Original Article

Interchangeability of retinal perfusion indices in different-sized angiocubes: An optical coherence tomography angiography study in diabetic retinopathy

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Purpose: To evaluate the differences in vascular indices in different scan sizes of optical coherence tomography angiography (OCTA) images in normal persons versus persons with diabetic retinopathy. **Methods:** OCTA scans of diabetic patients and age-matched controls were performed by a single operator. Automated quantification of vascular indices of the superficial plexus was analyzed in two angiocubes of 3 × 3 mm and 6 × 6 mm, respectively. The agreement was analyzed with the intraclass correlation coefficient (ICC) and Bland–Altman plots. **Results:** Forty-eight eyes with DR, 36 eyes with no diabetic retinopathy (No DR), and 26 eyes of age-matched normals were scanned. The foveal avascular zone (FAZ) area and perimeter were highly reliable and interchangeable in both angiocubes of the healthy eyes (ICC 0.94, 0.75), No DR (ICC 0.92, 0.85), and DR eyes (ICC 0.97, 0.89). The vessel density (VD) and perfusion density (PD) showed excellent agreement in normal (ICC 0.89, 0.80) and No DR eyes (ICC 0.92, 0.81). But, only fair ICC was observed in DR eyes (0.56, 0.42). **Conclusion:** The FAZ area and perimeter showed excellent reproducibility. The macular perfusion parameters are not interchangeable despite automated estimation. The variability is more with changes in the vascular network like DR. This variability should be considered while comparing different scans.

Key words: Angiocubes, diabetic retinopathy, FAZ area, optical coherence tomography angiography, retinal perfusion indices, vascular indices

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Optical coherence tomography angiography (OCTA) is widely being used to analyze the vascular disorders of the retina. It is a noninvasive procedure that allows three-dimensional visualization of the retinal and choroidal vasculature without the need for dye injection.[1] An accurate image of the vascular network is produced by sequential B-scans, which detect the motion of particles in the blood vessels and differentiate them from the static tissue.[2] With recent developments in the OCTA technology, a higher number of B-scans, per second have led to a higher spatial resolution of the image. Due to the closely spaced B-scans, the tissues can be segmented at any level and capillary plexuses at various depths can be outlined separately.[2] Unlike the conventional fluorescein angiography (FA), the OCTA images can be postprocessed with the help of various algorithms to provide a lot of quantitative data, such as vascular indices and perfusion parameters. Many vascular disorders are now being analyzed with the help of these indices, giving us newer insights into these diseases.

However, the scan size can affect the measurements of these indices, and different scan sizes of the same individual might give different information. Several studies have reported interchangeability. Dong *et al*.[3] reported interchangeability between 3 × 3 mm and 6 × 6 mm scans in healthy Chinese adults. Rabiolo *et al*.[4] found different values with different reliability in healthy versus diabetic retinopathy (DR) subjects with different scan sizes and different plexuses.

We evaluated the reliability of various indices in two different scan sizes of healthy subjects versus diabetic patients, with and without DR.

Methods

In a prospective study done at our institute, between November 2017 and August 2018, a total of 110 eyes were evaluated using OCTA. All subjects gave written informed consent for the study, which was approved by the institutional review board. The study adhered to the tenets of the Declaration of Helsinki. A detailed medical and ocular history was taken for all subjects. All subjects also underwent estimation of fasting blood sugar levels (FBS), postprandial blood sugar (PPBS), glycosylated hemoglobin (HbA1C), and routine urine examination. We also measured the blood pressure (BP) and body mass index (BMI)

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of all the subjects. Any of the control subjects with an FBS of 100 to125 mg/dl and/or HbA1C of 5.7 to 6.4% were labeled as prediabetic and were excluded from the study. Any subjects with a history of dyslipidemia, chronic renal disorder, uncontrolled hypertension, and/or ischemic heart disease were excluded from the study. Also, subjects who were chronic smokers were excluded. All subjects underwent detailed ophthalmic evaluation, including a dilated fundus examination by a retina specialist (DR). Patients with media opacities, refractive error more than +/−6 diopters, ocular pathology other than DR, and any history of intravitreal injection, laser, or major ocular surgery in the past 4 months were excluded from the study. DR was defined according to the ETDRS criteria.[5] Patients were grouped into controls, diabetic patients with no diabetic retinopathy (No DR) and diabetic patients with DR.

Data acquisition

All subjects underwent OCT angiography after dilation with tropicamide with the Zeiss AngioPlex OCTA 5000 (Carl Zeiss Meditec, Inc., Dublin, CA, USA). All the measurements were taken by a single operator (DD). Centered on the fovea, 3 × 3 mm and 6 × 6 mm square cube angio scans were taken. The machine provides noninvasive, high-quality images of retinal and choroidal vasculature using a wavelength of 840 nm and 68000 A-scans per second. Cirrus OCTA generates contrast associated with motion, i.e., the motion of blood through vasculature by using the differences between B-scans. B-scans are repeated several times consecutively, and the comparison of contrast change over time in these consecutive scans in the same location is used to image vascular flow. Temporal contrast change in a specific location is due to erythrocyte motion and indicates vessel location. Using the intensity-based frequency filtering technique, 3 × 3 mm, 6 × 6 mm, and 8 × 8 mm square cube images of detailed vasculature can be generated. Accuracy and sensitivity are improved by optical microangiography algorithm (OMAG) and tracking is enabled using FastTrac ™ retinal tracking technology. Vessel density (VD) is defined as the total length of perfused vasculature per unit area in a region of measurement and perfusion density (PD) is defined as the total area of perfused vasculature per unit area in a region of measurement. Automated segmentation is done by the software. The superficial layer is between the internal limiting membrane (ILM) and the inner plexiform layer (IPL). The IPL boundary is estimated by the following equation:

$$ZIPL = ZILM + 70\% \times (TILM - OPL)$$

Where ZIPL is the boundary location of the estimated IPL, ZILM is the boundary location of the ILM, and TILM-OPL is the thickness between ILM and the outer plexiform layer (OPL).

Perfusion indices and FAZ measurements for the superficial retinal plexus are provided automatically for the 3 × 3 mm and 6 × 6 mm angio scans by the built-in software. The regions of the tissue were subdivided according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields. Measurements provided in both tabular form and as density maps (ETDRS grid) through the AngioPlex metrics toolbox were used for the analysis. Scans with poor signal strength (less than 5) and motion artifacts were excluded for analysis. Only the center and inner rings in the ETDRS grid were included from the 6 × 6 mm scans to be compared with 3 × 3 mm cube [Fig. 1].

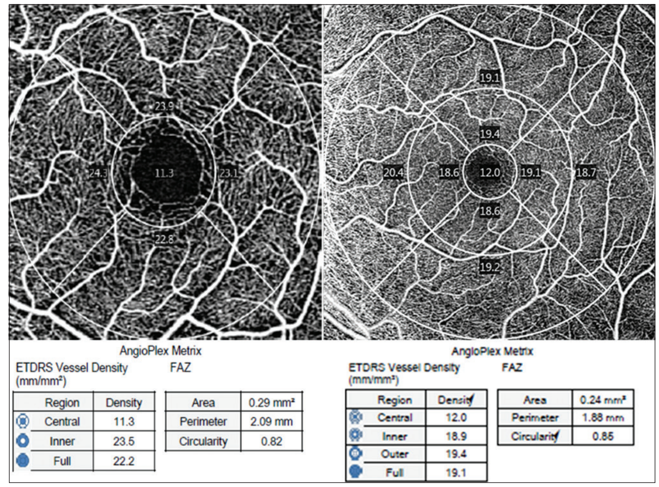

Figure 1: The overlay of the Early Treatment Diabetic Retinopathy Study grid onto the 3 × 3 mm (on the left) and 6 × 6 mm scans, showing the segmentation and the automated measurement of indices in the different quadrants

Statistical analysis

The variables included for the analysis are the FAZ area, circularity and perimeter, and VD and PD in the central and the inner rings. Their reliability across the two scans was assessed by the intraclass correlation coefficient (ICC) for controls, No DR, and DR patients. The agreement between two measurements was assessed using Bland–Altman plots. All statistics were performed using Statistical Package for Social Sciences (SPSS) Version 20.0 software (IBM Corp, Armonk, NY) and Bland–Altmann plots were done using MedCalc for Windows version 18.6 (Medcalc software, Ostend, Belgium).

Results

The study included 48 eyes of 25 diabetic patients with DR, 36 eyes of 19 diabetic patients with No DR and 26 eyes of 13 age and sex-matched controls. The mean age of diabetic patients was 53.5 ± 9.8 years and controls were 49.38 ± 7 years ($P = 0.112$) There were 28 (63.6%) males and 16 (36.4%) females in diabetic group and 9 (69.2%) males and 4 (30.8%) females in the control group. The following parameters were measured and analyzed for the 2 scans, namely, foveal avascular zone (FAZ) area, perimeter and circularity, VD and PD in the central and inner ETDRS areas, in superficial capillary plexus. All the measurements were automated except in some eyes with DR manual marking of FAZ was done when the automated measurement failed. Table 1 gives the mean values for all the vascular parameters for all the groups in both 3 × 3 and 6 × 6 scans. Table 2 lists the mean difference in the parameters between the two scan sizes. The ICC values were calculated to determine the reliability of measurements in the two scan sizes. Table 3 lists these values. The FAZ area showed an excellent ICC in all the 3 groups, viz. controls, No DR and DR (0.939, 0.92, 0.968 respectively). FAZ perimeter also showed excellent ICC in all the groups (0.751, 0.85, 0.892 in controls, No DR and DR respectively). FAZ circularity showed good ICC in No DR (0.67) and DR (0.689) group whereas poor ICC (-0.078) in controls. VD in the center ring showed excellent ICC in normal (0.892) and No DR (0.92) whereas it was fair in the DR group (0.562). VD in the inner ring showed fair ICC across all the groups (0.57, 0.49, 0.528 in controls, No DR, DR respectively). The PD ICC values for the central ring were excellent in controls (0.80) and No DR (0.81) groups but only fair in the DR (0.42) group. Similarly, PD in the inner ring showed good ICC in normal (0.727), but fair ICC in No DR and DR group (0.53, 0.526).

Table 1: Mean difference in the parameters between the 3 × 3 mm and 6 × 6 mm scan sizes in eyes with and without DR and normal controls

	Controls			No DR			*P*	DR			*P*
	Mean	SD	95% CI	Mean	SD	95% CI		Mean	SD	95% CI	
FAZ (3×3)											
Area	0.36	0.11	0.32-0.41	0.37	0.13	0.33-0.41	0.117	0.55	0.36	0.44-0.65	0.00
Perimeter	2.64	0.48	2.44-2.83	2.74	0.58	2.54-2.93	0.361	3.76	1.1	3.43-4.08	0.00
Circularity	0.65	0.08	0.62-0.68	0.62	0.11	0.58-0.65	0.282	0.48	0.12	0.45-0.52	0.00
FAZ (6×6)											
Area	0.35	0.1	0.31-0.40	0.33	0.11	0.29-0.37	0.035	0.48	0.3	0.39-0.57	0.01
Perimeter	2.56	0.46	2.38-2.75	2.46	0.51	2.28-2.63	0.043	3.27	0.98	2.98-3.56	0.00
Circularity	0.68	0.11	0.63-0.7	0.69	0.13	0.64-0.73	0.617	0.56	0.11	0.53-0.59	0.00
VD (3×3)											
Center Avg	8.46	2.85	7.31-9.61	8.38	3.15	7.31-9.44	0.336	6	2.56	5.25-6.75	0.00
Inner Avg	20.65	2.32	19.71-21.59	20.76	2.04	20.07-21.45	0.925	16.68	2.01	16.09-17.27	0.00
VD (6×6)											
Center Avg	8.38	3.72	6.88-9.89	8.7	3.07	7.66-9.74	0.351	7.35	4.12	6.14-8.56	0.24
Inner Avg	17.44	2.19	16.56-18.33	17.85	2.06	17.15-18.54	0.515	14.75	3.02	13.87-15.64	0.00
PD (3×3)											
Center Avg	0.15	0.05	0.13-0.18	0.15	0.06	0.13-0.17	0.462	0.11	0.04	0.10-0.12	0.00
Inner Avg	0.38	0.04	0.36-0.39	0.38	0.04	0.37-0.40	0.843	0.33	0.04	0.32-0.34	0.00
PD (6×6)											
Center Avg	0.19	0.09	0.16-0.23	0.2	0.07	0.17-0.22	0.381	0.16	0.09	0.14-0.19	0.20
Inner Avg	0.42	0.06	0.40-0.44	0.43	0.05	0.42-0.45	0.213	0.36	0.08	0.34-0.39	0.00

DR=Diabetic retinopathy present, No DR=No diabetic retinopathy, SD=Standard deviation, CI=Confidence interval, FAZ=Foveal avascular zone, Avg=Average, VD=Vessel density, PD=Perfusion density

Table 2: Mean difference in the parameters between the 3 × 3 mm and 6 × 6 mm scan sizes in eyes with and without DR and normal controls

Mean difference between 3 × 3 mm and 6 × 6 mm scans	Control		No DR		DR	
	Mean	SD	Mean	SD	Mean	SD
FAZ						
Area	0.01	0.05	0.04	0.03	0.07	0.12
Perimeter	0.08	0.42	0.28	0.23	0.49	0.54
Circularity	0.03	0.14	0.07	0.11	0.07	0.11
VD						
Center ring	0.07	2.1	0.33	1.56	1.36	4.34
Inner ring	3.2	1.43	2.91	2.04	1.93	3.12
PD						
Center ring	0.04	0.05	0.05	0.04	0.05	0.1
Inner ring	0.04	0.03	0.05	0.05	0.03	0.08

DR=Diabetic retinopathy present, No DR=No diabetic retinopathy, SD=Standard deviation, FAZ=Foveal avascular zone, VD=Vessel density, PD=Perfusion density

In the Bland–Altman plots, [Figs. 2 and 3], differences in the FAZ area and perimeter were close to zero across all groups, indicating good agreement. However, the perfusion indices between the two scans showed more differences in the DR eyes.

Discussion

We assessed the reliability and agreement between two scan sizes with a commercially available spectral-domain OCTA machine, in healthy people and diabetic patients with and without DR. We used the inbuilt software for automated analysis of various macular perfusion parameters of the superficial capillary plexus. Our results showed that the two scan sizes 3 × 3 mm and 6 × 6 mm did not differ in the measurement of the FAZ area and perimeter. So, these parameters can be used interchangeably between the two scans. The ICC values for VDand PD were excellent in normal and in diabetic patients without DR, indicating good reliability. But, they were only fair in patients with DR. Except for the ICC for FAZ circularity in controls, all ICC values were highly significant.

In eyes with DR, the FAZ showed a significant widening of its area and perimeter with a significant reduction in circularity. The FAZ is a sensitive indicator of ischemia and can be affected very early in DR. Therefore, the measurement of the FAZ area and perimeter are valuable for visual prognosis. This study showed that FAZ measurements were highly reproducible across both the scan sizes in healthy and DR eyes. Similar results have been reported by other authors.[3,4,6-8] Dong *et al.*[3] reported interchangeability of measurements in two angiocubes of 3 × 3 mm and 6 × 6 mm sizes in healthy Chinese adults using an automated method in spectral-domain optical coherence tomography angiography (SDOCT-A) device. Rabiolo *et al.*[4] found excellent reliability with ICC values of >0.90, for FAZ measurements in all scan sizes, for all plexuses and all subgroups. Thus, it would be safe to infer that measurement of the FAZ area and perimeter is a highly reproducible and reliable criterion across different scan sizes and populations. In a study, using the standard ETDRS protocols, when compared to the conventional FA, the OCTA showed moderate agreement in the grading of macular ischemia.[9] There was a substantial intergrader agreement. The parafoveal flow indices of the

Table 3: The reliability of quantitative parameters using the ICC among different groups for 3 × 3 mm and 6 × 6 mm scans

	Controls			No DR			DR		
	ICC	95% CI	*P*	ICC	95% CI	*P*	ICC	95% CI	*P*
FAZ									
Area	0.94	0.86-0.97	0.00	0.92	0.74-0.96	0.00	0.97	0.90-0.99	0.00
Perimeter	0.75	0.44-0.89	0.00	0.85	0.38-0.95	0.00	0.89	0.40-0.96	0.00
Circularity	−0.08	−1.41-0.52	0.57	0.67	0.25-0.85	0.00	0.69	0.23-0.85	0.00
VD									
Center Avg	0.89	0.76-0.95	0.00	0.92	0.84-0.96	0.00	0.56	0.23-0.75	0.00
Inner Avg	0.57	−0.16-0.87	0.00	0.49	−0.22-0.81	0.00	0.53	0.06-0.75	0.00
PD									
Center Avg	0.80	0.38-0.92	0.00	0.81	−0.042-0.94	0.00	0.42	−0.02-0.67	0.00
Inner Avg	0.73	−0.13-0.92	0.00	0.53	−0.20-0.80	0.00	0.53	0.16-0.73	0.00

ICC=Intraclass correlation coefficient, DR=Diabetic retinopathy, No DR=No diabetic retinopathy, FAZ=Foveal avascular zone, CI=Confidence interval, Avg=Average, VD=Vessel density, PD=Perfusion density

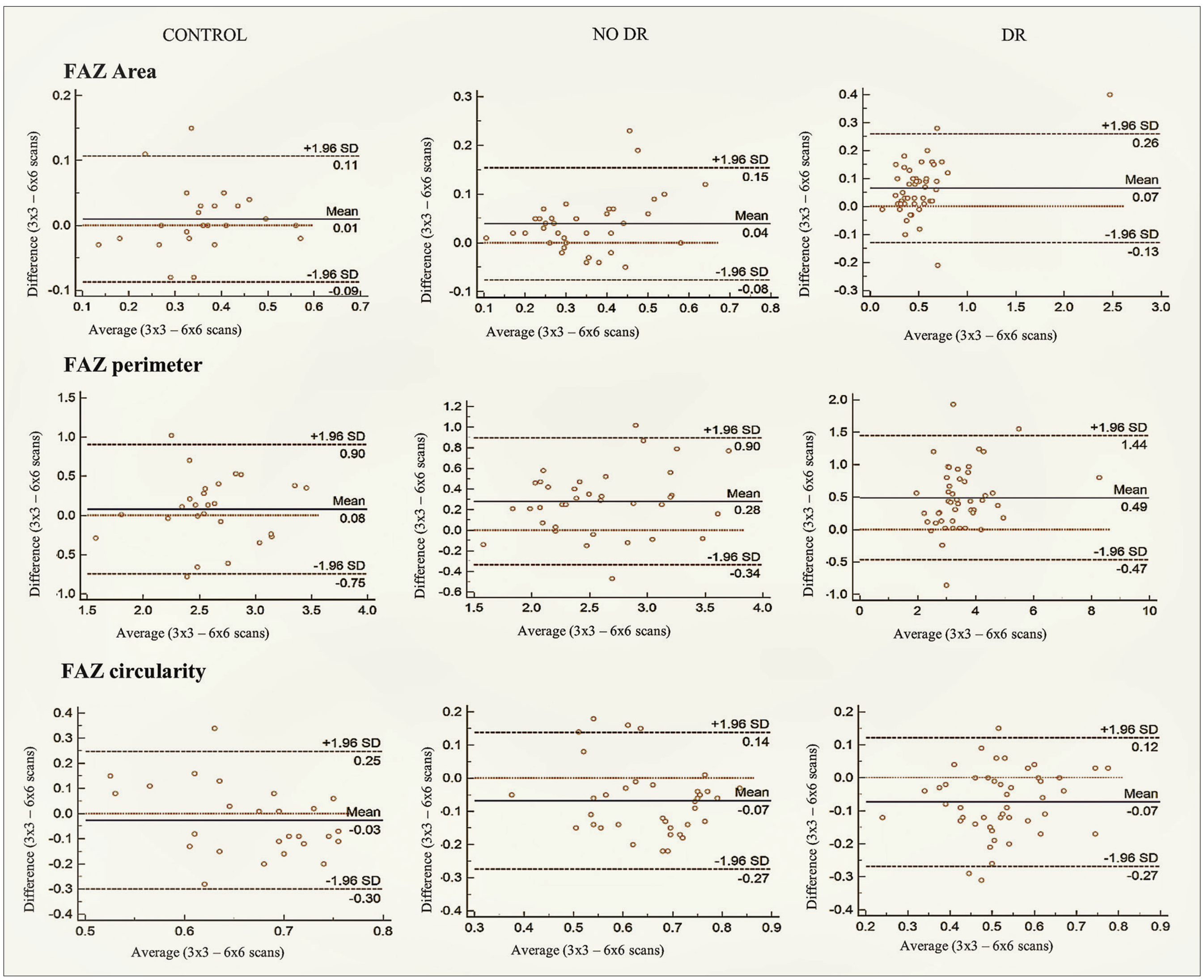

Figure 2: The Bland–Altman plots for foveal avascular zone area, perimeter, and circularity, comparing different scan sizes of 3 × 3 mm and 6 × 6 mm in controls and in diabetic patients with and without diabetic retinopathy. The horizontal axis represents the averages for each scan size and the vertical axis shows the differences. The two dotted lines indicate 95% confidence limits. The graphs reveal excellent agreement between the two scan sizes for all the groups

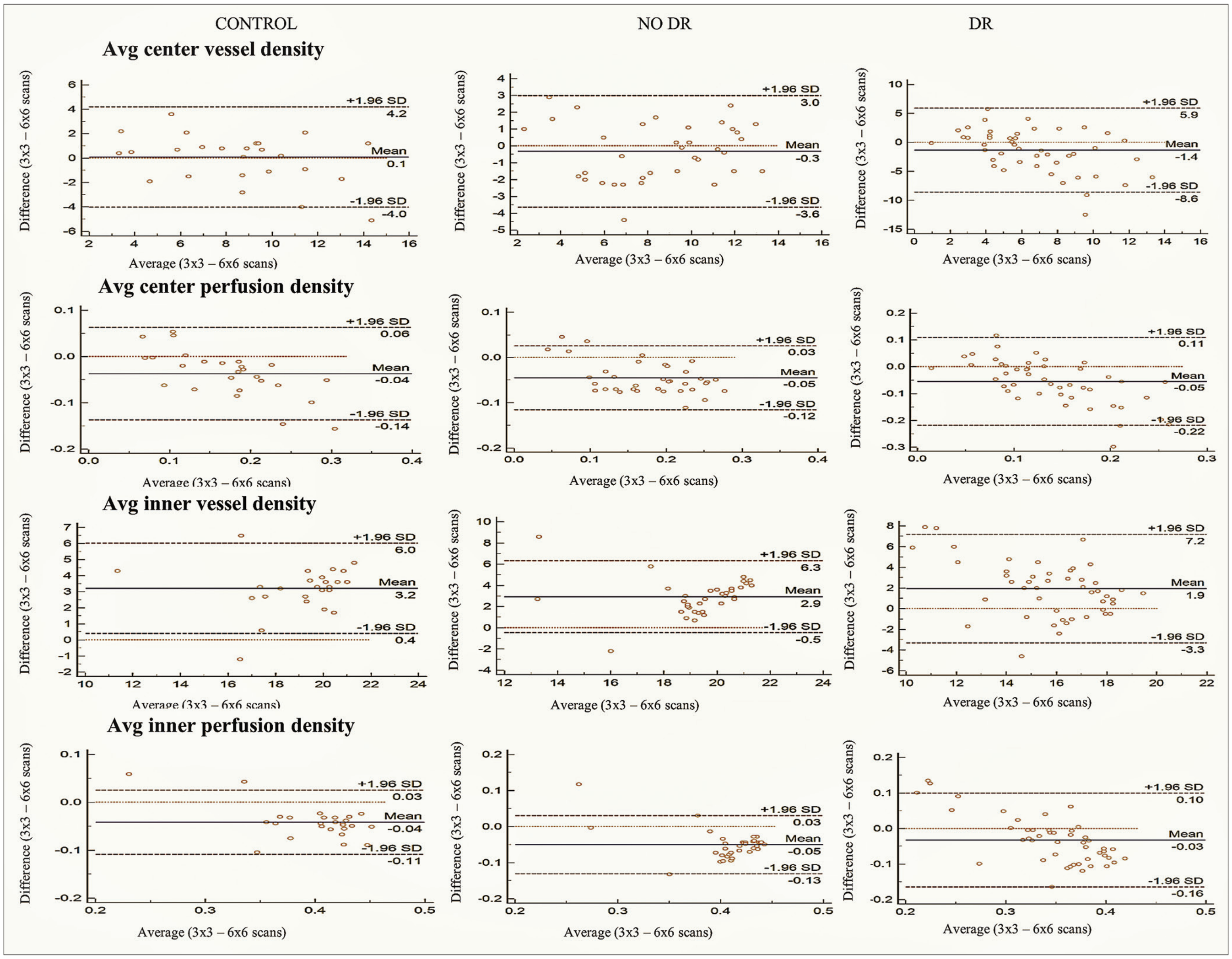

Figure 3: The Bland–Altman plots for inner and central average vessel density and perfusion density in controls and in patients with and without diabetic retinopathy. There is a greater variation and only fair reliability between the two scan sizes of 3 × 3 mm and 6 × 6 mm, as far as the perfusion indices are concerned. The differences were more in vessel density and in patients with diabetic retinopathy

superficial plexus showed a significant correlation with macular ischemia. Thus, the OCTA can prove to be a highly useful, noninvasive tool for early diagnosis and detection of progression of macular ischemia in various vascular disorders of the retina.

We analyzed the superficial plexus as the measurements are easy and reliable. Also, in the Angioplex 5000 machine, the automated calculations of the various indices are available for superficial plexus only. Manual measurements at the deep capillary plexus are difficult due to poor demarcation of the vessels, and it is prone to errors due to projection artifacts.[4,10] However, as far as the FAZ is concerned, it would not be absolutely correct to segregate it into superficial and deep plexus, as both these plexuses merge at the edge of FAZ.[11]

The ICC values for VD across the two scans were excellent in controls and in eyes with no DR, but only fair in eyes with DR. Rabiolo *et al.*[4] noted poor reliability and interchangeability of VD, across different angiocubes for every plexus and every subgroup. Similarly, Dong *et al.*[3] reported a significant difference in the VD values between the 3 × 3 mm and 6 × 6 mm scan sizes. They noted that the VD values in the 3 × 3 mm scan were higher than the values in the 6 × 6 mm scan, with the ICC values in the lower range. The software automatically measures the VD by measuring the length of the perfused vessels per unit area. A change in the area of interest can thus lead to changes in the measurements, especially in eyes with vascular disorders. Different machines use different algorithms to calculate the VD and PD indices. The OMAG algorithm in the AngioPlex machine analyzes the amplitude and phase information present in the optical signals from four repeated scans at the same retinal position.[2,8] The other algorithms are the split spectrum amplitude-decorrelation angiography algorithm (SSADA) for RTVue XR Avanti (Optovue Inc., Fremont, CA, USA),[12] OCT-A ratio analysis (OCTARA) for DRI OCT Triton (Topcon, Tokyo, Japan),[13] and full-spectrum amplitude decorrelation algorithm (FSADA) for Heidelberg (Spectralis; HRA Heidelberg, Heidelberg, Germany).[14] All these algorithms are based on the assumption that erythrocytes flowing in blood vessels are the only moving structures that are detected by the sequential B-scans; therefore, they can be used as a motion contrast to differentiate vessels from static tissues.[1] The AngioPlex machine uses the FastTrac technology to reduce the effect of eye movements; however, various factors including eye movements, different scan patterns, different signal strengths, segmentation algorithms, and the threshold value to detect vessels can affect the vascular indices.[4]

The Bland–Altman plots were used to assess the agreement or differences between the two scan sizes. It is a simple method to evaluate the bias between the mean differences between the two methods and define the limits of agreement, within which 95% of the differences fall. The horizontal axis represents the averages for each scan size, and the vertical axis shows the differences. The two dotted lines indicate 95% confidence limits. The closer the central bold line is to zero, the better the reliability. In the FAZ measurements, the differences for all eyes are closer to zero, indicating excellent reliability and reproducibility. The average mean difference in the FAZ area measurements between the two scan sizes varied from 0.01 to 0.07 among controls, No DR, and DR eyes. [Table 2] The differences between the VD and PD were significantly higher, indicating poor agreement and interchangeability. The differences were seen to be larger in eyes with DR. The machine-related factors responsible for these differences could be the different number of A-scans used for the 3 × 3 mm and 6 × 6 mm scans. The 3 × 3 mm scan has 300 × 300 A-scans with a mean distance of 12.2 μm between each scan;[15] whereas the 6 × 6 scan has 500 × 500 A-scans. Also, the wider scan has poorer resolution with increased spacing between pixels, *viz*. 2.9 versus 5.9 μm for 3 × 3 mm and 6 × 6 mm scan, respectively.[4] The total number of pixels also varies, from 245 pixels for the 3 × 3 mm scan and 350 pixels for the 6 × 6 mm scan.

Furthermore, it has been shown that DR leads to reduced VD with increased spacing between large vessels.[11] This is likely to affect the per unit measurement of VD, leading to poor agreement between the two scan sizes. The clinicians need to bear this in mind while evaluating scans from two eyes or the same eye at different visits.

There are certain limitations to our study, a relatively small sample size being one of them. Larger sample size would help in consolidating these findings. We have taken only one measurement for these parameters in each scan by a single observer. Although that eliminated the inherent bias, which exists among two different observers, it is still possible that our subjects could have a different within-the-subject variation for the two methods of scanning used for the 3 × 3 mm and 6 × 6 mm scans. However, the AngioPlex has been documented to give quite accurate measurements by other authors;[8] therefore, we can assume that the repeatability coefficient for both the scans would be high. We compared the scans performed on one machine only, namely the AngioPlex 5000. As different machines use different algorithms, our results may not hold true for other machines.

Conclusion

The ability to do quantitative analysis of the vascular indices gives OCTA an edge over the conventional FA. Retinal perfusion analysis is a great value addition, and it has the potential to provide newer insights into various retinal vascular disorders. However, care must be taken while comparing and interpreting results from different machines or different scan sizes from the same machine. Our results showed that the FAZ measurements were reliable across both scans and in all the eyes. But, the perfusion indices were not interchangeable between the 3 × 3 mm and 6 × 6 mm scan sizes, especially in eyes with DR. We highlight the fact that reliability varies depending on the population in which measurements are made, and not just on the measurement errors of the different methods.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rabiolo A, Carnevali A, Bandello F, Querques G. Optical coherence tomography angiography: evolution or revolution? Expert Rev Ophthalmol 2016;11:243-5.
2. Rosenfeld PJ, Durbin MK, Roisman L, Zheng F, Miller A, Robbins G, *et al*. ZEISS angioplex spectral domain optical coherence tomography angiography: technical aspects. Dev Ophthalmol 2016;56:18-29.
3. Dong J, Jia Y, Wu Q, Zhang S, Jia Y, Huang D, *et al*. Interchangeability and reliability of macular perfusion parameter measurements using optical coherence tomography angiography. Br J Ophthalmol 2017;101:1542-9.
4. Rabiolo A, Gelormini F, Marchese A, Cicinelli MV, Triolo G, Sacconi R, *et al*. Macular perfusion parameters in different angiocube sizes: Does the size matter in quantitative optical coherence tomography angiography? Invest Ophthalmol Vis Sci 2018;59:231-7.
5. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–An extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology 1991;98:786-806.
6. Carpineto P, Mastropasqua R, Marchini G, Toto L, Di Nicola M, Di Antonio L. Reproducibility and repeatability of foveal avascular zone measurements in healthy subjects by optical coherence tomography angiography. Br J Ophthalmol 2016;100:671-6.
7. La Spina C, Carnevali A, Marchese A, Querques G, Bandello F. Reproducibility and reliability of optical coherence tomography angiography for foveal avascular zone evaluation and measurement in different settings. Retina 2017;37:1636-41.
8. Guo J, She X, Liu X, Sun X. Repeatability and reproducibility of foveal avascular zone area measurements using AngioPlex spectral domain optical coherence tomography angiography in healthy subjects. Ophthalmologica 2017;237:21-8.
9. Bradley PD, Sim DA, Keane PA, Cardoso J, Agrawal R, Tufail A, *et al*. The evaluation of diabetic macular ischemia using optical coherence tomography angiography. Invest Ophthalmol Vis Sci 2016;57:626-31.
10. Shahlaee A, Pefkianaki M, Hsu J, Ho AC. Measurement of foveal avascular zone dimensions and its reliability in healthy eyes using optical coherence tomography angiography. Am J Ophthalmol 2016;161:50-55.e1.
11. Bhanushali D, Anegondi N, Gadde SG, Srinivasan P, Chidambara L, Yadav NK, *et al*. Linking retinal microvasculature features with severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthalmol Vis Sci 2016;57:519-25.
12. Huang D, Jia Y, Gao SS, Lumbroso B, Rispoli M. Optical coherence tomography angiography using the optovue device. Dev Ophthalmol 2016;56:6-12.
13. Huang Y, Zhang Q, Thorell MR, An L, Durbin MK, Laron M, *et al*. Swept-source OCT angiography of the retinal vasculature using intensity differentiation-based optical microangiography algorithms. Ophthalmic Surg Lasers Imaging Retina 2014;45:382-9.
14. Coscas G, Lupidi M, Coscas F. Heidelberg spectralis optical coherence tomography angiography: Technical aspects. Dev Ophthalmol 2016;56:1-5.
15. Munk MR, Giannakaki-Zimmermann H, Berger L, Huf W, Ebneter A, Wolf S, *et al*. OCT-angiography: A qualitative and quantitative comparison of 4OCT-A devices. PLoS One 2017;12:e0177059.