Validity and Reliability of Semiautomatic Ocular Cycloposition Measurement With Spectralis Optical Coherence Tomography

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• PURPOSE: Disc-fovea angle determined by fundus photography (P-DFA) is considered the gold standard for cycloposition assessment. Fovea-to-disc alignment (FoDi) software of the spectral-domain optical coherence tomography (SD-OCT) (Spectralis) also measures the DFA (O-DFA) based on subject fixation and offers important clinical advantages. This study aimed to analyze the validity and reliability of measuring cycloposition using OCT and to determine its performance in eyes with poor foveal definition.

• DESIGN: Validity and reliability analysis.

• METHODS: In 60 eyes with normal foveal definition and 32 eyes with poorly defined fovea, ocular cycloposition was assessed by 2 observers using 5 fundus photographs and 5 FoDi analyses each. Patients were repositioned after every capture.

• RESULTS: Cycloposition assessed by O-DFA was 7.6 ± 3.5-degrees, and P-DFA was 7.9 ± 3.8-degrees. The concordance between methods was good (intraclass correlation coefficient [ICC], 0.71), with absolute differences ranging from zero to 4-degrees in 85% of the subjects. The precision was 1.4-degrees for O-DFA and 3.0-degrees for P-DFA. Repeatability and reproducibility were excellent in both techniques. In the group of patients with poor foveal definition, the precision of P-DFA changed from 3.0-degrees to 4.8-degrees, whereas the O-DFA remained stable.

• CONCLUSIONS: OCT had a good agreement with the fundus photography method. O-DFA showed better precision than P-DFA. O-DFA repeatability and reproducibility were excellent and unconditioned by foveal status. (Am J Ophthalmol 2021;222:248–255. © 2020 Elsevier Inc. All rights reserved.)

AT THE POSTERIOR POLE OF A HEALTHY EYE, THE OPtic disc is localized in a nasal and slightly superior position to the fovea. The angle subtended by these 2 landmarks is called ocular cycloposition and presents large interindividual variability.[1] Cycloposition out of the normal range is considered objective ocular torsion and indicates an anomalous rotation of the globe. Ocular torsion may appear because of primary cyclovertical strabismus[2] or extraocular muscle conditions.[3] It may also be associated with orbital disorders[4] or induced by ocular surgery.[5] In all these cases, cycloposition provides essential information about the torsional component of the ocular deviation, which must be complemented by the subjective ocular torsion measurement. The objective cycloposition becomes of particular interest in ocular torsion monitoring and the quantification of torsional changes after extraocular muscle surgery.[6] In addition, it is considered a stable anatomic landmark in healthy eyes, valuable in refractive surgery[7] and in retinal pathology analyses.[8]

The gold standard for evaluating cycloposition is the quantification of the disc-fovea angle (DFA) in fundus photographs.[1,4,9–11] It is determined by the inclination of a line connecting the fovea and the optic disc center in fundus images. In normal subjects, its value is approximately 7-degrees, with the fovea below the center of the optic disc, and the technique provides repeatable[10,12–15] and reproducible measurements.[11–13,15]

The procedure requires pupillary dilation to obtain a quality image in most cases, even with non-mydriatic fundus cameras. In addition, visible light revealing the retina for previous adjustments besides the light pulse for obtaining the image, causes an uncomfortable fixation, far from natural viewing conditions. Other inconveniences are the need for exporting the fundus image to an external measurement software and manual determining the accurate fovea position, which becomes complicated in eyes with macular area pathology or under conditions such as high myopia, where a poor macular differentiation may occur.

The Spectralis system from Heidelberg Engineering (Heidelberg, GM) is a diagnostic image platform that combines spectral-domain optical coherence tomography (SD-OCT) and confocal scanning laser ophthalmoscopy. Its retinal nerve fiber analysis includes the built-in fovea-to-disc alignment (FoDi) (Heidelberg Engineering) software,

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which determines semiautomatically the disc-fovea axis orientation. This axis is considered the starting point for the circular volume scans and the center of the temporal sector of the retinal nerve fiber layer thickness, so that successive measurements use the same anatomic reference independence of any improper head position or physiological cycloposition of the eye. Therefore, even though FoDi software was built to improve the retinal nerve fiber assessment, it provides a semiautomatic measurement of the DFA as it has been recently described by Lengwiler and associates.[16]

OCT analysis does not require pupillary dilation nor export of the image to an external device for measuring cycloposition. The examination uses infrared light, and the only visible light toward the eye comes from the fixation stimulus and the scan lines, so it is conducted with a relaxed gaze. FoDi software determines the fovea automatically based on subject fixation, which is valuable in poor macular definition. The present authors have no references from studies about cycloposition comparing the angle provided by Spectralis tomography versus the DFA in fundus photography. The goal was to analyze the validity and reliability of the method and study whether automatic determination of the fovea could be an advantage in eyes with poor foveal definition.

METHODS

A PROSPECTIVE CROSS-SECTIONAL STUDY WAS CONDUCTED in the Ophthalmology Department of San Carlos Clinical Hospital of Madrid. The study adhered to Declaration of Helsinki standards for research involving human participants and was approved by the Institutional Review Board of the San Carlos Clinical Hospital of Madrid (15/570-E and 18/533-E).

• **PATIENTS:** All patients underwent a complete ophthalmological examination. They were informed about the study and signed informed consent. Only right eyes were included. Eyes with medium opacity were excluded. The study compared photographically determined DFA (P-DFA) with OCT-determined DFA (O-DFA). Both methods were tested in 2 different scenarios. First, eyes considered normal (designated group A) were evaluated with a clear definition of the fovea and optic nerve and a minimum visual acuity of 0.1 logMAR (Figure 1A). Thus, 60 patients were included in group A.

The second phase aimed to assess eyes in which, due to their particular anatomic characteristics, there was poor definition of the fovea (designated group B). A minimum visual acuity of 0.3 logMAR was required to ensure a proper fixation (Figure 1B). A total of 32 eyes formed group B.

• **MEASUREMENTS:** The main outcome measurement was the ocular cycloposition. All analyses were performed twice by 2 independent observers (A.V. and E.P.). First, 10 digital fundus photographs of right eyes (5 from each observer) were obtained by non-mydriatic fundus photography (Canon CR-model DGI EOS 30D; Canon, Tokyo, JA), so that the observers would not be influenced by the FoDi automatic measurement. Second, 10 nerve fiber analyses (5 from each observer) were made by using FoDi software of SD-OCT (Spectralis HRA+OCT version 6.0.11.0; Heidelberg Engineering), available by selecting the retinal nerve fiber layer acquisition protocol. The fovea position was automatically determined as the subject's fixation position, not through anatomical landmarks, and a live infrared reflectance image showing simultaneously optic disc and fovea was displayed. A 12-degrees diameter circle appeared, superimposed in a standard position of 7.9-degrees nasal and upper from the fovea. The observer placed the circle around the optic disc and started the peripapillary nerve fiber analysis.

Although OCT analysis does not usually require mydriasis,[17] every measurement was made under pupillary dilation (tropicamide 1%) to obtain a quality fundus photograph. The patient was asked to look at the internal fixation stimulus, and the patient's head position was carefully maintained as straight and stable as possible on the head support. To simulate a clinical scenario with the 2 methods, the subject was requested to move the head back and place it again between measurements, with the consequent realignment.

P-DFA was obtained in the exported fundus images with a specific custom-designed software using MATLAB language (MathWorks, Carlsbad, California, USA). Each observer marked 10 equidistant points of the optic disc margin, obtaining the circle that best fitted them. After that, the observers marked the fovea position, and the software provided the angle between it and the center of the circle. The angle was positive when the fovea was below the center of the optic disc (Figure 1C) and negative when the fovea was above it. FoDi software provided the O-DFA displayed on an infrared image at the end of the nerve fiber examination (Figure 1D). Unlike the standard notation in strabology, FoDi showed a negative DFA when the fovea was inferior to the center of the optic disc. The sign of these results was changed to compare both methods.

• **STATISTICAL ANALYSIS:** The validity of the O-DFA measurement was evaluated using the correlation with P-DFA, the gold standard, provided by the intra-class correlation coefficient (ICC), using a 2-way random effects model, absolute agreement, and single measurement. Results were interpreted by using the Altman estimation.[18] Bland-Altman graphic analysis revealed the agreement between the methods by the presence of systematic differences (biases) and the 95% limits of agreement. The

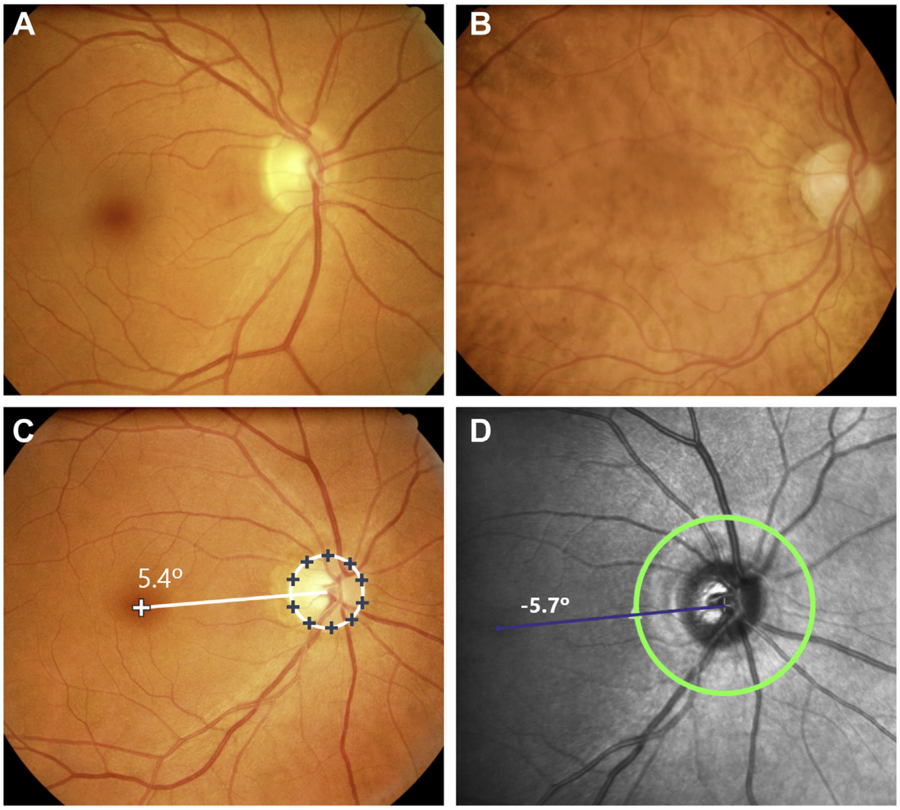

FIGURE 1. (A) Right fundus from a group A eye in which the fovea could be easily localized. (B) Right high-myopic eye from group B with fundus tessellation, preventing a proper definition of the foveal position. (C) Cycloposition shown by measuring the disc-fovea angle on a right-fundus image. (D) Cycloposition of the same eye provided by FoDi software on an infrared fundus image and with negative sign. FoDi = fovea-to-disc alignment.

trend of the regression line of the differences and heteroscedasticity by the Kendall tau-b of the absolute differences were evaluated. Statistical significance was defined as $P < .05$.

Reliability was assessed by considering the repeatability of the 5 measurements (ICC through 2-way mixed effects model, absolute agreement, and single measurement) and the interobserver agreement (ICC through 2-way random effects model, absolute agreement, and single measurement). The precision was based on the within-subject standard deviation (SW), obtained as the residual mean square in the analysis of variance of repeated measurements.[19,20] The precision of each method was calculated as 1.96 SW.

The instrumental torsional zero error was analyzed at the fundus camera as well as at the OCT. A systematic error was found in both devices. The fundus camera showed an anticlockwise image tilt of 0.55 ± 0.07-degrees (0.45- to 0.62-degrees), and OCT had a clockwise image tilt of 0.47 ± 0.05-degrees (0.41- to 0.54-degrees). This torsional zero error was subsequently corrected to obtain the cycloposition values described below.

Statistical analysis and graphic construction were performed using SPSS software version 25.0 (IBM, Armonk, New York, USA) for Windows (Microsoft, Redmond, Washington, USA). The sample size calculation was done with GRANMO version 7.11 software (IMIM, Mar Hospital, Barcelona, SP).

RESULTS

RIGHT EYES OF 51 MEN AND 41 WOMEN WERE INCLUDED. THE age was 56.1 ± 16.6 years in group A and 67.2 ± 14.6 years in group B. The spherical equivalent refractive error was 0.19 ± 1.67 in group A and −0.77 ± 4.02 in group B. The logMAR corrected visual acuity was −0.06 ± 0.12 in group A and 0.02 ± 0.11 in group B.

• **OCT-DETERMINED CYCLOPOSITION:** O-DFA results were compared to those achieved by the gold standard in order to analyze the validity of the method. The mean value of the 5 repeated measurements of each observer was considered to minimize the influence of the repeatability. Cycloposition results are described in Table 1.

TABLE 1. Cycloposition by Means of OCT-Determined DFA and Photographically Determined DFA. Agreement and Absolute Differences Between Methods

	Method	M ± SD (degrees)	CoV (%)	*P* value	95% LA (degrees)		Absolute differences (degrees)		ICC	ICC Low	ICC Up
					Low	Up	M ± SD	Up to 4° (%)			
Ob1	O-DFA	7.48 ± 3.51	46.89	0.006	−5.80	4.28	2.16 ± 1.58	89	0.71	0.57	0.80
	P-DFA	8.20 ± 3.72	45.38								
Ob2	O-DFA	7.62 ± 3.58	47.02	0.613	−5.76	5.46	2.28 ± 1.73	80	0.70	0.57	0.79
	P-DFA	7.73 ± 3.97	51.39								

CoV = coefficient of variation; ICC = intraclass correlation coefficient between methods; ICC Low = 95% lower limit of ICC; ICC Up = 95% upper limit of ICC; LA = limits of agreement; Low = lower limit; M = mean; Ob1 = observer 1; Ob2 = observer 2; OCT = optical coherence tomography; O-DFA = OCT-determined disc-fovea angle; P-DFA = photographically determined disc-fovea angle; SD = standard deviation; Up = upper limit.

Mean O-DFA was 7.6 ± 3.5-degrees, and mean P-DFA was 7.9 ± 3.8-degrees, with similar variability (the coefficient of variation was 47% in O-DFA, 48% in P-DFA). The aim of the study was to compare results of cycloposition in the same patient using both methods, so previous binocular examinations were not included, and the cycloposition obtained should not be considered representative of the normal population. There was a statistical significance in the differences between methods only in group A and for 1 of the observers, whereas in the remaining analyses, the differences were not significant.

There was no significant bias between methods, and 95% limits of agreement were 5.3-degrees. The distribution of the differences was heteroscedastic in all cases (observer 1, $P = .62$; observer 2, $P = .11$). The absolute differences between methods was 2.2-degrees. Half of the subjects studied had a difference of up to 2-degrees and approximately 85% of up to 4-degrees between methods. The ICC between methods was 0.71, considered by Altman[18] a good correlation.

• **REPEATABILITY AND INTEROBSERVER AGREEMENT:** Repeatability of O-DFA and P-DFA (Table 2) was excellent in all patients. In group A (well-defined fovea) the repeatability of O-DFA was better than P-DFA (ICC, 0.91 versus 0.80, respectively). Poor definition of the fovea (group B) affected repeatability of P-DFA, whereas that of the O-DFA remained unchanged.

The absolute difference between the first and second measurement of the same eye was equivalent in both groups with O-DFA (group A, 1.1-degrees; group B, 1.0-degrees). That difference was higher using P-DFA, especially in group B (group A, 1.7-degrees; group B, 2.8-degrees). Finally, the precision of O-DFA was better than that of P-DFA (1.4-degrees versus 3.0-degrees, respectively, in group A; 1.6-degrees versus 4.8-degrees, respectively, in group B).

The interobserver agreement results were comparable to those of the repeatability (Table 2). The agreement was excellent with both methods, but all parameters of P-DFA were affected when the position of the fovea was poorly defined (eg, the precision changed from 1.5-degrees in group A to 3.3-degrees in group B).

The Bland-Altman analysis (Figure 2) exhibited an absence of bias when first and second measurements were compared. The 95% limits of agreement of O-DFA were 2.2-degrees for group A and 2.4-degrees for group B. In the P-DFA, the limits of agreement were 4.1-degrees for group A and 6.2-degrees for group B, supporting the results of precision.

DISCUSSION

OCULAR TORSION CAN BE ASSESSED BY AN OBJECTIVE OR A subjective method. The objective assessment quantifies the angle of rotation of the globe by means of the relative position between fovea and optic nerve head (DFA). However, the normal range of DFA extends from 0-degrees (with the fovea at the level of the disc center) to approximately 12- to 13-degrees (with the fovea at the inferior margin of the optic disc).[4] This variability prevents establishment of the baseline position of the eye and reduces its diagnostic value in small torsions.

Subjective methods evaluate the patient's perception of the environment rotation. The normal value corresponds to no subjective torsion, so the amount of torsion is simple to determine. Nevertheless, it is difficult to assess in children, and patients with torsional disorders frequently do not refer to subjective torsion because of adaptation mechanisms. Thus, both objective and subjective evaluation methods are necessary to determine the presence and quantity of ocular torsion.

In other scenarios, for example, strabismus monitoring and the analysis of torsional changes after extraocular muscle surgery, the DFA measurement may be the method of choice, due to its objectivity and good reliability).[10–15] P-DFA presents some clinical inconveniences that could be improved by the use of the OCT.

TABLE 2. Repeatability and Interobserver agreement of OCT-Determined DFA and Photographically Determined DFA Influence of Foveal Definition on the Measurements

		O-DFA			P-DFA		
	Group	ICC	Precision (degrees)	ABS Diff (degrees)	ICC	Precision (degrees)	ABS Diff (degrees)
Repeatability	A	0.91	1.42	1.08	0.80	2.99	1.71
	B	0.93	1.58	1.00	0.71	4.84	2.75
Interobserver agreement	A	0.87	2.34	1.19	0.95	1.49	0.85
	B	0.89	2.42	1.46	0.82	3.29	1.93

ABS Diff = absolute difference between first and second measurements for the repeatability and between observers for the interobserver agreement; O-DFA = OCT-determined disc-fovea angle; P-DFA = photographically determined disc-fovea angle; Group A = well-defined fovea; Group B = poorly defined fovea; ICC = intraclass correlation coefficient.

Mean value between observers is shown in repeatability.

• **GOOD AGREEMENT BETWEEN OCT AND PHOTOGRAPHIC DETERMINATION:** The P-DFA method in normal patients has been widely studied, and its value ranged from 5.1 ± 2.8-degrees[9] to 7.8 ± 3.6-degrees.[21] The disc-fovea axis inclination was evaluated in healthy eyes by OCT FoDi software in 3 previous studies. Valverde and associates[22] found an inclination of 7.3 ± 3.6-degrees in 66 eyes. Lee and associates[23] obtained a 7.5 ± 3.7-degree value in 71 eyes, and Lengwiler and associates[16] found a 6.6 ± 2.8-degree value in 31 eyes. The present study result of 7.9 ± 3.6-degrees is concordant with those studies. These authors have no knowledge of publications comparing the DFA provided by the OCT and that assessed by fundus photography in the same patient.

Good agreement was found between O-DFA and P-DFA. There was no systematic bias between them, and the interindividual variability was similar. The Bland-Altman plot showed 95% limits of agreement near 5-degrees. The expected disparity between methods had been previously estimated as the 95% limits of agreement of repeated measurements with the gold standard, which were approximately 4-degrees. The mean absolute difference between methods was 2.2-degrees, and in approximately 85% of patients, the variation reached 4-degrees, so the difference between methods was slightly larger than expected in a small percentage of patients.

Several factors could justify differences found in disc-fovea inclination on a fundus photograph and an infrared image provided by OCT. The absence of a proper rotational calibration of both the fundus camera and the OCT may cause a systematic error. Unnoticed head tilt of the patient could cause different ocular cycloposition. The last factor to consider is that the foveal position was manually determined in the fundus photograph and automatically with OCT. The manual identification was made by delimiting the center of the darker zone in the macular region, due to the thinning of the retina in this area. For the automatic determination, the patient was asked to fixate on the internal stimulus, and the software considered the fovea as the area used to fixate. Thus, the anatomical fovea was determined in the first case and the functional fovea in the second case.

The anatomical fovea center and the locus of the retinal fixation do not necessarily coincide. According to Zeffren and associates,[24] the fixation area did not match the center of the foveal avascular zone, but an eccentric position 67 μm away from this center in a random direction. Putnam and associates[25] found the center of fixation displaced from the highest foveal cone density by approximately 50 μm. That disagreement can be detected by Spectralis OCT, with a transversal resolution of 14 μm.[26] Therefore, considering the anatomical fovea in fundus photography and the functional fovea with the OCT may justify a certain degree of discrepancy in a small percentage of eyes.

• **SUPERIOR REPEATABILITY AND PRECISION OF OCT METHOD:** Quantification of DFA in fundus photography has proven to be a repeatable method. Simiera and Loba[15] studied 32 patients in whom 2 consecutive measurements were taken, moving their heads away from the device and readjusting the parameters for the next measurement. The ICC was 0.98 and 0.99, respectively, for the 2 observers who made the evaluations.

Using FoDi software, Denniss and associates[27] made 10 repeated measurements in 10 subjects, asking them to recline and replace the head between analyses; they obtained a SW of 0.97-degrees. Lengwiler and associates[16] analyzed 3 measurements of 31 patients also moving the patient away between determinations. The ICC of the repeatability was 0.96.

The present results in group A (60 eyes) showed a better repeatability of the O-DFA (ICC, 0.91) than the P-DFA (ICC, 0.80). The precision of O-DFA was also better, doubling that of the gold standard (O-DFA, 1.4-degrees; P-DFA, 3.0-degrees). The Bland-Altman limits of agreement (Figure 2) confirmed these results: approximately 2-degrees in O-DFA and approximately 4-degrees in P-DFA. The patient fixation in the stimulus center could be more accurate in repeated measurements than the manual determination of the fovea, explaining the results.

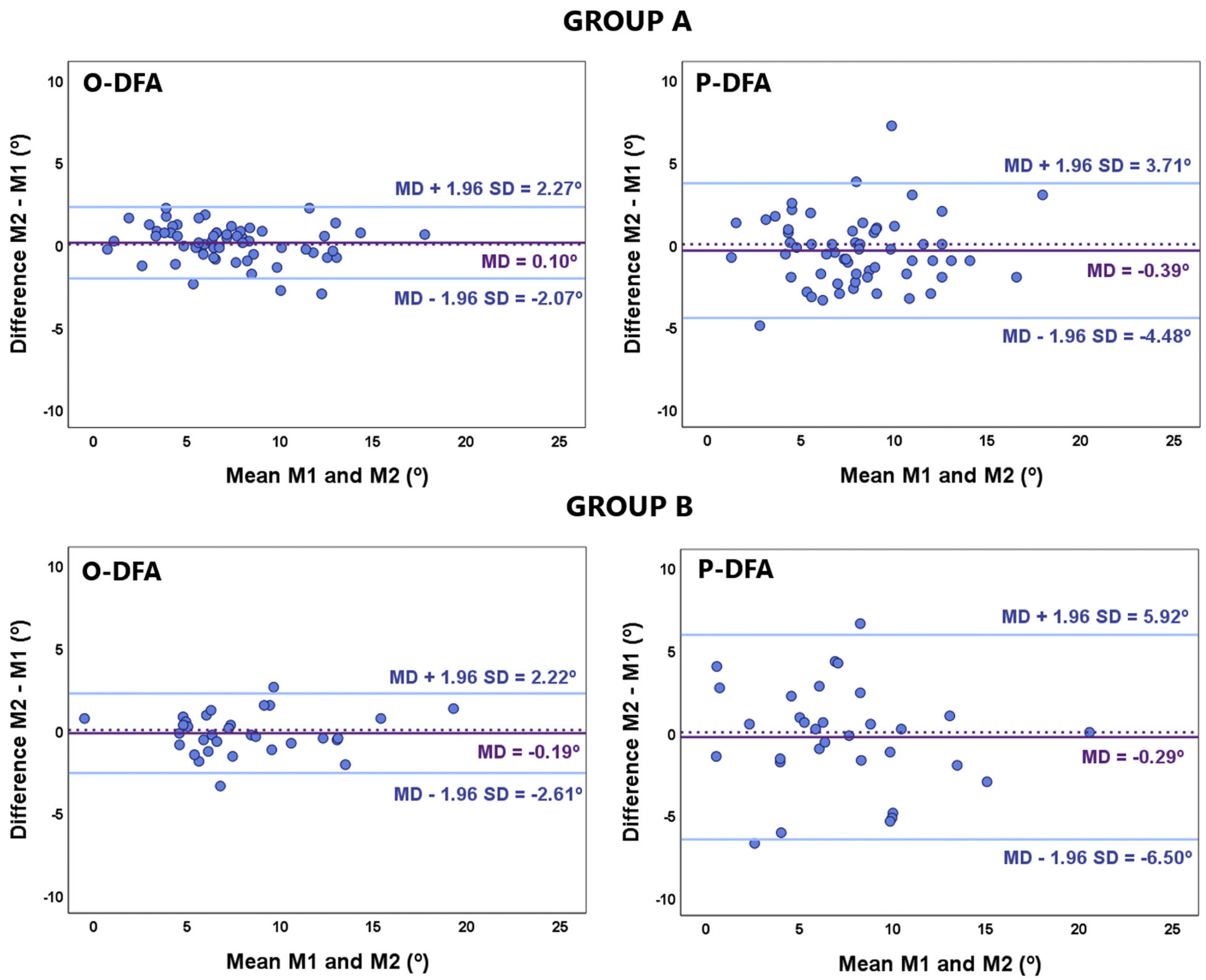

FIGURE 2. Bland-Altman plots comparing first and second measurements of cycloposition with O-DFA and P-DFA in group A and group B. Y axis represents the difference between measurements and X axis the mean value between them. The solid line corresponds to the mean of the differences (MD) and the dashed lines to the limits of agreement. M1 = measurement 1; M2 = measurement 2; O-DFA = optical coherence tomography-determined disc-fovea angle; P-DFA = photographically determined disc-fovea angle.

Furthermore, the relatively narrow range of cycloposition in the present patients could provide more favorable outcomes than if they were strabismus patients with a wider range of torsion. Additional studies in patients with ocular torsion are desirable to confirm those results.

• **INFLUENCE OF THE FOVEAL DEFINITION:** Several ocular motility disorders are associated with retinal pathology, such as restrictive myopic myopathy[28]; strabismus caused by microvascular diseases such as diabetes mellitus[29] or hypertension[30]; or sensory strabismus by vision loss in severe macular pathology.[31] In other situations, retinal surgery may cause a secondary strabismus, as in retinal detachment surgery.[32] In those cases, the assessment of the torsional component of the deviation could contribute to the motor diagnostic, but in fundus the anatomic foveal position may be difficult to determine.

Group B consisted of 32 right eyes with poor foveal definition. The 2 observers agreed that they could not precisely determine the foveal position in these eyes, whereas they could suppose the approximate location by previous experience. Repeatability and reproducibility of P-DFA were diminished in this group (Table 2), whereas those of the O-DFA remained unchanged.

These results revealed an evident loss of precision of the gold standard method, P-DFA, when the fovea was not clearly detected. Because the observer deduced the foveal position by the center of the avascular zone or the vascular arcades course, the determination could be imprecise. FoDi software of the OCT used the fixation to locate the functional fovea, and with an adequate visual acuity and an appropriate collaboration, the fixation was more accurate in repeated analyses, as shown in Figure 3.

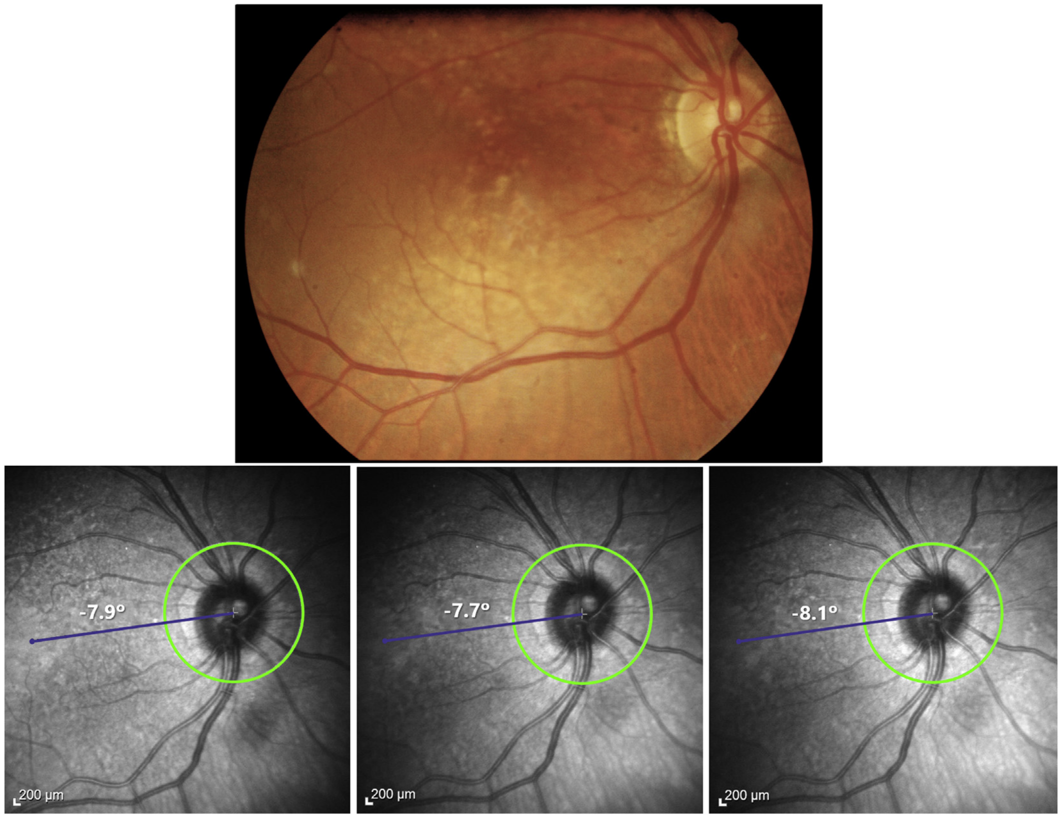

FIGURE 3. (Upper) Right fundus showing the difficulty of precisely determining the foveal position due to the presence of macular drusen. (Lower) Three infrared images of the same eye provided by FoDi software, where a great stability of fixation in repeated measurements is observed. FoDi = fovea-to-disc alignment.

In the present study, all eyes presented a minimum visual acuity of 0.3 logMAR to facilitate a suitable fixation, which was controlled in the live infrared image during the examination. In the event of lower visual acuity due to retinal pathology or inadequate patient cooperation, the automatic determination of the fovea could be incorrect[33–35] and the OCT-determined cycloposition could lose precision. In that situation, the software allows manual location of the fovea in the infrared image before the analysis, partially compensating this limitation.

• **RELEVANCE FOR CLINICAL PRACTICE:** Assessment of the cycloposition by means of the OCT improved several aspects compared to the measurement on the fundus image. Pupillary dilation was not necessary except in patients with strong pupillary miosis. The evaluation was more comfortable for the patient, and the angle of the cycloposition was immediately obtained, avoiding the step of exporting the image for the measurement. In addition, the final report of the analysis included the disc-fovea axis inclination superimposed on the infrared fundus image, confirming that the fovea had been properly located.

Cycloposition results with OCT had a good concordance with results of the gold standard. OCT offered more precise and repeatable measurements in healthy eyes, with an excellent reproducibility. When the fovea was not well defined in the fundus photograph, the precision of the DFA was reduced, whereas the OCT results were not affected, due to automatic foveal determination.

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