Repeatability, interocular correlation and agreement of quantitative swept-source optical coherence tomography angiography macular metrics in healthy subjects

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ABSTRACT

Purpose To investigate the repeatability, interocular correlation and agreement of quantitative swept-source optical coherence tomography angiography (SS-OCTA) metrics in healthy subjects.

Methods Thirty-three healthy normal subjects were enrolled. The macula was scanned four times by an SS-OCTA system using the 3 mm×3 mm mode. The superficial capillary map images were analysed using a MATLAB program. A series of parameters were measured: foveal avascular zone (FAZ) area, FAZ perimeter, FAZ circularity, parafoveal vessel density, fractal dimension and vessel diameter index (VDI). The repeatability of four scans was determined by intraclass correlation coefficient (ICC). Then the averaged results were analysed for intereye difference, correlation and agreement using paired t-test, Pearson's correlation coefficient (r), ICC and Bland-Altman plot.

Results The repeatability assessment of the macular metrics exported high ICC values (ranged from 0.853 to 0.996). There is no statistically significant difference in the OCTA metrics between the two eyes. FAZ area (ICC=0.961, r=0.929) and FAZ perimeter (ICC=0.884, r=0.802) showed excellent binocular correlation. Fractal dimension (ICC=0.732, r=0.578) and VDI (ICC=0.707, r=0.547) showed moderate binocular correlation, while parafoveal vessel density had poor binocular correlation. Bland-Altman plots showed the range of agreement was from −0.0763 to 0.0954 mm^2 for FAZ area and from −0.0491 to 0.1136 for parafoveal vessel density.

Conclusions The macular metrics obtained using SS-OCTA showed excellent repeatability in healthy subjects. We showed high intereye correlation in FAZ area and perimeter, moderate correlation in fractal dimension and VDI, while vessel density had poor correlation in normal healthy subjects.

INTRODUCTION

The human body has highly bilateral mirror symmetrical structures in the mid-sagittal plane, such as the eyes, ears and limbs. Biometric parameters obtained in one eye are more likely to be similar to those of the fellow eye than those obtained from an unrelated person.[1] Using comparative data analysis, numerous studies have already assessed the interocular symmetry of several biometric parameters in healthy individuals, such as spherical equivalent of refractive error (SE), axial length, higher order aberrations, intraocular pressure, cup to disc ratio and retinal nerve fibre layer (RNFL) thickness.[2–4]

Interocular symmetry is a pervasive feature of great use in both scientific research and clinical application. In scientific research, allowing for the mirror symmetry between the right and the left eyes, one may either use only the right or only the left eyes for a study, or use the fellow eye as a 'control'.[5] In clinical application, this feature has been helpful, including in planning for strabismus,[6] predicting refraction for cataract surgery,[7] detection of anatomy abnormalities and disease diagnosis.[8] High interocular symmetry may also be helpful in verifying the accuracy of binocular data, so asymmetric data may be required for remeasurement.[9] Excess interocular asymmetry of intraocular pressure, RNFL and appearance of the optic disc is a well known sign of glaucoma.[8]

Optical coherence tomography angiography (OCTA) is a novel, non-invasive, three-dimensional imaging technology which can image the detailed vasculature of the retina. Existing studies have reported enlarged foveal avascular zone (FAZ) area in retinal ischaemic diseases such as diabetic retinopathy (DR)[10] and retinal vascular obstruction (RVO)[11]; decreased FAZ area in retinopathy of prematurity[12]; decreased vessel density in DR[10] and glaucoma[13]; lower fractal dimension in RVO,[11] DR[10] and uveitis eyes[14]; increased vessel diameter index (VDI) in RVO[11] and DR[10]; and decreased FAZ circularity in glaucoma[15] and DR.[10] These studies demonstrate that quantitative OCTA metrics may provide useful information for the diagnosis of ocular diseases potentially.

However, a certain extent of non-pathological asymmetry can be a normal variation between fellow eyes.[16] Therefore, it is essential to know the range of interocular symmetry for normal subjects. The present study was designed to investigate repeatability and the range of binocular symmetry, and provide reference data for macular metrics on normal subjects.

METHODS

Subjects

Each of the subjects was informed of the nature of the study, and their willingness to participate was documented with their signature on a consent form approved by the institutional review board.

In this cross-sectional study, healthy Chinese subjects between 18 and 40 years of age were recruited. All measurements were obtained in the same environment using the same instruments which were operated by a single technician. All participants had normal retina and no visual symptom. They had best-corrected visual acuity of at least 20/20 using the Snellen chart, intraocular pressure less than 21 mm Hg, refractive error within ±6D and had less than 2 dioptre difference between the two eyes. Subjects were excluded if they had any evidence of systemic or ocular diseases. Low image quality scans were excluded, which were defined as scans with quality index <60 (ranged from 0 to 100).

The sample size for repeatability was calculated under the assumption that the 95% CI of within-subject SD (Sw) is estimated within 15% of Sw, $1.96\frac{Sw}{\sqrt{2n(m-1)}}=15\% \times$ Sw. Then n=1.96/[2(m-1)×0.15], with n and m representing the number of subjects and observation times, respectively. Because we performed four measurements on each subject, n was calculated to be 30.[17]

The sample size of agreement was calculated according to the formula $n \geq \frac{\log(1-\beta)}{\log(1-\alpha)}$, where n is the sample size, α is the discordance rate and β is the tolerance probability, respectively (when α=0.05 and β=80%, n≥32).[18]

OCTA imaging

A swept-source OCT device (DRI OCT Triton; Topcon Corporation, Tokyo, Japan) was used to perform OCTA imaging. The pupils of all subjects were dilated to at least 6 mm diameter with topical 0.5% tropicamide. Both eyes were scanned four times using the macular 3 mm×3 mm scan protocol. The device uses an innovative OCTA algorithm OCTARA, which is used for OCTA ratio analysis of motion contrast.

Using a built-in software (ImageNet V.6: based on the automated layer segmentation algorithm), key layers were automatically generated, including the superficial capillary plexus, the deep capillary plexus, the outer retina and the choroidal capillaries. The en face images of the superficial capillary map were formed from the internal limiting membrane to just below the inner plexiform layer. The results of the retinal layer segmentation were reviewed to ensure correct segmentation and the en face images were generated correctly. The superficial capillary maps were exported for quantification. We did not use the deeper capillary plexus because they are confounded by a shadow graphic flow projection artefacts.

Quantitative assessment of superficial capillary network

The superficial capillary map images were imported into a customised MATLAB program. The details of the algorithm were reported in our previous publication.[10] The following parameters were calculated: The area of FAZ was measured by counting the total number of pixels within FAZ in a scale multiplying the dimension of a pixel. FAZ perimeter was calculated as the length of the contour based on pixel-to-pixel distance in a scale. FAZ circularity index was calculated as the ratio of the measured area FAZ to the expected area. Vessel density was defined as the ratio of the area occupied by white pixels divided by the total area. Parafoveal region was defined as the ring between the 3 mm and 1 mm circle. Fractal dimension was then calculated using the box-counting method. VDI was the average vessel calibre on the OCTA image.

Statistical analysis

In the repeatability analysis, four measurements from each eye were performed. The following parameters were calculated: Sw, precision (repeatability coefficient) (1.96×Sw), coefficient of variation (CoV) (100×Sw/overall mean) and intraclass correlation coefficient (ICC).

In the interocular correlation and agreement analysis, paired t-test was used to determine the significance of interocular differences. Pearson's correlation coefficient was calculated to assess the linear correlation between the bilateral eyes of the OCTA macular metrics. For all analyses, statistical significance was defined as $p<0.05$. ICCs were also calculated to investigate the interocular correlation. ICCs are classified as good to excellent if they are greater than or equal to 0.75, fair to good if between 0.4 and 0.74, and poor if less than 0.4. Bland-Altman plots were used to demonstrate the agreement between the two eyes of the same healthy subjects graphically.

RESULTS

A total of 33 healthy subjects (12 men and 21 women) were enrolled in the study. The mean±SD of the subjects' ages was 24.9±2.5 years (range: 20–35 years). The mean SE was −2.32±1.93 D (range: −5.50–+0.75 D) in the right eye and −2.27±2.11 D (range: −5.75 to +0.75 D) in the left eye. The mean image quality index was 72.4±2.72 (range: 65.5–78.5) in the right eye and 71.9±2.45 (range: 67.75–76.5) in the left eye. There was no statistical significance in SE (p=0.732) and image quality index (p=0.372) between the two eyes.

Table 1 presents the mean and repeatability macular metrics values. All the metrics have good to excellent repeatability as shown by the ICC >0.853 and CoV <8.581%.

Table 2 demonstrates the paired t-test and correlation of the OCTA metrics between the two eyes. Generally, there was no statistically significant difference between the two eyes in all metrics. FAZ area (ICC=0.961, r=0.929) and FAZ perimeter (ICC=0.884 r=0.802) showed good to excellent binocular correlation. Fractal dimension (ICC=0.732, r=0.578) and VDI (ICC=0.707, r=0.547) showed fair to good binocular correlation, while the parafoveal vessel density (ICC=0.215, r=0.120)

Table 1 Means and intrasession repeatability of the OCTA macular superficial vessel metrics

	Left eye					Right eye				
	Mean±SD	Sw	CoV	Precision	ICC	Mean±SD	Sw	CoV	Precision	ICC
Foveal avascular zone area (mm^2)	0.357±0.118	0.016	4.458	0.031	0.996	0.347±0.108	0.014	3.977	0.027	0.996
Foveal avascular zone perimeter (mm)	2.190±0.431	0.139	6.354	0.273	0.975	2.155±0.365	0.131	6.06	0.256	0.969
Foveal avascular zone circularity	0.687±0.080	0.059	8.581	0.116	0.871	0.693±0.078	0.054	7.815	0.106	0.884
Parafoveal vessel density	0.550±0.022	0.016	2.849	0.031	0.869	0.558±0.022	0.017	3.012	0.033	0.853
Fractal dimension	1.687±0.005	0.003	0.165	0.005	0.931	1.687±0.006	0.003	0.184	0.006	0.93
Vessel diameter index (mm^{22}/mm)	0.012±0.000	0.000	1.835	0.000	0.916	0.012±0.000	0.000	2.264	0.001	0.881

CoV, coefficient of variation; ICC, intraclass correlation coefficient; OCTA, optical coherence tomography angiography; Sw, within-subject SD.

Table 2 Correlation coefficients of the OCTA macular superficial vessel metrics between the two eyes

	Paired t-test p	Intraclass correlation	Pearson's correlation	Pearson's correlation p
Foveal avascular zone area	0.218	0.961	0.929	<0.001
Foveal avascular zone perimeter	0.436	0.884	0.802	<0.001
Foveal avascular zone circularity	0.743	0.258	0.148	0.411
Parafoveal vessel density	0.136	0.215	0.120	0.505
Fractal dimension	0.980	0.732	0.578	<0.001
Vessel diameter index	0.067	0.707	0.547	<0.001

OCTA, optical coherence tomography angiography.

and FAZ circularity (ICC=0.258, r=0.148) had poor correlation between the two eyes.

Figures 1 and 2 demonstrates the Bland-Altman plots of the OCTA measurements between the two eyes. Generally, the FAZ area difference from the contralateral eye of 0.09 mm^2 can be considered as within normal range. The ranges of agreement of other metrics are listed in table 3.

DISCUSSION

Our study found that the OCTA metrics of macular superficial capillary had excellent repeatability. There was no statistically significant difference in the OCTA metrics between the two eyes. FAZ area and perimeter had good correlation, fractal dimension and VDI had moderate correlation, while parafoveal

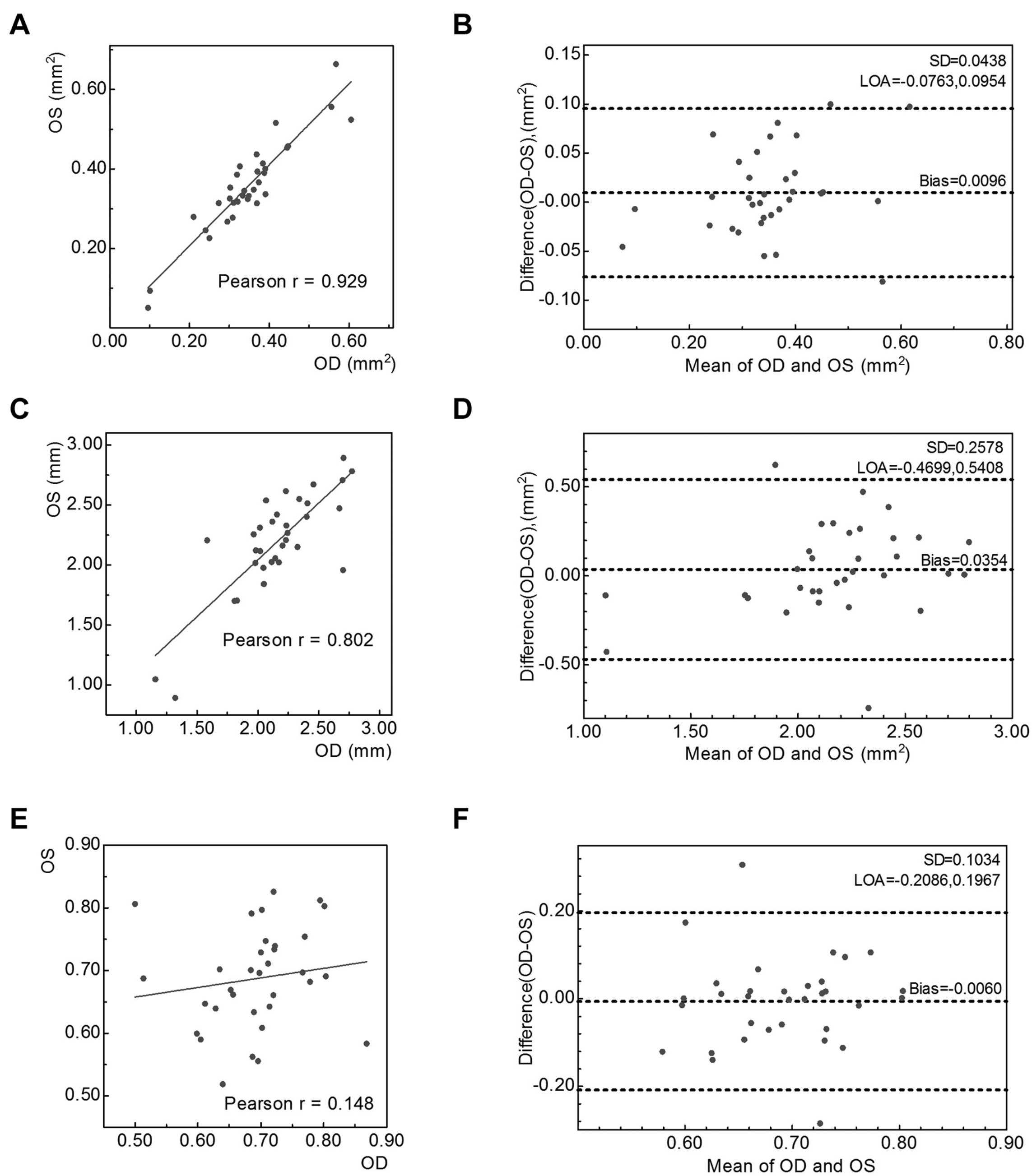

Figure 1 Scatter plots (A,C,E) and Bland-Altman plots (B,D,F) of foveal avascular zone area (A,B), perimeter (C,D) and circularity (E,F) of the left and right eyes. OS, left eye; OD, right eye; LOA, 95% limits of agreement.

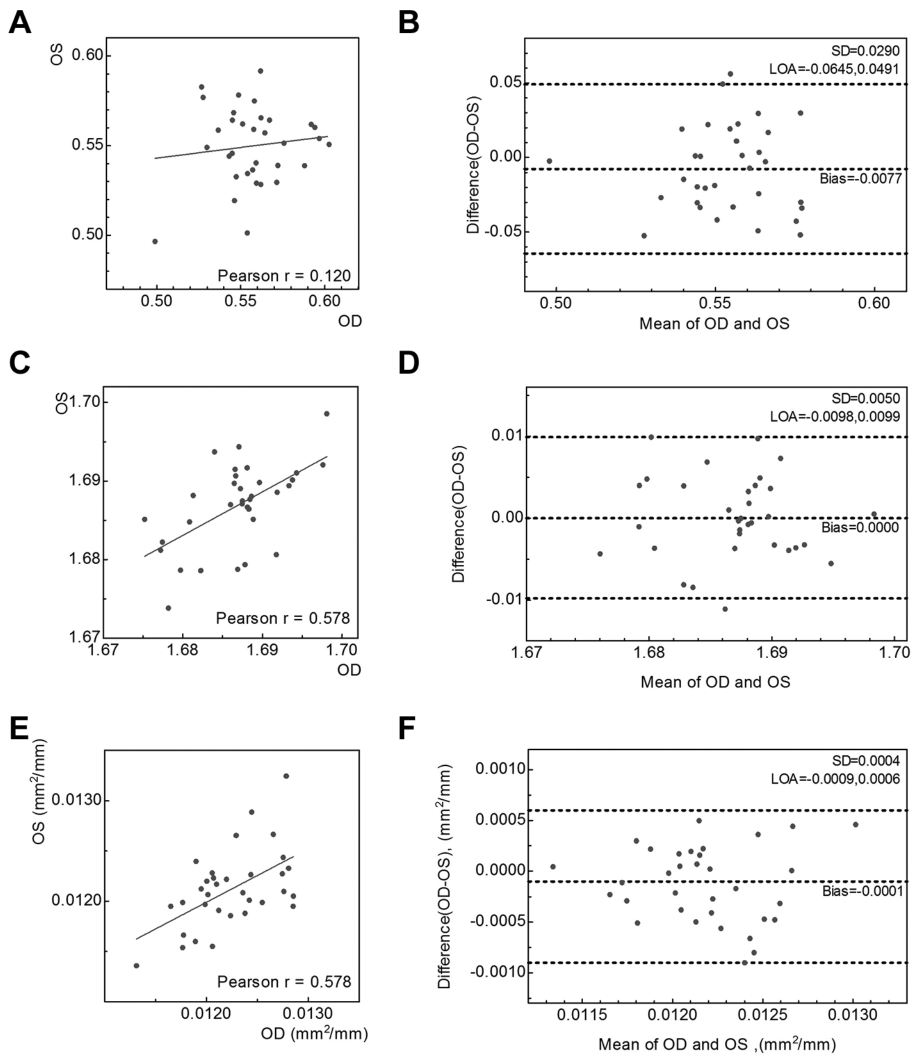

Figure 2 Scatter plots (A,C,E) and Bland-Altman plots (B,D,F) of parafoveal vessel density (A,B), fractal dimension (C,D) and vessel diameter index (E,F) of the left and right eyes.

vessel density had no correlation. The ranges of agreement of the OCTA macular metrics were determined. This information would help us to choose proper control and interpret whether the differences between two eyes are within normal range.

In scientific research and clinical practice, we need a control to assess whether the measurement is within or out of normal range. If the contralateral eyes have good intraclass correlation and narrow range of agreement, they are a better control, otherwise the eyes from unrelated subjects should be used. Furthermore, the eyes are usually highly correlated. In some studies, the two eyes are treated as independent eyes, while in other studies only the left eye or the right eye or the average value of the two eyes was used. A review of 161 research articles published in five ophthalmology journals indicated that many studies did not make good use of all the available data and that a considerable number of them used inappropriate statistical methods.[1] If studies choose these analytic approaches without interocular correlation being considered, the studies may be invalid because of the great loss of statistical information.

The metrics of FAZ are important parameters in assessing many conditions, especially retinal ischaemic diseases. There are three articles[19–21] that compared FAZ area and one article[22] that compared FAZ diameter between the left and the right eyes, and all of them found no statistically significant difference. Our results are consistent with these literature reports. There are two study articles that reported good correlation of FAZ area between the two eyes using Spearman's correlation (r=0.934) and Pearson's correlation (r=0.958), respectively.[21 23] Our study also found that FAZ area and FAZ perimeter had almost excellent correlation between the two eyes. There is large variance in unrelated healthy subjects,[24]

Table 3 Summary of the interocular agreement of the OCTA macular superficial vessel metrics between the two eyes

	Mean difference	95% CI upper	95% CI lower	Range of agreement
Foveal avascular zone area (mm^2)	0.0096±0.0438	−0.0763	0.0954	0.1717
Foveal avascular zone perimeter (mm)	0.0354±0.2578	−0.4699	0.5408	1.0107
Foveal avascular zone circularity	−0.0060±0.1034	−0.2086	0.1967	0.4053
Parafoveal vessel density	−0.0077±0.0290	0.0645	0.0491	0.1136
Fractal dimension	0.0000±0.0050	−0.0098	0.0099	0.0197
Vessel diameter index (mm^2/mm)	−0.0001±0.0004	−0.0009	0.0006	0.0015

OCTA, optical coherence tomography angiography.

while the difference between the fellow eyes is smaller. This suggests that the contralateral eye is a better choice as a control than the eyes from unrelated subjects for quantitative investigation of FAZ area or perimeters in unilateral diseases, especially in a small sample size. However, the circularity of FAZ did not have significant correlation.

Our study found that there was no significant difference in parafoveal vessel density between the two eyes. Our results were consistent with most literature reports which found no significant difference in macular vessel density between the contralateral eyes.[20 25 26] However, a recent report from Liu *et al*[21] found that the macular vessel density was higher in the right eye than in the left eye. They suggest the domination of eye may explain the difference.

To our surprise, our study found there was no significant correlation in the parafoveal vessel density between the fellow eyes. In the literature, a study by Liu *et al*[21] reported moderate correlation for the superficial capillary plexus density (Spearman's correlation r=0.402) between the fellow eyes, while another article by Zhang *et al*[23] used Pearson's correlation and found the foveal vessel density has high correlation (r=0.888). There are two possible reasons for the inconsistency between our results and the literature. The first one is the difference in statistical analysis. Spearman's correlation is a non-parametric statistical method which can only demonstrate the trend of variance between the two eyes. The key difference between Pearson's correlation and ICC is that the data are centred and scaled using a pooled mean and SD in ICC, but each variable is centred and scaled by its own mean and SD in the Pearson's correlation. Therefore, ICC is a better method to investigate the symmetry between the two eyes. The second reason is the difference in the region of interest. In Zhang *et al*'s study,[23] they investigated the foveal region, where the avascular area is largely made up of FAZ, while in Liu *et alet al*'s study[21] only the vessel density at the 3×3 region, which may also be affected by FAZ, was investigated. We used the parafoveal region because it is less affected by the FAZ and may better represent the density of vessel. Our study found that the difference in the parafoveal vessel density between the two eyes was even larger than the variance in unrelated individuals. Therefore, when investigating vessel density, unrelated subjects should be used instead of the fellow eye.

Fractal dimension is a parameter for complexity of retinal vasculature. There is a study reporting no statistically significant difference in fractal dimension between the two eyes in normal subjects; however, it used optic disc centred fundus photography.[27] Our study investigated the fractal dimension of the superficial macular vascular plexus and found that there was no significant difference between the fellow eyes and that there was moderate interocular correlation. Therefore, the fellow eye can be used as a control.

VDI is a parameter that represents the diameter of the retinal vessel. An article reported that there was substantial correlation between the eyes in the parapapillary vessel calibre (Pearson's r=0.71 and 0.74 for artery and vein, respectively).[28] Our study found that there was no significant difference and the interocular correlation of macular VDI was moderate between the two eyes. Therefore, the fellow eye can also be a good control.

The repeatability of macular superficial capillary OCTA metrics is high, as indicated by all intrasession ICC >0.853 and all CoV <8.581%. Our results are consistent with literature reports on the OCTA metrics for macular superficial capillary.[29] The high repeatability suggests that the moderate interocular correlation of fractal dimension and VDI and poor interocular correlation of the parafoveal vessel density are not due to variation in measurements.

Although there are several published articles investigating the OCTA metrics in normal subjects, our manuscript added some new information. (1) We found that the interocular correlation of vessel density is low and suggest that the contralateral eye is not used as a control when investigating vessel density. (2) We are the first to investigate the repeatability and interocular correlation/agreement of factual dimension and VDI on OCTA. (3) We are the first to investigate the interocular correlation and agreement of the OCTA metrics using swept-source OCT.

We recognised some limitations in the current study. First, our included subjects are all young people with a narrow age range. The metrics of OCTA can be affected by various factors, for example, axial length, refractive error and age. Further studies including more subjects with wider range are needed. Second, the algorithm is not always perfect in the segmentation of blood vessel on OCTA images. Third, the intraocular pressure was measured just to exclude subjects with IOP >21 mm Hg, but the results were not recorded and we did not measure blood pressure. Therefore, we cannot analyse the relationship between interocular vessel density difference and interocular IOP difference or mean ocular perfusion pressure.

In conclusion, the macular metrics obtained using swept-source OCTA showed excellent repeatability in healthy subjects. We found that FAZ area and perimeter, but not vessel density, had good correlation and agreement between the two eyes. Our data would help to choose proper control and interpret whether the differences between two eyes are within normal range.

Contributors DF: conducted the study and drafted the manuscript. FYT: analysed the images. HH: recruited the subjects. CYC: analysed the images and revised the manuscript. HC: designed the study and revised the manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Joint Shantou International Eye Center of Shantou University and The Chinese University of Hong Kong.

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