• Clinical Research •

Reproducibility of macular perfusion parameters in non-proliferative diabetic retinopathy patients by two different OCTA sweep modes

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Abstract

● **AIM:** To assess the reproducibility of macular perfusion parameters in non-proliferative diabetic retinopathy (NPDR) patients measured by different examiners and two different sweep modes of optical coherence tomography angiography (OCTA).

● **METHODS:** Ninety-eight (98 eyes) patients with NPDR were included in this study. All participates were performed three times using Cirrus OCTA with Angiography 3×3 mm^2 and 6×6 mm^2 sweep mode by two examiners. The macular foveal avascular zone (FAZ) and vessel density (VD) in the superficial retinal layer (SRL) were measured. The reproducibility of the measurements was evaluated with intraclass correlation coefficients (ICC) and coefficient of variation (CoV).

● **RESULTS:** The intra-mode ICCs of Angiography 3×3 mm^2 and 6×6 mm^2 sweep mode were 0.957 to 0.959 and 0.964 to 0.977, respectively; and the inter-mode ICCs were 0.962 to 0.970. The intra-examiner ICCs of macular perfusion parameters were >0.950; and the inter-examiner ICCs were 0.928 to 0.969. All CoVs were <1.0%.

● **CONCLUSION:** Cirrus OCTA can measure macular perfusion parameters in NPDR patients with excellent reproducibility. The measurements of FAZ and VD in the SRL determined by Angiography 3×3 mm^2 and 6×6 mm^2 sweep mode are highly consistent and both sweep modes are suitable for macular perfusion parameters measurement.

● **KEYWORDS:** optical coherence tomography angiography; macular perfusion parameters; reproducibility; non-proliferative diabetic retinopathy

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INTRODUCTION

Diabetic retinopathy (DR) is the most severe complication in diabetic eye diseases causing irreversible blindness[1]. It is a worldwide problem and the leading cause of low vision in the west[2]. In our country, the incidence rate of DR up to 11.9%-43.1% among patients with diabetes mellitus[3-5]. One of the important factors of visual impairment in DR is disruption of macular circulation[6]. The capillary network in the macular area forms an avascular area in the fovea: foveal avascular zone (FAZ). Once FAZ is affected by the disease, it will cause different degrees of vision loss. Therefore, early monitoring and evaluation of FAZ status can provide objective basis for the progress of prevention of DR[7]. The introduction of optical coherence tomography angiography (OCTA) has enable *in vivo* structural and quantitative assessment of retina and choroid blood perfusion[8]. In addition to FAZ, macular perfusion parameters also included vessel density (VD) in superficial retinal layer (SRL), which are followed closely by change in DR patients' conditions[9-10]. OCTA can provide two macular sweep modes: Angiography 3×3 mm^2 and 6×6 mm^2. Generally, we used sweep mode for macular perfusion parameters analysis is Angiography 6×6 mm^2. In clinical work, we often use Angiography 3×3 mm^2 sweep modes according to the needs of diagnosis or treatment. Compared to Angiography 6×6 mm^2, 3×3 mm^2 sweep mode has a higher resolution, which allow us to better see the subtle blood perfusion in the macular area[11]. Theoretically, it could increase accuracy and reliability of measuring results. Many studies[12-13] have demonstrated that OCTA can measure macular perfusion parameters with excellent reproducibility in healthy people. At present, there are few studies on the reproducibility or consistency of OCTA in the measurements of perfusion parameters in macular area of DR patient[14]. The purpose of our study was to evaluate the reproducibility and consistency of intra- and inter-examiner,

Table 1 Macular perfusion parameters measured by two examiners using angiography 3×3 mm^2 sweep mode

Parameters	Examiners	Measurements			P^a	P^b
		1	2	3		
FAZ (mm^2)	A	0.38±0.11	0.39±0.17	0.39±0.20	0.939	0.847
	B	0.38±0.23	0.38±0.15	0.39±0.19	0.928	
VD (%)	A	31.13±2.57	32.20±2.51	32.19±2.48	0.923	0.855
	B	32.19±2.42	32.22±2.46	31.27±2.56	0.947	

FAZ: Foveal avascular zone; VD: Vessel density. [a]Comparison of the three repeated measurements by each examiner; [b]Comparison the mean value of measurements between two examiners.

and intra- and inter-sweep mode in assessment macular perfusion parameters in patients with non-proliferative diabetic retinopathy (NPDR) using OCTA.

SUBJECTS AND METHODS

Ethical Approval The entire experimental procedure followed the tenets of the Declaration of Helsinki, and the mode was approved by the Institutional Review Board of Tongji Hospital Affiliated to Tongji University. Written informed consent was obtained from all participants which were told potential risks and benefits.

Participants A totally of 98 patients with NPDR referred from the Department of Endocrinology of Tongji Hospital were enrolled this study. Among them, 58 cases were male, and 40 cases were female. All participates got routine ophthalmic examination including best corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP) measurement using non-contact tonometer, medical optometry, direct ophthalmoscopy, B-scan ultrasound, fluorescein fundus angiography (FFA), and OCTA examination. The inclusion criteria include: 1) patients were diagnosed with NPDR, according to the international standard of diabetic retinopathy stage based on the results of fundus photography, OCT and FFA; 2) BCVA better than or equal to 0.5; 3) refractive degree range is -3 to +3 D, binocular anisometropia less than 1.5 D; 4) intraocular pressure less than 21 mm Hg (1 mm Hg=0.133 kPa); 5) optical media transparency examined by slit lamp; 6) eye position is parallel and normal foveal position; 7) the image signal strength is greater than or equal to 6. Exclusion criteria: 1) history of eye diseases such as age-related macular degeneration, high myopia, glaucoma and so on; 2) previous eye surgery or ocular trauma; 3) systemic diseases which may affect the retina.

Optical Coherence Tomography Angiography Examination All examination of macular perfusion parameters performed by the two sophisticated ophthalmic technician using Cirrus OCTA. Before each scanning, the pupil was dilated to 6 mm with tropicamide 1% eye drops. OCTA scanning sequences automatically identified macular zone, starting by scanning the macular area with Angiography 3×3 mm^2 sweep mode. And then, the macular area was scanned three times in Angiography 6×6 mm^2 sweep mode. All of the above procedures are performed again by another technician. The average value of the two examiners was selected as the result. OCTA software system was used for image analysis: the SRL is defined as 10 μm above the inner limiting membrane (ILM) to the inner plexus layer (IPL). The FAZ and VD in the macular SRL was calculated by OCTA software.

Statistic Analysis SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data with normal distribution were expressed as mean±standard deviation (SD). The macular perfusion parameters measured between different examiners and different sweep modes were compared by Student's *t*-test. Reproducibility was assessed with the coefficient of variation (CoV) and the intraclass correlation coefficient (ICC) with 95% confidence interval (CI). ICC greater than 0.80, 0.60 to 0.80 means medium, 0.41 to 0.60 means ordinary, 0.11 to 0.40 means lower, less than 0.10 means un-consistence[15-16].

RESULTS

A total of 98 patients were enrolled in our study. Of these, 10 patients were excluded from the study group because their OCTA images quality was substandard. So, the analyses in our research were based on data from 88 subjects (51 males and 37 females). The age ranged from 24 to 57y (54.67±13.70y). The IOP ranged from 11 to 20 mm Hg (13.3±3.7 mm Hg). The spherical equivalent ranged from -3.00 to +3.00 D and the mean axial length was 24.24 mm (from 22.19 to 24.27 mm). Considering that the axial length of eye could affect the measurement of macular perfusion parameters, the Littman and the modified Bennett formulae were using to calculate the picture size[17]. All data in the paper are obtained after correction of the above formula.

FAZ and VD measured by the two examiners using Angiography 3×3 mm^2 sweep mode were displayed in Table 1. Table 2 showed the mean values of macular perfusion parameters measured by the two examiners using Angiography 6×6 mm^2 sweep mode.

The intra-examiner ICC of the two examiners and the inter-examiner ICC ranged between 0.963-0.977, 0.952-0.966 and 0.928-0.969, respectively (Table 3).

Table 2 Macular perfusion parameters measured by two examiners using angiography 6×6 mm^2 sweep mode

Parameters	Examiners	Measurements			P^a	P^b
		1	2	3		
FAZ (mm^2)	A	0.41±0.19	0.42±0.21	0.41±0.22	0.944	0.868
	B	0.41±0.22	0.41±0.18	0.42±0.17	0.951	
VD (%)	A	31.87±2.99	32.01±1.54	31.79±2.46	0.932	0.848
	B	32.03±2.22	31.20±2.36	31.67±2.51	0.926	

FAZ: Foveal avascular zone; VD: Vessel density. [a]Comparison of the three repeated measurements by each examiner; [b]Comparison the mean value of measurements between two examiners.

Table 3 Intra- and inter- examiner reproducibility of macular perfusion parameters measurements

Parameters	Examiner A		Examiner B		Inter-examiner	
	ICC (95%CI)	CoV (%)	ICC (95%CI)	CoV (%)	ICC (95%CI)	CoV (%)
FAZ (mm^2)	0.963 (0.986-0.990)	0.54	0.966 (0.979-0.989)	0.49	0.969 (0.977-0.987)	0.51
VD (%)	0.977 (0.955-0.967)	0.71	0.952 (0.958-0.969)	0.69	0.928 (0.977-0.9870)	0.63

FAZ: Foveal avascular zone; VD: Vessel density; ICC: Intraclass correlation coefficient; CI: Confidence interval; CoV: Coefficients of variation.

Table 4 Macular perfusion parameters determined by two sweep modes

Parameters	Mode	Measurements			P^a	P^b
		1	2	3		
FAZ (mm^2)	3×3 mm^2	0.38±0.23	0.38±0.42	0.38±0.29	0.926	0.828
	6×6 mm^2	0.40±0.33	0.41±0.23	0.41±0.11	0.937	
VD (%)	3×3 mm^2	31.21±3.55	32.22±3.68	32.29±4.52	0.907	0.801
	6×6 mm^2	33.14±3.21	33.03±4.26	32.13±5.20	0.911	

FAZ: Foveal avascular zone; VD: Vessel density. [a]Comparison of the three repeated measurements by each mode; [b]Comparison the mean value of measurements between two modes.

Table 5 Intra- and inter- mode reproducibility of macular perfusion parameters measurements

Parameters	Angiography 3×3 mm^2		Angiography 6×6 mm^2		Inter-mode	
	ICC (95%CI)	CoV (%)	ICC (95%CI)	CoV (%)	ICC (95%CI)	CoV (%)
FAZ (mm^2)	0.957 (0.974-0.989)	0.52	0.977 (0.978-0.982)	0.50	0.970 (0.968-0.978)	0.59
VD (%)	0.959 (0.964-0.969)	0.69	0.964 (0.951-0.961)	0.66	0.962 (0.965-0.977)	0.63

FAZ: Foveal avascular zone; VD: Vessel density; ICC: Intraclass correlation coefficient; CI: Confidence interval; CoV: Coefficients of variation.

Mean values of macular perfusion parameters determined by Angiography 3×3 mm^2 and 6×6 mm^2 sweep mode was displayed in Table 4.

The intra-mode ICC of the two modes and the inter-mode ICC ranged between 0.957-0.959, 0.964-0.977 and 0.962-0.970, respectively (Table 5).

DISCUSSION

DR is one of the most common and serious microvascular complications of diabetes mellitus. The current theory holds that capillaries will be blocked, lost or degenerated and other pathological changes in ischemia and hypoxia of the retina. The impaired capillary network and decreased VD in macular area are the main causes of visual impairment caused by DR. Through FFA, Bresnick *et al*[18] found that the range of FAZ of DR patients was expanded, and it is related to the non-perfusion of capillary. Kim *et al*[16] and Tam *et al*[19] also demonstrated that as DR progressed, FAZ expanded accordingly. Therefore, the measurement of changes in FAZ is helpful for the early detection of DR and guidance for the diagnosis and treatment of DR. Compared with FFA, OCTA can more clearly observe the boundary of FFA and the abnormality of retinal microvascular morphology[20-22]. It can not only show the morphology and distribution of retinal blood vessels noninvasively, but also distinguish superficial and deep capillaries and analyze them quantitatively[23]. Some scholars[24-26] used OCTA to measure the macular perfusion parameters in normal population, and found that FAZ and VD had fine reproducibility, and there was good consistency between the two sweep modes. Evaluation of the reproducibility and consistency of macular perfusion parameters under different sweep modes may be helpful for the screening accuracy of OCTA in early DR[27-28].

In this study, we found that there was no significant different of the three repeated measurements of macular perfusion parameters by each examiner (all P>0.900). And the difference of the macular perfusion parameters measured

by the two examiners also shown no statistic significant (P>0.05). All intra- and inter-examiner ICCs of macular perfusion parameters ranged from 0.962 to 0.974, and the CoVs were <1.0%. This suggests that OCTA measurements are less affected by the examiner's experience. The results are consistent with previous research by other scholars. Wang *et al*[29] accessed the reproducibility of macular perfusion parameters in 46 patients with mild NPDR. The ICCs were between 0.909 and 0.956. Previous studies[12-13] have shown that OCTA has good reproducibility in measuring FAZ and VD in macular area of normal population. The results of this study further confirmed that OCTA had good reproducibility in measuring the macular perfusion parameters in patients with early DR. The main reasons for our analysis include: 1) Cirrus OCTA's own real-time tracking system: FastTrac™ retinal tracking system allows for accurate alignment and scanning without the subject shaking or blinking; 2) Cirrus OCTA's OMAG (optical microangiography) algorithm, which can synthesize the characteristics of amplitude signal and phase signal, thus better retinal angiography can be obtained.

The results of consistency analysis of the two sweep modes in this study show that nearly all intra- and inter- mode ICCs were greater 0.90. Al-Sheikh *et al*[13] found that two sweep modes measured the ICCs of FAZ and VD were 0.992 and 0.997, 0.889 and 0.972, respectively. Dong *et al*[25] and his associates also concluded that the two sweep modes were reliably consistent in measuring macular perfusion parameters. There was no significant difference of the three repeated measurements of macular perfusion parameters determined by two modes, and the difference of the macular perfusion parameters determined by each mode also showed no statistical significance (all P>0.05). We are confident that the two sweep modes show excellent consistency in measuring FAZ and VD. The important thing to note here is, with the enlargement of scanning range, the resolution of blood perfusion image will decrease gradually. This also suggests that the sweep mode should be selected purposely in clinical practice according to the type of disease, the size of lesion range and the location of lesion[30].

There are still some deficiencies in this study. In view of the limited conditions, there is no comparative study with other types of OCTA; Normal population and patients with proliferative diabetic retinopathy (PDR) were not included in this study; The blood perfusion parameters of choroid and other retinal regions were not measured. In future studies, we need to verify the results of scanning multiple retinal regions in a larger sample of patients with different severity of DR.

In conclusion, we think that both sweep modes of Cirrus OCTA can provide satisfactory reproducibility for macular perfusion parameters measurements in patients with NPDR. And the results are barely affected by the examiner's experience.

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