12.11)	11.47 ± 0.35 (10.73–12.08)	0.27 ± 0.22 (0.01–0.84)	0.438
DCP, %				
Vessel density	35.29 ± 0.79 (33.65–36.43)	35.50 ± 0.73 (33.78–36.66)	0.56 ± 0.48 (0.02-1.67)	0.151
Vessel length density	11.62 ± 0.29 (10.89–12.09)	11.67 ± 0.24 (11.08–12.05)	0.14 ± 0.13 (0-0.47)	0.128
CC, %				
Flow deficits	21.65 ± 2.41 (17.37–26.10)	21.06 ± 2.19 (16.59–24.63)	0.89 ± 0.67 (0.10–2.71)	0.005

Values are mean ± SD (range).
|Δ|, absolute difference.

the tilted scan images, but the difference did not reach statistical significance (0.274 ± 0.090 vs. 0.269 ± 0.094, $P = 0.068$).

For the SCP, VDs were 37.83 ± 0.97 and 38.07 ± 0.97 in horizontal and tilted images, respectively ($P = 0.262$). VLD also showed no significant difference between horizontal and tilted images (11.52 ± 0.29 vs. 11.47 ± 0.35, $P = 0.438$). Both VD and VLD of the DCP were not significantly different between horizontal and tilted scans (35.29 ± 0.79 vs. 35.50 ± 0.73, $P = 0.151$, and 11.62 ± 0.29 vs. 11.67 ± 0.24, $P = 0.128$, respectively). For the CC, however, the mean FD was 21.65 ± 2.41 in horizontal and 21.06 ± 2.19 in tilted images, which was significantly different ($P = 0.005$, Fig. 3). The CC FD of the tilted scan was lower than that of the horizontal scan in 20 eyes (74%). The mean absolute difference of FD was 0.89 ± 0.67 (range, 0.10–2.71).

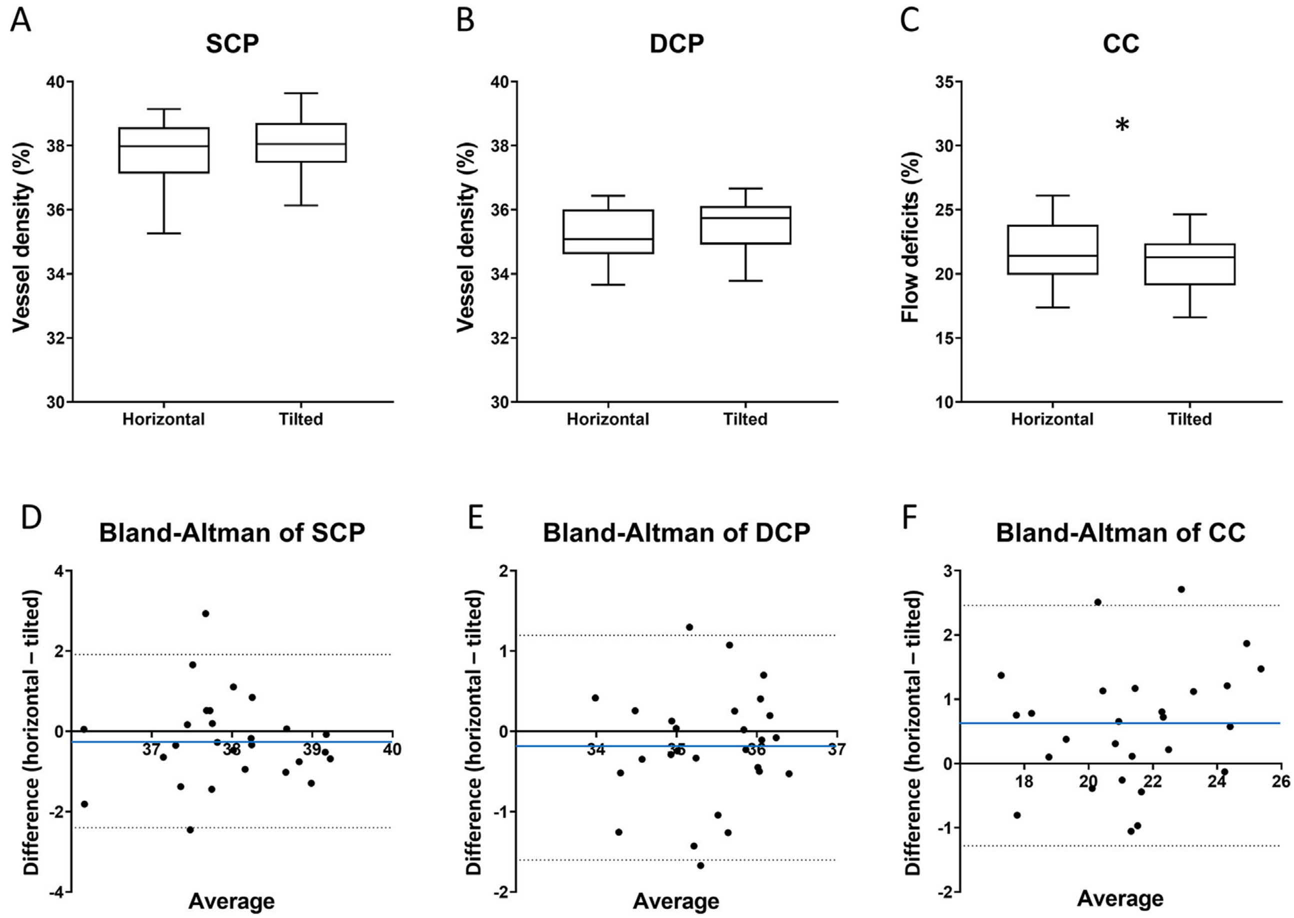

Figure 3. (A, B) The vessel density in SCP and DCP showed no significant difference between horizontal and tilted images (37.83 ± 0.97 vs. 38.07 ± 0.97, $P = 0.262$, and 35.29 ± 0.79 vs. 35.50 ± 0.73, $P = 0.151$, respectively). (C) For the CC, the mean flow deficits were 21.65 ± 2.41 in the horizontal images and 21.06 ± 2.19 in the tilted images, which was significantly different ($P = 0.005$). (D–F) Bland-Altman plots for SCP, DCP, and CC. The *blue horizontal line* represents the mean difference between the two scans and the two *dotted horizontal lines* represent the 95% limits of agreements (1.96 SD). Each point represents the difference (horizontal–tilted) of vessel density (SCP, DCP) or flow deficits (CC) between horizontal and tilted scans in each case. (F) The CC FD of the tilted scan was lower than that of the horizontal scan in most cases (20 eyes, 74%).

The interscan repeatability demonstrated an ICC of 0.753 (95% confidence interval [CI], 0.459–0.888) for VD and 0.796 (95% CI, 0.553–0.907) for VLD of SCP. The ICC was 0.780 (95% CI, 0.517–0.900) and 0.829 (0.624–0.922) for VD and VLD of the DCP, respectively. The ICC for the CC FD was 0.950 (95% CI, 0.890–0.977).

Discussion

Recent advances in OCTA have made it possible to scan wider fields, including more peripheral regions of the retina. However, due to the curvature of eye, the peripheral retina generally only needs to be scanned obliquely, and not perpendicularly to its surface. In addition, in poor fixating or poorly cooperative patients, it is not always possible to obtain scans through the center of the pupil, thus resulting in tilted images upon scan acquisition. In this study, we evaluated the effect of scan tilting on quantitative parameters in healthy eyes using SS-OCTA. While we observed no significant difference in retinal vascular metrics, we did observe a significantly lower CC FD in tilted images.

En face OCTA image is a reconstructed image in which a three-dimensional structure is projected onto a plane. As seen on the two-dimensional map of the Earth, distortion of the peripheral regions may occur. This is a well-known phenomenon with planar widefield images, and stereographic projection

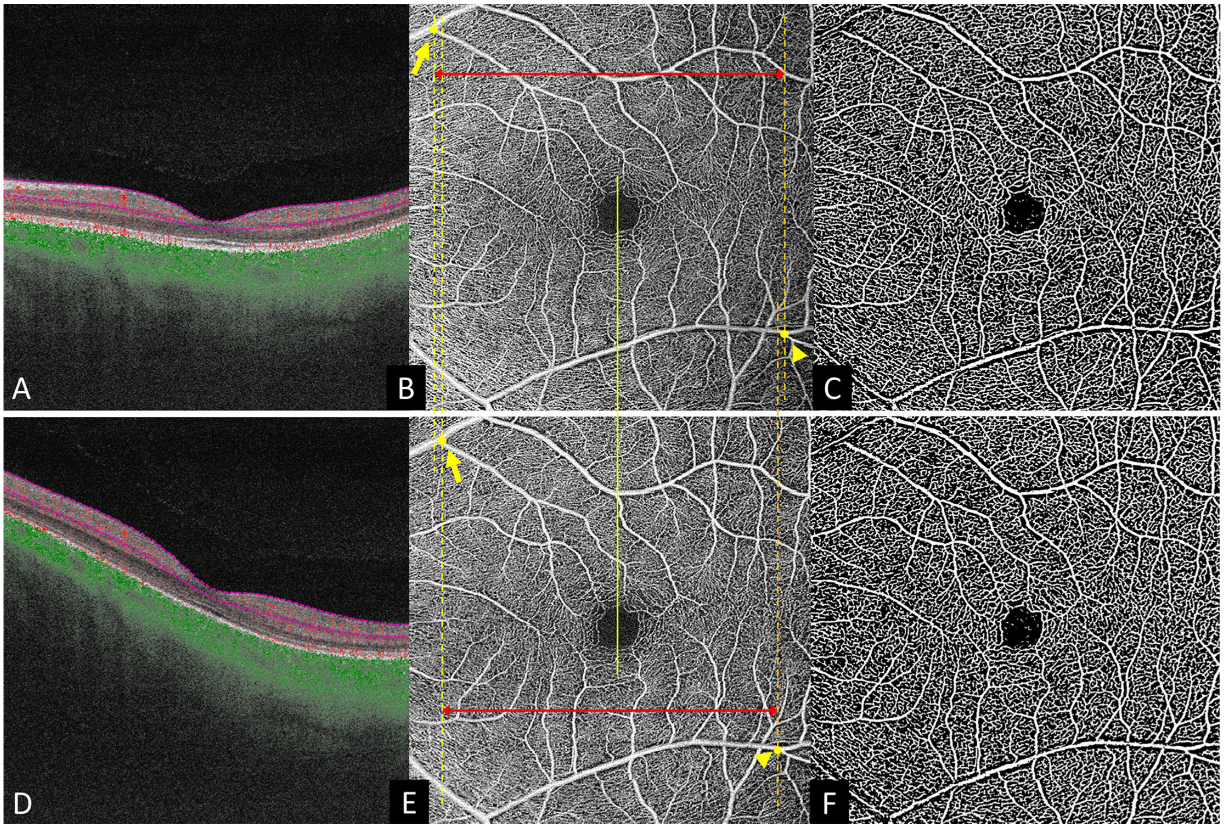

Figure 4. (A, D) B-scan images of horizontal and tilted scans. (B, E) SCP en face images and (C, F) binarized SCP images. When the foveal centers of the two images are aligned (*yellow line*), areas of nonoverlap can be observed in the peripheral vessels. The *dotted lines* indicate vertical lines passing through the same bifurcation points (*yellow arrow* and *arrowhead*) in the horizontal and tilted scans. The distance (*red line*) between the two *dotted lines* (*yellow and orange lines*) is shorter in the tilted scan, which means that a wider area is projected. The SCP and its binarized images show that more peripheral regions of the blood vessels are evident in the two-dimensional image of the tilted scan.

tools have been developed to standardize measurements obtained using these distorted images.[20] Thus, while distortion is not a significant problem when analyzing small central scans (e.g., 3 × 3 mm), caution should be taken when analyzing wider field images. In Figure 4, two SCP en face images from horizontal and tilted images show the difference in projected area. When the foveal centers of the two images are aligned, areas of nonoverlap can be observed in the peripheral vessels. The dotted lines indicate vertical lines passing through the same bifurcation points in the horizontal and tilted scans. The distance between the two dotted lines (yellow and orange lines) is shorter in the tilted scan, which means that a wider area is projected. The overall effect of the peripheral distortion is that the actual region imaged is larger than the dimensions would indicate. This is consistent with the observation of Kadomoto et al.[8] They calculated the corrected OCTA area by superimposing a 12 × 12–mm en face OCTA image on the corresponding ultrawidefield fluorescein angiography image. The mean area of retina measured on a single nonpanoramic 12 × 12–mm OCTA image was 152.4 mm^2, which is greater than the expected area of 144 mm^2. In this study, although the FAZ was not significantly different between horizontal and tilted images ($P = 0.068$), there was a trend for the FAZ area to measure smaller in tilted images.

Despite the anticipated distortion in tilted scans, no significant differences were observed in the VD and VLD for both the SCP and DCP. SCP and DCP OCTA images are derived from thick slabs between the internal limiting membrane and internal plexiform layer, as well as between internal plexiform layer and outer plexiform layer, respectively. The three-dimensional capillary networks in these thick slabs are projected onto the plane. One possible explanation is that some adjacent capillaries located in the tilted slab can be projected to overlap each other, resulting in a lower vessel density than one might otherwise predict, thus masking a potential increase in vessel density from scan tilting. The CC slabs, on the other hand, use relatively

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thin (10–20 μm) slabs, which may be more affected by the scan tilting. Although we did not observe significant differences in vessel density measurements in this cohort, tilting may still be a concern in more myopic eyes, which may demonstrate a greater curvature of the posterior eye wall, which may magnify the impact of tilting.

Dolz-Marco and Freund[12] reported that directional changes in the reflectivity of Henle's fiber layer can affect the detection of deep capillary plexus flow imaged with OCTA by influencing the projection of superficial flow onto the deeper retinal layers. They did not observe any evidence of segmentation error for the retinal layers. In our study, in order to ameliorate the effect of projection artifact, the projection removal function of the device was applied, and in addition, the superficial large vessel regions were masked from analysis on DCP and CC (Fig. 2) en face images. After removing the projection effect of superficial flow, there was no significant difference between horizontal and tilted images for VD and VLD of DCP.

We observed that scan tilting did have an impact on the CC FD measurement with a significantly lower CC FD in the tilted images. This makes sense as one would expect a larger physical region to be projected onto the two-dimensional image, and thus the choriocapillaris would appear to be spaced closer together. Although the mean difference in CC FD between horizontal and tilted scans was not great, the difference (delta) can vary by an average of 0.89 and a maximum of 2.71, which may be clinically relevant.[21] Furthermore, the Bland-Altman plot for the CC analysis shows a tendency for the CC FD of the tilted scan to be lower than that of the horizontal scan in most cases (20 eyes, 74%) (Fig. 3F). Recently, a number of studies have reported on quantitative analysis of the retinal microvasculature using OCTA and have observed high repeatability and reproducibility.[22–26] In contrast, relatively few studies have addressed CC repeatability.[26,27] When evaluating repeatability with two repeated scans at the same position, our results showed a high ICC of 0.950 for CC FD, which is consistent with previous reports.

In this study, 6 × 6–mm en face OCTA images were used for analysis. As many recent quantitative OCTA studies, including many studies of the CC, are using this 6 × 6 pattern,[14,15,28,29] our findings are of relevance. In myopic eyes, even these 6 × 6–mm scans can manifest evidence of the natural curvature of the eye. In such eyes/scans, the peripheral regions of the scan would be expected to behave similarly to the tilted scans obtained in our study. It is advantageous to use the wider field images to demonstrate the impact of the natural retinal curvature or scan tilting on quantitative analyses. While OCTA devices are now featuring much larger scan patterns (12 × 12 mm, 15 × 9 mm), these are generally not used for quantitative analyses, primarily because of the lower resolution. If these images are used, however, the impact of oblique scanning and peripheral distortion may be of much greater relevance.

Our study has several limitations to be considered when assessing our findings. First, the sample size was relatively small, and thus we may have been underpowered to detect even smaller differences in vessel flow metrics between scans. On the other hand, differences smaller than this may not be of clinical relevance. For example, the mean difference in VD for both the SCP and DCP was less than 0.25 (less than a 1% difference in the measurement). Even the observed significant mean difference in CC FD between horizontal and titled scans is numerically quite small, despite the high interscan repeatability. However, the range was quite larger, with absolute differences in CC FD between horizontal and tilted scans of 2.71%. Further studies are under way in a larger number of normal and myopic participants. Second, only a single OCTA device was used with the manufacturer's default slab settings. Different slab positions and thicknesses could yield different results. Third, this study was limited to normal eyes with a narrow age range. Vessel densities, particularly in the CC, can vary with age, and it is possible that the impact of scan tilting could vary depending on age. A fourth limitation of our study is that it was limited to tilting angles on average of only 13° even in the tilted scans. One would expect that the impact on vessel measurements would be greater in more myopic eyes with greater eye wall curvature.

In conclusion, quantitative CC analyses can be impacted by the tilt angle of the scan, with the CC FD tending to be lower in the tilted scans in the majority of cases. These findings highlight the importance of capturing on-axis (pupil-centered) scans and suggest caution in analyses of eyes with significant posterior eye wall curvature, which can lead to a tilt of the retina relative to the scanning beam.

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