EJO
ISSN 1120-6721

Eur J Ophthalmol 2016; 00 (00): 000-000
DOI: 10.5301/ejo.5000858

ORIGINAL ARTICLE

Reproducibility and repeatability of foveal avascular zone area measurements using swept-source optical coherence tomography angiography in healthy subjects

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ABSTRACT

Purpose: To assess the reproducibility and repeatability of foveal avascular zone (FAZ) area measurements using swept-source optical coherence tomography angiography (SS-OCTA) in healthy subjects.

Methods: Sixty-four eyes of 64 healthy volunteers were randomly subjected to FAZ area measurements using SS-OCTA by 2 examiners in 2 different sessions.

Results: The FAZ areas measured by the first and second observer were 0.269 ± 0.092 mm^2 and 0.270 ± 0.090 mm^2, respectively. Within subjects, the coefficients of variations were 2.44% (95% confidence interval [CI] 1.95% to 2.93%) and 2.66% (95% CI 2.00% to 3.31%) for the first and second observers, respectively. The coefficient of repeatability average measurements of FAZ area were 0.021 mm^2 and 0.024 mm^2. The intraclass correlation coefficient values were 0.993 (95% CI 0.989 to 0.996) and 0.991 (95% CI 0.986 to 0.995). Interobserver and intraobserver concordance correlation coefficients ranged from 0.998 (95% CI 0.997 to 0.999) to 0.999 (95% CI 0.998 to 0.999) and from 0.989 (95% CI 0.982 to 0.993) to 0.987 (95% CI 0.979 to 0.992), respectively.

Conclusions: The FAZ area measurements by means of SS-OCTA showed high reproducibility and repeatability in healthy eyes.

Keywords: Foveal avascular zone, Repeatability, Reproducibility, Swept-source optical coherence tomography angiography

Introduction

It has been over 50 years since fundus fluorescein angiography (FFA) was introduced as an invasive imaging technique that enables the study of the circulating blood in the human retina (1). This method has been extensively used for imaging the retinal vascular network and for evaluating the foveal avascular zone (FAZ) in normal and pathological subjects (1). In the last 20 years, optical coherence tomography (OCT) has radically changed retinal diagnosis (2). However, for many years, a limit of this technique was the inability to provide the functional information of the retinal microvasculature. Optical coherence tomography angiography (OCTA) is an easy, fast, noninvasive, 3D imaging method that is able to visualize intravascular flow at the microcirculation level of the eye (3). Two major motion contrast techniques, phase-based and amplitude-based, are used to render depth imaging of retinal and choroidal microvasculature (4-6).

These methods were implemented using both spectral-domain and swept-source imaging systems (7). Optical coherence tomography angiography provides noninvasive imaging of the FAZ that is comparable to, if not better than, invasive angiographic imaging (3). The quantification of FAZ may be useful for detecting and monitoring the progression of retinal vascular diseases. Reproducibility and repeatability are indicators of the applicability of any instrument as a diagnostic tool in clinical practice. They refer to the degree of agreement between independent measurements that are obtained with the same method/instrument on identical test material under different conditions (i.e., different operators) and under

Accepted: July 27, 2016
Published online: September 9, 2016

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the same condition (i.e., same operator performing consecutive measurements), respectively. The aim of this study was to evaluate both the intrasession and intersession reproducibility and repeatability of FAZ area measurements using swept-source OCT (SS-OCT) DRI OCT Triton plus (Topcon Corporation, Tokyo, Japan) with the full-spectrum intensity ratio angiography algorithm in healthy subjects.

Methods

The study was performed at the Ophthalmology Clinic of the University of Chieti-Pescara, Italy. A total of 64 healthy volunteers aged between 21 and 54 years were enrolled in the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Informed consent was obtained before the scanning sessions. Each subject underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (VA) (using an Early Treatment Diabetic Retinopathy Study chart), slit-lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, dilated funduscopic examination using a 78 D lens, and visual field testing using the Humphrey 30-2 Swedish Interactive Thresholding Algorithm (Carl Zeiss Meditec Inc., Dublin, CA, USA). Inclusion criteria were best-corrected VA of 20/25 or better, spherical refraction within ± 3.0 D, and cylinder correction within ± 2.0 D. Subjects were declared healthy if the visual field mean deviation, pattern standard deviation, and glaucoma hemifield test were all within normal limits for at least 2 reliable visual field tests. Visual fields were considered reliable if fixation losses, false-negative results, and false-positive results were <30%. Subjects were excluded if they had any previous history of ocular disease, lens opacities, surgery, laser or medical treatments, or any systemic disease with ocular involvement. Additionally, subjects were excluded if the visual field mean deviation or pattern standard deviation was below 5% cutoffs or the glaucoma hemifield test was outside normal limits reproducibly in at least 2 reliable visual field tests. If the glaucoma hemifield test was borderline, mean and pattern standard deviation were <10% but >5%, or defects were inconsistent between visual fields, the subject was categorized as a glaucoma suspect and was removed from the dataset. Eyes with optical medium opacity, maculopathy, retinal disease, uveitis, or glaucomatous or nonglaucomatous optic neuropathy were excluded from the investigation.

Imaging with swept-source DRI OCT Triton

A commercially available DRI OCT Triton Plus with a high speed of 100,000 axial scans/s, center wavelength of 1,050 nm, and a digital and optical axial resolution of 2.6 µm and 8 µm in tissue, respectively, was used. IMAGEnet®6 (version 1.14), a Web-based ophthalmic data management system, incorporates visualization of angiographic datasets, providing for both standard and customizable en face and cross-sectional views of OCTA data. Swept-source OCT angiography (SS-OCTA) is based on motion contrast measure using a ratio method, called OCT angiography ratio analysis (OCTARA), where the full spectrum is kept intact and therefore the axial resolution is preserved. Optical coherence tomography angiography images were generated by computing a ratio-based result, r, between corresponding image pixels:

$$r(x,y) = 1 - \frac{1}{N}\sum_{i,j}^{N}\frac{\min(Ii(x,y),\ Ij(x,y)}{\max(Ii(x,y), Ij(x,y)}$$

where I(x,y) is the OCT signal intensity, N is the number of scanned B-scan combinations at the given location, and i and j represent the 2 frames within any given combination of frames. This formula represents a relative measurement of OCT signal amplitude change that optimizes angiographic visualization over both the retina and choroid. It also enhances the minimum detectable signal relative to amplitude decorrelation. It should be noted that the directionality of the ratio is arbitrary (i.e., numerator versus denominator) and that the subtraction from unity is an optional operation that serves to conveniently orient the direction of the display range similarly to other calculation methods such as differentiation and decorrelation. Furthermore, this method preserves the integrity of the entire spectrum and therefore does not suffer from compromised axial resolution. High-quality OCT structural images were generated by averaging registered B-scans. Segmentation of retinal layer boundaries was performed on OCT structural images. Pupils were dilated with a combination of 1% tropicamide and 2.5% phenylephrine. Study participants underwent SS-OCTA imaging following a protocol that included both color fundus picture and a volumetric OCT dataset of 3 × 3 mm consisting of 320 × 320 pixels in the transverse dimension. The image capturing time required from 4 to 10 seconds for each OCT scan. Each B-scan position was repeatedly scanned 4 times. An internal fixation light was used to center the scanning area. The OCT signal position and signal quality were automatically optimized by means of machine before acquiring OCT image. After completion of the volumetric OCT dataset, the software applied motion control technology to remove saccades and minor loss of fixation. Low-quality scans (i.e., if the subject blinked or the scan had significant motion artefacts) were excluded and repeated until good-quality scans were achieved. Two different measurement sessions were performed in one randomly selected eye of each subject at baseline (T0) and after 30 days (T2). Randomization was achieved using the random number generator Pro 1.89 (free software that is available online). In the first session, 2 measurements were acquired using the DRI OCT Triton Plus unit, each by 2 different trained observers. Thirty minutes later (T1), measurements were repeated in the same fashion but with an inverted observer order. At the end of the first session, each eye received 2 SS-OCTA scans by each observer. During the second session, the scans were repeated by the same 2 observers using the same SS-OCTA. To minimize systematic bias, both examiners were masked with respect to subject clinical information. After each acquisition, the observers were masked to measurements. The FAZ area was measured in square microns only at the end of the second session. Briefly, a non-flow measurement on a superficial reference plane (superficial vascular plexus) of en face projection was selected. The reference plane for determining the superficial plexus was defined at the inner limiting membrane with a 60-µm section. The user manually outlined the

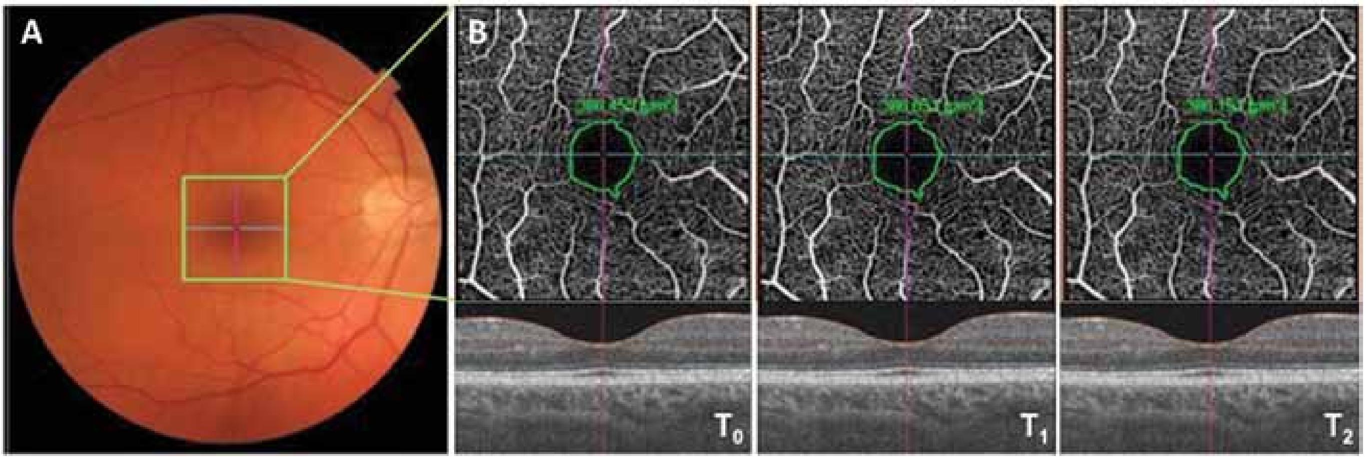

Fig. 1 - Color fundus picture of a young healthy eye (**A**). The green square outlines the area of the 3.3-mm optical coherence tomography angiogram (OCTA). 333-mm square OCTA scans (**B**) at level of the superficial vascular plexus (top) and coregistered spectral-domain OCT B-scans (bottom) centered at the fovea show foveal avascular zone area measurement at T0 (baseline), T1 (after 30 minutes), and T2 (after 30 days).

FAZ contour, and the embedded software calculated the area in square microns (Fig. 1), then converted to square millimeters.

Sample size and statistical analysis

This study was designed to estimate the reproducibility and repeatability of FAZ area measurements. Assuming a within-subject standard deviation of 13% and 3 measurements per subject by 2 observers, using a Bland formula, the sample size required to estimate the width of the 95% confidence intervals (CIs) within 13% was 60 subjects. All qualitative characteristics of the subjects were summarized as frequency and percentage; quantitative characteristics were summarized as the mean and standard deviation. Intrasession repeatability for each observer was measured using 2 measurements (T0 and T1). The intraobserver repeatability was evaluated by calculating within-subject standard deviation (Sw), coefficient of repeatability (CR), coefficient of variation (CVw), and intraclass correlation coefficient (ICC). A Bland-Altman plot was used to assess the repeatability of the method by comparing repeated measurements for each single examiner (8). Because the same method is used for the repeated measurements, the mean difference should be zero. The CR was calculated as 1.96 (approximately 2) times the SD of the differences between the measurements. The interobserver reproducibility was evaluated with a 2-way mixed model with the subjects as a random effect and the observers as the fixed effect. The observer-effect estimates indicated the magnitude for bias between observers. In addition, Lin's concordance correlation coefficient (CCC) was calculated along with its 95% CI (9). Statistical analysis was performed using the computing environment R (10).

Results

A total of 64 eyes of 64 subjects (30 male and 34 female) underwent FAZ area measurements with the previously described protocol. All measurements provided high-quality scans and were prospectively included in the study. The sample age ranged from 19 to 54 years (mean ± SD 34.4 ± 10.9 years). Additional demographic and clinical characteristics of the enrolled subjects are reported in Table I. The mean ± SD FAZ area measurements are shown in Table II. Overall FAZ areas measured by the first and second observers were 0.269 ± 0.092 mm² and 0.270 ± 0.090 mm², respectively. As calculated from the means of the Bland-Altman plots (Fig. 2, A and B), CRs for average FAZ area were 0.021 mm² and 0.024 mm² for the first and second operators, respectively. The indicators of repeatability, CVw, CR, and ICC, resulting from statistical analysis are shown in Table III.

TABLE I - Patient characteristics

Variables	**Mean ± SD or n (%)**
Age, y	34.4 ± 10.9
Sex	
Female	34 (53.1)
Male	30 (46.9)
Eye	
Right	31 (48.4)
Left	33 (51.6)
Intraocular pressure, mm Hg	15.3 ± 1.7
Visual field mean deviation, dB	+0.5 ± 0.9

Interobserver intrasession CCCs of FAZ area measurements were 0.998 (95% CI 0.997 to 0.999) at T0, 0.998 (95% CI 0.997 to 0.999) at T1, and 0.999 (95% CI 0.998 to 0.999) at T2 (Tab. IV). The estimate of the effect of the observer, which indicates the bias between observers, was not statistically significant for any time point (p = 0.963, p = 0.959, and p = 0.932). Intraobserver intersession CCCs of FAZ area measurements were 0.989 (95% CI 0.982 to 0.993) at T0 and 0.987 (95% CI 0.979 to 0.992) at T2 (Tab. V).

TABLE II - Foveal avascular zone area, mm²

Observer	T0	T1	T2	Overall
1	0.269 ± 0.092	0.268 ± 0.092	0.270 ± 0.093	0.269 ± 0.092
2	0.270 ± 0.089	0.269 ± 0.091	0.271 ± 0.090	0.270 ± 0.090

Values are mean ± SD.

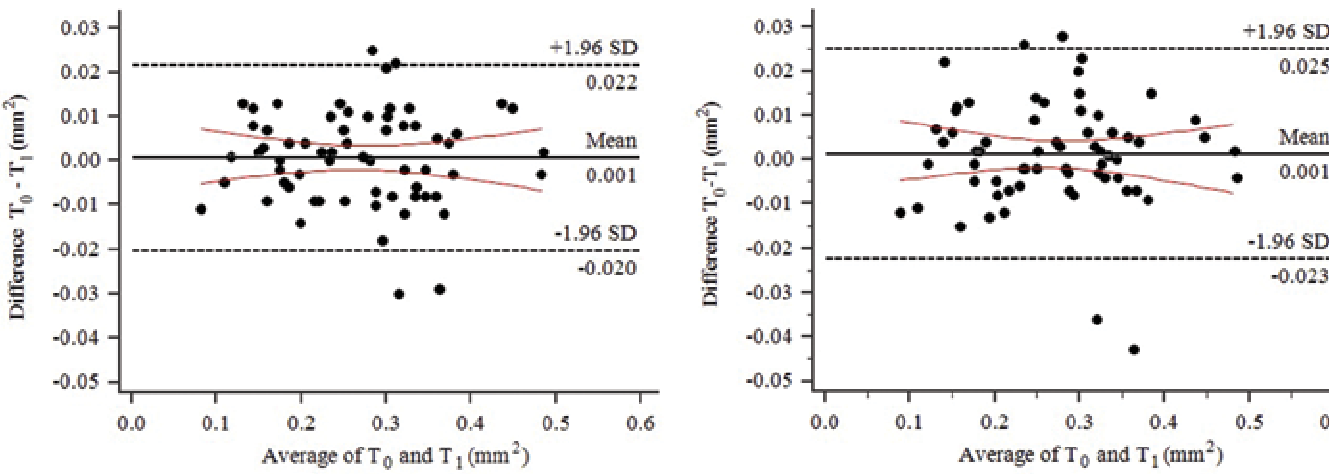

Fig. 2 - Bland-Altman plots show the intraobserver (observer 1, **A**; observer 2, **B**) deviation of the foveal avascular zone area at T0 from T1. T0 represents measurements by the observer during the first session; T1 represents repeated measurements by the same observer during the same session.

TABLE III - Intrasession repeatability of measurements

Observer	CVw, % (95% CI)	CR, mm² (95% CI)	ICC (95% CI)
1 (T0 vs T1)	2.44 (1.95-2.93)	0.021 (0.017-0.025)	0.993 (0.989-0.996)
2 (T0 vs T1)	2.66 (2.00-3.31)	0.024 (0.020-0.028)	0.991 (0.986-0.995)

CI = confidence interval; CR = coefficient of repeatability; CVw = within-subject coefficient of variation; ICC = intraclass correlation coefficient.

TABLE IV - Interobserver reproducibility of foveal avascular zone area measurements

	CCC	95% CI
T0 (observer 1 vs observer 2)	0.998	0.997 to 0.999
T1 (observer 1 vs observer 2)	0.998	0.997 to 0.999
T2 (observer 1 vs observer 2)	0.999	0.998 to 0.999

CCC = concordance correlation coefficient; CI = confidence interval.

TABLE V - Intraobserver intersession reproducibility of foveal avascular zone area measurements

Observer	CCC	95% CI
1 (T0 vs T2)	0.989	0.982 to 0.993
2 (T0 vs T2)	0.987	0.979 to 0.992

CCC = concordance correlation coefficient; CI = confidence interval.

Discussion

Foveal avascular zone is the macular capillary-free zone that is used as an anatomic landmark for locating the retinal point of fixation (11). It is surrounded by terminal retinal capillary ring originating from the 2 major branches of the central retinal artery. Its size reflects the condition of the microcapillary circulation in the foveal area. The FAZ dimension has a strong positive correlation with the severity of capillary nonperfusion in several retinal vascular diseases (12).

Vision-threatening retinal vascular diseases such as diabetic retinopathy, retinal vein occlusion, and macular telangiectasia involve retinal microcirculation by modifying the FAZ size (13-16).

Studies (14, 15, 17) using FFA to analyze the FAZ size demonstrated large variability of FAZ measurements in healthy subjects, with area data ranging from 0.205 to 0.405 mm^2. John et al (18) hypothesized that the use of the contrast-adjusted method could be a better tool for studying digital angiogram pictures. They found that the FAZ area outlined by the conventional method was larger than by the contrast-adjusted method. The high variability of measurements using FFA cast doubt on the reliability of this diagnostic method to measure FAZ size. Moreover, it is limited by the superimposition of the capillary network and leakage during FFA examination. Optical coherence tomography angiography is a new dye-less method for assessing the 3D microcirculation imaging of the retina, and providing a clean and continuous microvascular network around the FAZ (6). Kim et al (19) first reported the ability to detect FAZ area by means of phase-variance OCTA. Huang et al (20) measured FAZ diameter in 4 healthy subjects by means of OCTA using a modified Cirrus prototype with a swept-source laser provided by Carl Zeiss Meditec (Dublin, CA, USA), but the FAZ area was not detected. Carpineto et al (21) first reported the reliability of FAZ area measurements by means of SD-OCTA. Reliability refers to the property of a measurement instrument that enables it to give similar results for similar inputs. We investigated the reliability of SS-OCTA to measure FAZ area in healthy subjects using the high-speed (100,000 A-scans/s) 1,050 nm wavelength DRI SS-OCT Triton Plus (Topcon Corporation) with the full-spectrum OCTARA algorithm. This algorithm can be used to distinguish blood flow by calculating the decorrelation of the signal amplitude from 4 consecutive B-scans at the same retinal location. It creates a contrast between static and nonstatic tissue that allows visualization of the blood flow in the retinal capillary bed (3). In this observational instrument validation study evaluating reproducibility and repeatability of FAZ area measurements using SS-OCTA in healthy subjects, 2 experienced operators independently performed 2 measurements in the first session and repeated the measurements in the second session 30 days later. Repeatability was tested by means of CVw, ICC, and CR. The within-subject coefficient of variation is the ratio between the within-subject standard deviation and the mean; the smaller the CVw, the better the repeatability. The ICC is the ratio of the intersubject component of the variance to the total variance. The higher the ratio, the better the repeatability; the variability of measurements is primarily the result of interindividual differences. There are some basic differences between the 2 measures. The ICC is scaled relative to the population mean, while CVw is scaled relative to the between-subject variance. The CVw, unlike the ICC, is sensitive to a shift in scale. This is because it combines both precision (variation) and accuracy (bias) measures so that it measures the repeatability in both senses (22). The CR is the value below which the absolute differences between 2 measurements would lie with 0.95 probability; it is directly related to the 95% limits of agreement proposed by Bland and Altman that contain 95% of the differences between repeated measurements on the same subjects (8). Intrasession and intersession reproducibility were evaluated by means of CCC. The CCC evaluates the degree to which pairs of observations fall on the 45° line through the origin (9). It contains a measurement of precision ρ (the Pearson correlation coefficient, which measures how far each observation deviates from the best-fit line) and accuracy Cb (a bias correction factor that measures how far the best-fit line deviates from the 45° line through the origin): $\rho c = \rho\ Cb$. The study showed both promising reproducibility and repeatability results for both operators. The within-subject coefficients of variations were 2.44% and 2.66% for the first and second observers, respectively. The ICCs were 0.993 for the first observer and 0.991 for the second observer. The coefficients of repeatability of average FAZ area measurements were excellent, resulting in 0.021 mm^2 for the first observer and 0.024 mm^2 for the second observer.

Both interobserver intrasession and intraobserver intersession reproducibilities were very high, with CCC values ranging from 0.998 to 0.999. In addition, FAZ area mean value (0.270 mm^2) was similar to the results obtained by John et al (18) using contrast-adjusted FFA, Kim et al (19) using phase-variance OCT compared to FFA, and Carpineto et al (21), Samara et al (23), and Shahlaee et al (24) using SD-OCTA. We found a high reproducibility and high repeatability of the FAZ area measurements by mean SS-OCTA. Technically, the high reproducibility may be a result of the automatic detection and calculation of the FAZ area using the OCTARA algorithm that is included in the SS-OCTA software. These results confirm the reliability of the measurements obtained by means of automated systems by using the FFA (17) or OCTA (21) computerized techniques for automated segmentation of the FAZ.

Reliability of FAZ measurements makes OCTA an interesting potential diagnostic tool for retinal pathologies involving microcirculation because the FAZ size is correlated to vision-threatening diseases (12-17). A limitation of the present study is that the population included only healthy subjects. In addition, given the relatively young age of our healthy population, the examination time in this study may be shorter than that encountered in older patients or patients with retinal vascular diseases (21). Moreover, patients with maculopathies with poor fixation or patients with optical medium opacities represent another limit for the reliability of the examination (20). Swept-source OCT angiography offers both the long wavelength and excellent signal to noise ratio of swept-source technology, allowing deeper imaging through opacities (25).

In conclusion, the results presented in this study showed excellent reproducibility and repeatability of FAZ area measurements in normal eyes using SS-OCTA. This noninvasive method is a potential diagnostic tool for disease detection and progression in retinal pathologies involving microcirculation.

Disclosures

Financial support: No financial support was received for this submission.
Conflict of interest: None of the authors has conflict of interest with this submission.

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