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Evaluation of corneal parameter changes under different accommodative stimuli with Scheimpflug imaging-based tomography

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引用:Bedrán-García FJ, Piñero DP. Scheimpflug 成像断层扫描评估不同调节刺激下角膜参数的变化.国际眼科杂志, 2024, 24(9):1357-1366.

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Received: 2023-04-15 Accepted: 2024-05-17

Scheimpflug 成像断层扫描评估不同调节刺激下角膜参数的变化

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摘要

目的:基于 Scheimpflug 成像系统评估健康眼角膜变化测量的可靠性,以及正常人群测量值的分布情况。

方法:前瞻性非随机对照研究。纳入 27 名健康受试者(54 眼),分为正视组(13 眼),近视组(17 眼),远视组(4 眼),散光组(20 眼)。所有病例接受了完整的眼科检查,使用 Pentacam AXL 系统分析不同调节刺激下(+2.00、0.00、-3.00 D)角膜检测参数变化。该研究分为2个阶段:重复性分析和健康人群不同调节刺激下角膜参数变化的特征。

结果:在重复性分析中,在三种调节刺激下高度不对称指数(IHA)表现出最大的变异性,其余参数结果良好。正视组中,最大角膜曲率(Kmax)位置有显著差异($P<0.05$);而散光组中 Kmax、最小角膜厚度(MCT)、角膜球面像差、总像差、低阶像差均有显著差异($P<0.05$)。近视组 Kmax 的水平位置在 2.00 D 和-3.00 D 时的位移存在显著差异($P=0.033$),正视组 Kmax 的矢量大小变化也存在显著差异($P<0.05$)。MCT 在不同调节刺激下无显著差异($P\geqslant 0.109$)。

结论:在不同调节刺激下,Kmax 和 MCT 在健康角膜中的位置会发生显著变化,而这些调节相关角膜变化在屈光不正人群中有不同的趋势。Scheimpflug 成像系统测量结果具有一致性。

关键词:角膜生物力学;角膜曲率;角膜厚度;角膜测厚仪;角膜像差;Pentacam;调节

Abstract

• AIM: To evaluate the reliability of measurements of corneal changes with accommodation in healthy eyes using a Scheimpflug imaging-based system and how these measurements distribute in the normal population.

• METHODS: Prospective, non-randomized, comparative study including 27 healthy subjects (54 eyes), including emmetropia (13 eyes), myopia (17 eyes), hyperopia (4 eyes) and astigmatism (20 eyes) groups. In all cases, a complete eye examination was performed, including the analysis of corneal changes with different accommodative stimuli (+2.00, 0.00 and -3.00 D) using the Pentacam AXL system. The investigation was structured in 2 phases: repeatability analysis and characterization of accommodation-related corneal changes in healthy populations.

• RESULTS: In the repeatability analysis, the index of height asymmetry (IHA) showed the greatest variability with the three accommodative stimuli, being the results for the rest of parameters acceptable. The group of emmetropes showed significant differences with accommodative changes in the position of maximum keratometry (Kmax; $P<0.05$), whereas in the astigmatism group, significant changes were not only observed in the position of Kmax, but also in minimum corneal thickness (MCT), corneal spherical aberration, and total and low order aberration root mean square (all $P<0.05$). Likewise, a significant difference was found in the displacement of the X position of Kmax with +2.00 D and -3.00 D in the myopia group ($P=0.033$) as well as in changes with +2.00 D and -3.00 D in the magnitude of the position vector of Kmax in the emmetropia group ($P<0.05$). No significant changes were found between accommodative stimuli in the displacement of coordinates of MCT ($P\geqslant 0.109$).

• CONCLUSION: The position of Kmax and MCT in healthy corneas can change significantly when presenting different accommodative stimuli using the accommodation mode of the Pentacam system, with different trends in these accommodation-related corneal changes between refractive errors. Likewise, the consistency of the measurements obtained with Scheimpflug has been confirmed.

• KEYWORDS: corneal biomechanics; keratometry; corneal thickness; pachymetry; corneal aberrations; Pentacam; accommodation
DOI:10.3980/j.issn.1672-5123.2024.9.03

Citation: Bedrún-García FJ, Piñero DP. Evaluation of corneal parameter changes under different accommodative stimuli with Scheimpflug imaging-based tomography. Guoji Yanke Zazhi(Int Eye Sci), 2024,24(9):1357-1366.

INTRODUCTION

The cornea is the optical element that provides the highest dioptric power to the ocular optical system, being considered as a static lens, without the ability to modify its conformational state (curvature, elevation, and thickness) to perform optical compensation functions. In contrast, the crystalline lens can experience significant modifications of its shape with the contraction of the ciliary muscle, with the aim of providing optical compensations for different focusing distances, which is known as accommodation. However, considering the viscoelastic character of the cornea, its proximity to the ciliary muscle and that some of the tendons of this muscle insert directly into the cornea[1], as well as the findings of some studies showing that the contraction of this muscle induces conformational changes in the cornea of some avian species[2], the static character of the cornea can be considered as questionable.

Some previous preliminary experiences on the analysis of corneal changes with accommodation found some results suggesting that potential changes could occur in the periphery of the human cornea during accommodation[3-5]. However, with the development of new technologies for the analysis of the ocular anterior segment, such as Scheimpflug imaging-based systems, the analysis of corneal changes with accommodation has become increasingly more accurate and sophisticated. Despite technological advances in diagnostic technology, contradictory outcomes concerning the modification of the corneal shape with accommodation have been reported, with most of studies concluding that accommodation does not significantly change corneal configuration[3-10].

Recently, the Scheimpflug imaging-based system Pentacam AXL® from Oculus Optikgerate GmbH (Wetzlar, Germany) has included a new tool to analyze the corneal modifications of the corneal shape occurring during accommodation. It consists of the combination of the already corneal analysis provided by this system with a fixation target that can be set to induce different levels of accommodative response. However, despite the potential interest of this tool, there are no studies to this date evaluating the performance of this new tool of the Pentacam system.The aim of the current study was to analyze the consistency of the measurements provided by this new tool and afterwards, if the level of intrasession repeatability is acceptable, to evaluate preliminarily with the changes occurring in corneal geometry and thickness distribution with different types of accommodative stimuli in a sample of healthy eyes with different levels of refractive error.

SUBJECTS AND METHODS

Subjects A cross-sectional non-comparative observational preliminary study was performed, including the first 54 consecutive eyes of 27 patients (22 female) measured with the new accommodation mode of the Pentacam system. Inclusion criteria were healthy eyes with spherical equivalent between +6.00 D and -6.00 D, and an astigmatism of more than 1.50 D. Exclusion criteria were active ocular disease, previous ocular surgery, corneal molding due to contact lens use, ocular allergy, strabismus, previous ocular trauma or ectatic or dystrophic corneal pathology, contact lens wearers were included in the study if they discontinued the use of the lenses before the study evaluation for 2 wk in the case of soft contact lenses and for a period of 4 wk in the case of rigid contact lenses. Each patient was informed about the characteristics and justification of the present study. All patients signed an informed consent form following the tenets of the Declaration of Helsinki. This research was approved by the Ethics Committee of the University of Alicante (No.UA-2021-01-14).

Initially, to confirm the potential validity of measurements of corneal changes with accommodation taken with this new system, an analysis of the consistency of such measures was performed. For this purpose, two consecutive measurements were obtained and the intrasession repeatability was assessed. Once this aspect was confirmed, a preliminary analysis of the measurements obtained with this system in a healthy population was performed to define a preliminary distribution of corneal changes in the healthy eye and to define the potential clinical utility of this type of examination. All measures were carried out at the optometric clinic of the University of Alicante. All tests performed in the scope of this study were non-invasive and were done by the same experienced examiner (FB).

Clinical Protocol In this study, all patients had a complete optometric examination (anamnesis, refraction, visual acuity, anterior and posterior segment evaluation, and tonometry), including two consecutive measurements with three different accommodative demands defined with the Scanner Accommodation settings of the Pentacam AXL system, as described in Table 1. This Scheimpflug system has a red light-emitting diode that serves as a fixation target and can be set to induce an accommodation state ranging from +2.00 D to -5.00 D in steps of 0.50 D[11]. Specifically, the following accommodation demands were used: 0 (combination of tonic accommodation + some accommodative response that may be present due to the proximity of the stimuli), +2.00 D (complete relaxation of the accommodative response), and -3.00 D (simulating the accommodative demand at near vision, 33 cm). As recommended by López-Gil *et al*[12], the subject was asked to maintain the fixation on the target for 2 seconds before obtaining the measurements. It should be considered that tonic accommodation is defined as the accommodative response in the absence of an adequate visual stimulus, which adopts an intermediate position of around 1.00 D[13].

Table 1 Pentacam AXL scanner configuration

Scanner configuration	Stimulus	Right eye	Left eye
3D-scan 50 pictures accommodation	+2.00	1 shot	1 shot
	0.00	1 shot	1 shot
	-3.00	1 shot	1 shot

The preparation of the patient and the performance of the corresponding measurements adhered to the descriptions given in the user's manual of the equipment (Pentacam AXL, Oculus ®). The following parameters were extracted and analyzed for this study: maximum frontal keratometry (Kmax) (with X and Y coordinates), apex (ACT), central (CCT) and minimum corneal thickness (MCT) (with X and Y coordinates), corneal diameter, corneal aberrations including total root mean square (RMS), high order RMS, low order RMS, primary spherical aberration coefficient (Z_4^0) and defocus, index of surface variability (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), center keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), and minimum radius (Rmin). Only data of adequate quality (Table 2) according to the guidelines given in the user's manual was considered for the study.

Besides all measures recorded and extracted that have been mentioned, the geometric calculation of a variable to determine the displacement of the X and Y coordinates of Kmax and the position of CCT with the change of the induced accommodative stimulus was performed (Figure 1). As shown in Figure 1, two points, (x,y) and (x',y'), in an ordered axis centered in O were measured that represent the change of the position on the cornea of Kmax or CCT with the accommodative stimulus. The distance between them and the center O was calculated using the Pythagorean analysis of right triangles, since these distances correspond to the length of the hypotenuse of a triangle: distance from point (x, y) to the center O represented by the letter "a" and the distance from the point (x',y') to the center O represented by the letter "b". Likewise, the distance between the points (x, y) and (x', y') represented by the letter "d" was obtained. According to the Pythagorean analysis of Figure 1, the parameters a, b and d were calculated with the following equations:

$$a = \sqrt{x^2 + y^2} \quad (1)$$

$$b = \sqrt{x'^2 + y'^2} \quad (2)$$

$$d = \sqrt{(x' - x)^2 + (y' - y)^2} \quad (3)$$

where the center O represents the location of the corneal apex, "a" represents the distance from the position of Kmax or CCT to the center O, with an initial accommodative stimulus, "b" represents the distance from the position of Kmax or CCT to the O-center, with each accommodative stimulus, and "d" is the difference between the location of these points, representing the scalar magnitude of the change in the position of Kmax or CCT associated to the accommodative response.

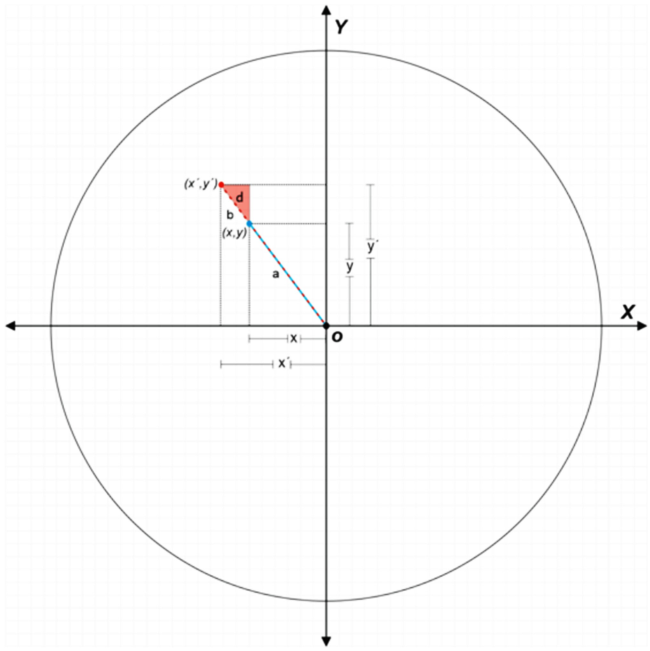

Figure 1 Method of calculation of the change (d) in the position of maximum frontal keratometry and central corneal thickness considering their X and Y coordinates.

Table 2 Criteria defined for the quality of the exam obtained with the Pentacam system

Anterior cornea	
Area analyzed	>60%
Valid data	>95%
Lack of segments	<1
Segment continuation	<1
Model deviation	<14
Posterior cornea	
Area analyzed	>50%
Valid data	>90%
Lack of segments	<1
Segment continuation	<1
Model deviation	<14
Alignment	
Alignment (XY)	<800
Alignment (Z)	<1000
Eye movements	<150

Data Analysis Statistical analysis was performed with the SPSS analysis package (IBM SPSS Statistics for Windows, version 23.0. Armonk, New York: IBM Corp.). The normality of data distributions was evaluated by means of the Kolmogorov-Smirnov test.

Despite existing several studies evaluating the level of intrasession repeatability of the different measures obtained with the Pentacam AXL Oculus® and even comparing with the measures obtained with other systems[14-20], there are no articles reporting the precision of measurements obtained with the accommodation mode of Pentacam AXL. For this reason, an intrasession repeatability evaluation was performed. For such purpose, the mean of the difference of the repeated measures and its standard deviation (S_w) were considered according to the procedure described by Bland and Altman[21]. The intrasession variability was also calculated as 2.77 * S_w (repeatability coefficient). The significance of the differences of the repeated measures of the study variables in each of the accommodative conditions was assessed with the paired Student *t*-test or Wilcoxon test depending on whether the data distributions compared were or not normally distributed, respectively.

Once tested the level of intrasession repeatability of the Pentacam AXL Oculus®, this device was used to characterize the potential accommodation-related corneal changes occurring in the healthy population examined. Specifically, a comparative analysis of corneal changes associated to each accommodative stimulation was performed separately for different groups of eyes with a specific refractive condition: 13 eyes in the emmetropia group (spherical equivalent between −0.25 D and +0.50 D and cylinder below 1.50 D), 17 eyes in the myopia group (spherical equivalent of −0.50 D or more and cylinder below 1.50 D), 4 eyes in the hyperopia group (spherical equivalent of +0.75 D or more and cylinder below 1.50 D), and 20 eyes in the astigmatism group (cylinder of 1.50 D or more with any type of sphere). For the comparison between accommodative stimuli for each refractive condition, the repeated measures ANOVA or the Kruskal-Wallis test was used depending if the data distributions were normally distributed or not, respectively. For the post-hoc comparisons from relaxation to tonic (+2.00 D to +0.00 D) and from tonic to activation (+0.00 D to −3.00 D) the paired Student *t* or Wilcoxon tests were used with the Bonferroni correction. The level of statistical significance in all tests was set at $P<0.05$.

RESULTS

In the repeatability analysis, the coefficients of repeatability (low coefficient represents higher level of repeatability) were low as well as the values of S_w, and therefore there was limited variability in the repeated measurements of the locations (Cartesian X and Y coordinates) and displacements of Kmax and MCT, as shown in Tables 3 and 4. Among the topometric indices, IHA showed the greatest variability with the three accommodative stimuli (Table 5). Regarding anterior corneal aberrations, all indices showed coefficients of repeatability and S_w values very low and close to zero in most of cases (Table 6).

Between the different accommodative states, the emmetropes showed significant differences in the values of the distance from the apex to the position of Kmax ($P=0.025$) and in hyperopes in the values of Z_4^0 ($P=0.032$) and IHA ($P=0.049$; Table 7). The results for the hyperopic group should be interpreted with caution due to the small sample size. The astigmatic group showed more variables with significant differences between accommodative states: distance from the apex to the position of Kmax ($P=0.004$), MCT ($P=0.038$), Z_4^0 ($P=0.006$), total RMS ($P=0.046$) and LOA RMS ($P=0.046$). In myopes, the mean values of the variables studied did not experience significant variations with the different accommodative stimuli (Table 7).

Table 3 Repeatability of maximum frontal keratometry data

Variables	Mean difference	S_w	Coefficient of repeatability
Corneal diameter (mm)	0.06	0.08	0.22
Kmax (+2.00 D)	0.10	0.10	0.26
X (+2.00 D) (mm)	0.10	0.10	0.28
Y (+2.00 D) (mm)	0.19	0.22	0.60
Displacement X (+2.00 to 0.00 D)	0.12	0.12	0.34
Displacement Y (+2.00 to 0.00 D)	0.33	0.26	0.71
d (+2.00 to 0.00 D)	0.27	0.26	0.72
Kmax (+0.00 D)	0.11	0.11	0.30
X (0.00 D) (mm)	0.10	0.08	0.22
Y (0.00 D) (mm)	0.18	0.17	0.46
Displacement X (0.00 to −3.00 D)	0.12	0.12	0.34
Displacement Y (0.00 to −3.00 D)	0.23	0.21	0.57
d (0.00 to −3.00 D)	0.18	0.18	0.50
Kmax (−3.00 D)	0.12	0.13	0.36
X (−3.00 D) (mm)	0.12	0.15	0.42
Y (−3.00 D) (mm)	0.20	0.16	0.46

Kmax: Maximum frontal keratometry; S_w: The intrasession standard deviation; d: Total displacement of the position of Kmax.

Table 4 Repeatability of minimum corneal thickness

Variables	Mean difference	S_w	Coefficient of repeatability
MCT (+2.00 D) (μm)	2.64	2.56	7.08
X (+2.00 D) (mm)	0.13	0.15	0.42
Y (+2.00 D) (mm)	0.09	0.08	0.21
Displacement X (+2.00 to 0.00 D) (mm)	0.19	0.21	0.57
Displacement Y (+2.00 to 0.00 D) (mm)	0.12	0.11	0.30
d (+2.00 to 0.00 D) (mm)	0.11	0.10	0.27
MCT (0.00 D) (μm)	3.57	2.60	7.21
X (0.00 D) (mm)	0.10	0.10	0.29
Y (0.00 D) (mm)	0.06	0.10	0.29
Displacement X (+0.00 −3.00) (mm)	0.13	0.12	0.34
Displacement Y (0.00 to −3.00 D) (mm)	0.08	0.11	0.30
d (0.00 to −3.00 D) (mm)	0.07	0.06	0.16
MCT (−3.00 D) (μm)	2.96	3.13	8.68
X (−3.00 D) (mm)	0.11	0.10	0.29
Y (−3.00 D) (mm)	0.06	0.06	0.16

MCT: Minimum corneal thickness; S_w: The intrasession standard deviation; d: Total displacement of the position of MCT.

Table 5 Repeatability of the topometric indices of the anterior corneal surface

Variables	Mean difference	S_w	Coefficient of repeatability
+2.00 D			
ISV	0.52	0.59	1.64
IHA	1.05	0.88	2.43
IVA	0.01	0.01	0.03
IHD	0.00	0.00	0.00
KI	0.00	0.01	0.01
Rmin	0.02	0.02	0.05
CKI	0.00	0.00	0.01
0.00 D			
ISV	0.35	0.49	1.35
IHA	1.25	1.17	3.23
IVA	0.01	0.01	0.02
IHD	0.00	0.00	0.00
KI	0.00	0.00	0.01
Rmin	0.02	0.02	0.05
CKI	0.00	0.00	0.01
−3.00 D			
ISV	0.61	0.66	1.82
IHA	2.08	2.90	8.04
IVA	0.01	0.01	0.03
IHD	0.00	0.00	0.01
KI	0.00	0.00	0.01
Rmin	0.02	0.02	0.05
CKI	0.00	0.00	0.01

ISV: Index of surface variability; IHA: Index of height asymmetry; IVA: Index of vertical asymmetry; IHD: Index of height decentration; KI: Keratoconus index; Rmin: Minimum radius; CKI: Center keratoconus index; S_w: The intrasession standard deviation.

The post-hoc analysis of comparisons between accommodative states by refractive group revealed that there were significant differences in the values of the distance from the apex to the position of Kmax between relaxation and tonic accommodation stimuli (+2.00 D to 0.00 D) ($P=0.003$), as well as between tonic accommodation and active accommodation (0.00 D to −3.00 D) ($P=0.002$) in the astigmatic group. Likewise, in this same group, MCT experienced a significant change between the tonic accommodation and active accommodation status (0.00 D to −3.00 D) ($P=0.046$), while Z_4^0 changed significantly only between relaxed and active accommodation status (+2.00 D to −3.00 D) ($P=0.010$), as well as between tonic accommodation and active accommodation

Table 6 Repeatability of anterior corneal aberrations

Variables	Mean difference	S_w	Coefficient of repeatability
+2.00 D			
Z_4^0 (μm)	0.011	0.010	0.029
Total RMS (μm)	0.065	0.059	0.163
HOA RMS (μm)	0.030	0.044	0.121
LOA RMS (μm)	0.072	0.059	0.164
Defocus (μm)	0.07	0.07	0.18
0.00 D			
Z_4^0 (μm)	0.016	0.015	0.042
Total RMS (μm)	0.085	0.079	0.219
HOA RMS (μm)	0.044	0.066	0.182
LOA RMS (μm)	0.089	0.082	0.226
Defocus (μm)	0.10	0.11	0.30
−3.00 D			
Z_4^0 (μm)	0.022	0.025	0.069
Total RMS (μm)	0.077	0.104	0.288
HOA RMS (μm)	0.026	0.027	0.074
LOA RMS (μm)	0.077	0.104	0.287
Defocus (μm)	0.14	0.14	0.39

Z_4^0: Primary spherical aberration; RMS: Root mean square; HOA: High order aberration; LOA: Low order aberration; S_w: The intrasession standard deviation.

Table 7　Descriptive statistics and comparative analysis between refractive error groups

Refractive error	Emmetropia (*n*=13)		Myopia (*n*=17)		Hyperopia (*n*=4)		Astigmatism (*n*=20)	
Variable Accom. Stimuli (D)	Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*	Mean±SD	*P*
Kmax +2.00	43.65±1.44	0.734	44.57±1.54	0.060	43.65±2.15	0.581	45.13±1.21	0.373
0.00	43.63±1.48		44.61±1.57		43.88±2.47		45.08±1.15	
-3.00	43.65±1.51		44.54±1.54		43.83±2.23		45.09±1.19	
Distance to center Kmax+2.00	1.55±1.00	0.025	0.71±0.58	0.985	0.85±1.05	0.583	1.45±0.91	0.004
0.00	0.81±0.23		0.74±0.21		0.89±0.06		0.66±0.22	
-3.00	1.44±0.98		0.71±0.82		0.60±0.53		1.45±0.86	
MCT+2.00	541.15±11.80	0.09	554.47±25.03	0.787	553.25±34.88	0.371	547.40±39.11	0.038
0.00	542.54±11.39		553.82±26.14		553.75±34.80		547.50±38.82	
-3.00	541.31±11.14		554.35±25.68		554.25±34.13		545.70±37.53	
Distance to center MCT +2.00	0.79±0.23	0.741	0.73±0.19	0.395	0.71±0.17	0.531	0.84±0.22	0.451
0.00	0.82±0.18		0.70±0.21		0.64±0.30		0.80±0.22	
-3.00	0.79±0.18		0.74±0.22		0.59±0.31		0.81±0.23	
ISV+2.00	16.46±5.21	0.537	14.41±2.09	0.851	13.25±1.71	0.25	16.85±7.32	0.537
0.00	16.31±5.28		14.47±2.50		13.75±2.06		16.75±7.30	
-3.00	16.46±5.36		14.35±2.34		13.00±1.63		16.65±7.37	
IHA+2.00	5.80±5.33	0.663	3.28±2.31	0.833	5.68±2.67	0.049	4.40±3.62	0.39
0.00	6.32±4.66		3.58±2.45		4.28±2.95		3.88±3.77	
-3.00	6.19±5.90		3.41±2.17		3.40±1.98		3.66±3.14	
IVA+2.00	0.12±0.09	0.635	0.09±0.02	0.128	0.09±0.04	0.167	0.11±0.06	0.627
0.00	0.12±0.09		0.09±0.02		0.10±0.03		0.11±0.06	
-3.00	0.12±0.09		0.09±0.03		0.09±0.03		0.11±0.06	
IHD+2.00	0.01±0.01	0.809	0.01±0.00	0.394	0.01±0.00	0.5	0.01±0.01	0.886
0.00	0.01±0.01		0.01±0.00		0.01±0.00		0.01±0.01	
-3.00	0.01±0.01		0.01±0.00		0.01±0.00		0.01±0.01	
KI+2.00	1.01±0.02	0.721	1.02±0.01	0.08	1.02±0.01	0.5	1.02±0.02	0.573
0.00	1.01±0.02		1.02±0.01		1.02±0.02		1.01±0.02	
-3.00	1.01±0.02		1.02±0.01		1.02±0.02		1.02±0.02	
Rmin+2.00	7.40±0.26	0.732	7.64±0.22	0.474	7.52±0.03	0.574	7.69±0.27	0.518
0.00	7.40±0.26		7.63±0.23		7.52±0.01		7.70±0.26	
-3.00	7.40±0.26		7.63±0.23		7.53±0.03		7.70±0.26	
CKI+2.00	1.01±0.01	0.999	1.01±0.00	0.542	1.01±0.00	0.999	1.01±0.01	0.145
0.00	1.01±0.01		1.01±0.00		1.01±0.00		1.01±0.01	
-3.00	1.01±0.01		1.01±0.01		1.01±0.00		1.01±0.01	
Z_4^0+2.00	0.22±0.06	0.258	0.18±0.05	0.063	0.16±0.04	0.032	0.19±0.08	0.006
0.00	0.22±0.07		0.17±0.04		0.19±0.05		0.20±0.07	
-3.00	0.23±0.07		0.17±0.06		0.16±0.04		0.21±0.08	
Total RMS+2.00	1.44±0.33	0.519	1.10±0.38	0.243	0.98±0.04	0.129	1.57±0.86	0.046
0.00	1.45±0.38		1.09±0.45		1.10±0.13		1.61±0.84	
-3.00	1.47±0.40		1.05±0.37		0.98±0.05		1.64±0.87	
HOA RMS+2.00	0.40±0.12	0.571	0.30±0.05	0.214	0.30±0.02	0.421	0.35±0.08	0.405
0.00	0.41±0.14		0.30±0.06		0.32±0.01		0.34±0.08	
-3.00	0.41±0.14		0.29±0.05		0.30±0.01		0.35±0.08	
LOA RMS+2.00	1.38±0.33	0.512	1.05±0.39	0.272	0.93±0.04	0.15	1.52±0.87	0.046
0.00	1.38±0.37		1.05±0.45		1.05±0.13		1.57±0.86	
-3.00	1.40±0.39		1.01±0.37		0.93±0.05		1.59±0.88	
Defocus+2.00	0.50±0.32	0.265	0.45±0.27	0.662	0.43±0.15	0.318	0.57±0.23	0.778
0.00	0.50±0.27		0.46±0.25		0.41±0.13		0.60±0.26	
-3.00	0.56±0.30		0.43±0.27		0.32±0.10		0.60±0.30	

SD: Standard deviation; Kmax: Maximum frontal keratometry; MCT: Minimum corneal thickness; ISV: Index of surface variability; IHA: Index of height asymmetry; IVA: Index of vertical asymmetry; IHD: Index of height decentration; KI: Keratoconus index; Rmin: Minimum radius; CKI: Center keratoconus index; Z_4^0: Primary spherical aberration; RMS: Root mean square; HOA: High order aberration; LOA: Low order aberration.

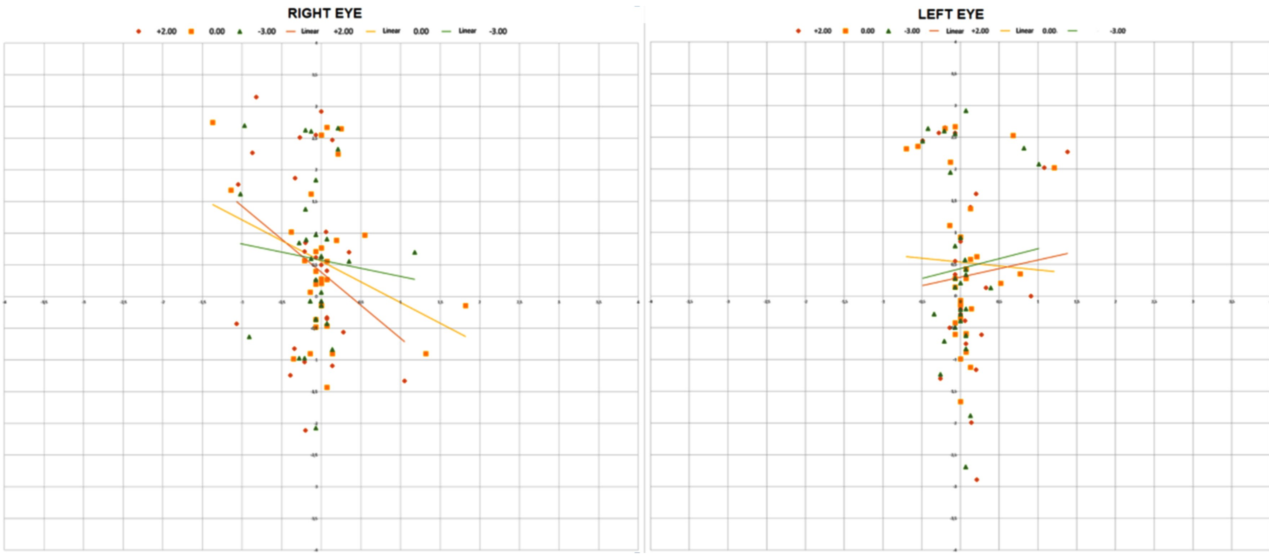

Figure 2　Cartesian representation of the distribution of the location of the point corresponding to the maximum keratometry (Kmax) in all right and left eyes evaluated in the study for the different accommodative stimuli used. Squares represent the positions of Kmax for the accommodative stimulation of 0.00 D, the triangles the positions of Kmax for the accommodative stimulation of −3.00 D and the diamonds the position of Kmax for the accommodative stimulation of +2.00 D. Likewise, a linear adjustment by means of least squares method was shown for the points corresponding to each level of accommodative stimulation.

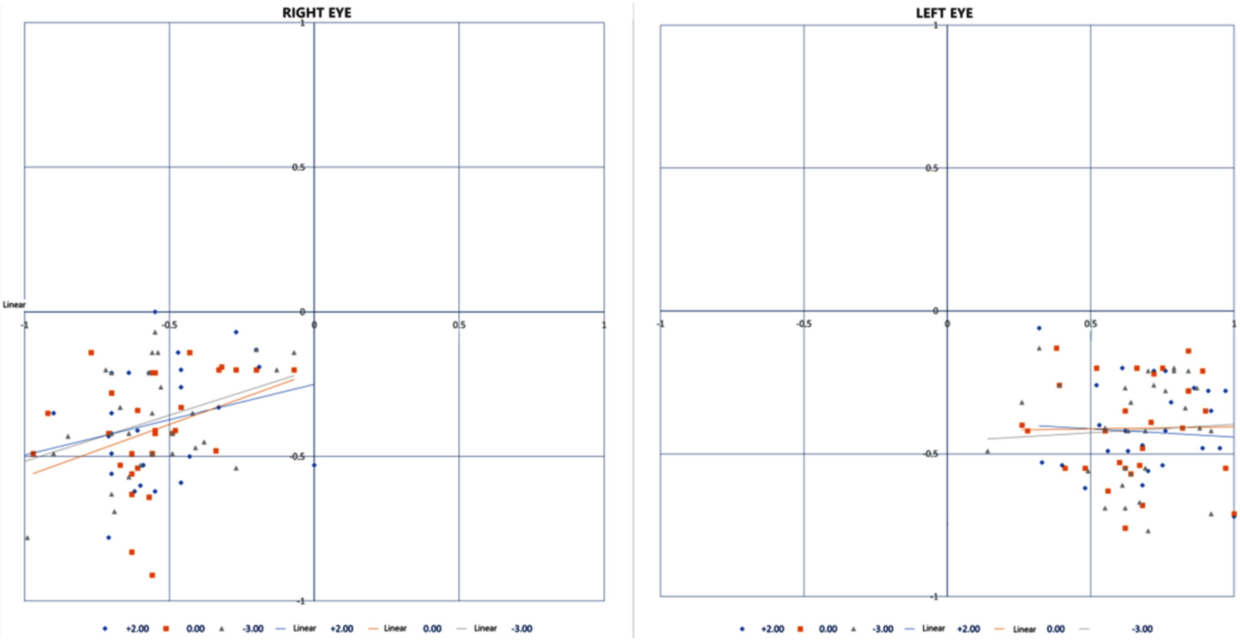

Figure 3　Cartesian representation of the distribution of the location of the point corresponding to the minimum corneal thickness (MCT) in all right and left eyes evaluated in the study for the different accommodative stimuli used. Squares represent the positions of MCT for the accommodative stimulation of 0.00 D, the triangles the positions of MCT for the accommodative stimulation of −3.00 D and the diamonds the position of MCT for the accommodative stimulation of +2.00 D. Likewise, a linear adjustment by means of least squares method was shown for the points corresponding to each level of accommodative stimulation.

status (0.00 to −3.00 D) (P=0.029). Likewise, LOA RMS changed significantly between +2.00 D and −3.00 D (P= 0.037). In the hyperopic group, there was a significant difference in IHA values between +2.00 D and 0.00 D accommodative stimuli (P=0.031) as well as in total RMS between +2.00 D and −3.00 D stimuli (P=0.039).

Figures 2 and 3 showed the changes in the X and Y coordinates of the positions of Kmax and MCT plotted on a Cartesian plane, respectively. Furthermore, differences in the parameter d according to the accommodative variation from +2.00 D to −3.00 D were investigated. A significant change was found in the value of d associated to the position of Kmax in the myopia group (change from +2.00 D to −3.00 D, P=0.033). Likewise, in the emmetropia group, significant differences in the parameter d were also found in the change of the position of Kmax with +2.00 D and −3.00 D (P=0.033). No significant changes were found in the parameter d associated to the changes in the coordinates of MCT in any of the groups evaluated (P≥0.109).

DISCUSSION

The development of diagnostic technology in the field of visual health has highlighted the importance of understanding the dynamics of the ocular optical system, which is assumed to be entirely attributed to the accommodation of the crystalline lens. However, this statement may be questioned when considering that the cornea is anatomically related to the ciliary muscle[1], and consequently potential morphological changes in the cornea are possible during the process of accommodation. In addition, several studies have clearly demonstrated that significant changes occur in the posterior pole of the eye during accommodation in both myopic and emmetropic subjects[22]. Considering that anterior and posterior segment are distal structures, it is coherent to think that those changes can also occur in the cornea, which is a structure close to the ciliary muscle. Indeed, Consejo *et al*[23] demonstrated that anterior scleral shape underwent changes with accommodation, being this phenomenon more pronounced in myopes than emmetropes.

Considering that currently available technology offers the possibility of quantifying corneal changes induced by accommodation, as the evaluation of Kmax and MCT displacement, this type of analysis could be a potentially valid tool for clinical decisions. Specifically, the length of this displacement (d) might be used as an indirect biomarker of the mechanical behavior of the cornea, assuming that the corneal biomechanical stability is potentially correlated with the length of the displacement of corneal tissue associated to the accommodative response. However, to this date, the clinical validity of this type of analysis has not been deeply investigated. This study was aimed at performing a preliminary evaluation of the accommodation configuration mode of the Scheimpflug imaging-based system Pentacam AXL, analyzing the consistency of the measurement of changes occurring in corneal geometry and thickness distribution with different types of accommodative stimuli in a sample of healthy eyes as well as the distribution of these changes according to the refractive status of the eye.

First, an intra-session repeatability analysis of the test-retest type was carried out prior to the measurements in order to confirm if this type of measurements were consistent. In general, the values obtained for the coefficient of repeatability and S_w were low, with values for Kmax, topometric indices, corneal aberrations and CCT for the three accommodative stimuli used consistent with those reported previously without using accommodative stimulation[24-25]. Likewise, the coefficient of repeatability and S_w corresponding to the position of Kmax and MCT for the different accommodative stimuli used were low, but it is difficult to define the clinical relevance of this level of consistency. It is important to note that to date there are no studies evaluating the variability of X and Y coordinates of the position of Kmax and MCT, although many studies have analyzed the accuracy of many other variables provided by the Pentacam system in healthy and pathological eyes[14,26-29]. In any case, the specific quadrant in which MCT and Kmax were located did not change among repeated measures, with only some level of variation in the magnitude of the coordinates. More studies are needed on the clinical relevance of the variability of the X and Y positions of Kmax and MCT, with special attention on the influence on keratoconus diagnosis.

After confirming the consistency of the measures obtained with the accommodation configuration of the Pentacam system, analysis is in terms of the distribution of changes in the position of Kmax and CCT was performed according to the refractive status, revealing some differences between refraction groups in the behavior of such changes. In a comparative analysis, the emmetropic group showed a statistically significant change in the distance of from the apex to the position of Kmax, decreasing in the transition from accommodation relaxation (+2.00 D) to tonic accommodation (0.00 D), and increasing again in the transition from tonic accommodation to active accommodation (-3.00 D). In the hyperopic and astigmatic groups, spherical aberration (Z_4^0) showed a tendency to become more positive with an increasing accommodative demand, with an associated increase in total and LOA RMS. These changes in anterior corneal aberrations due to accommodation obtained in our study agree with the results of previous studies on conformational and morphological changes of the cornea induced by accommodation[4-6]. Sisó-Fuentes *et al*[4] found in 12 eyes a stable linear trend with accommodation for corneal aberrations, although individual variations existed because of the high standard deviation values. Ni *et al*[5] demonstrated that accommodation could influence the corneal shape and curvature, leading to a decrease of corneal high-order aberrations. Therefore, as previously demonstrated using other devices[3-8], the accommodation mode of the Pentacam system allows detecting those corneal changes associated to accommodative variations. However, the current series has also demonstrated that there are some differences in changes occurring with accommodation in the position of Kmax and MCT between eyes with different refractive status (myopia, hyperopia, emmetropia and astigmatism). To this date, this is the first study reporting this preliminary finding that should be investigated further and could be potentially useful in clinical practice.

Despite the significance of corneal changes with accommodation in some refractive groups from our series, it should be considered that they may not have clinical significance as the magnitude and variability of changes in limited. However, the existence of variations in certain corneal parameters induced by the presentation of different accommodative stimuli may be a potential indicator for the identification of risk factors for corneal pathology. This is something that should be investigated further in future studies. Indeed, there are no previous studies analyzing the clinical utility of the accommodation mode of the Pentacam system in pathological corneas, such as keratoconus. In the current series, aspecific analysis of the possible displacements of the position of Kmax and MCT with accommodation was performed. The graphical representation of Kmax and CCT positions with the three different accommodative stimuli used in the overall sample in a Cartesian plane showed a trend to a vertical position of Kmax, remaining constant among the different refractive error groups. In contrast, MCT tended to be located on the infero-temporal quadrant of both eyes, with minimal differences among refractive error groups and accommodative stimuli. The potential diagnostic ability of all these changes should be investigated further in pathological corneas as well as their relationship with the mechanical properties of the cornea, comparing with the performance of other already tested corneal topographic, tomographic and biomechanical indices[30]. Likewise, the potential impact of these variations in ectatic corneas on the diagnostic capability of screening topometric indices of ectasia must be clarified.

Besides all these findings, a significant change was also found in the current study in the displacement of the X position of Kmax in the myopia group. This may be in relation to the peculiarities of the mechanical properties of the ocular globe in myopia. Consejo *et al*[23] found that sclera underwent significant changes in its shape with accommodation in young subjects able to accommodate but not for those with limited accommodation. These authors confirmed that this phenomenon was more pronounced in myopes (for a 4.0 D accommodative stimulus; nasal part: 560±350 μm) than emmetropes (nasal part: 220±120 μm). Sedaghat *et al*[31] analyzed the dynamic corneal response with the Corvis ST system and found evidence of biomechanical changes consistent with decreasing stiffness associated to increasing levels of myopia. Bueno-Gimeno *et al*[32] demonstrated using multiple linear regression analysis that lower corneal hysteresis and corneal resistance factor measured with the Ocular Response Analyzer were significantly associated with thinner CCT, longer axial length, and flatter corneal curvature. Considering this background and the results obtained in the current preliminary study, the analysis of corneal and even scleral changes with accommodation might be useful to characterize in clinical practice the myopic eye and even to predict the potential level of progression in combination with other parameters. Likewise, this analysis might be helpful in the monitoring over time of subjects prescribed with myopia control treatments[33]. More research is needed on this area to confirm this new potential utility of this type of corneal analysis.

In this study, it is assumed that differences in corneal changes with accommodation are mainly attributed to the mechanical properties of the cornea. This assumption can be considered as erroneous that these accommodative - based corneal modifications may be influenced by other factors, such as the hardness of the sclera, the geometrical properties of the cornea, the level of ciliary muscle action, or the intraocular pressure. It is true that these factors can have a significant influence but in this study several of them has been controlled. Only healthy eyes from young people without presbyopia were included. Therefore, the influence of corneal biomechanics seems to be a critical factor in the corneal changes associated to accommodation. This should be confirmed in future studies evaluating the correlation between the mechanical properties of the cornea and the accommodative-based corneal changes.

This study has several limitations that must be acknowledged. First, the sample size of the refractive error groups was limited, especially in the hyperopic group. For this reason, the findings obtained in this study should be considered as trends to investigate further in future trials. Special care should be taken with extracting conclusions with the data obtained in the hyperopic group as it wasmuch reduced and potentially not representative. Another limitation was the unavailability on our clinical setting of a device for measuring the corneal biomechanical properties of the eye in order to confirm if the potential variations in the corneal modifications with accommodation were associated with different biomechanical data profiles. This should be investigated deeply in future studies. Finally, in the astigmatic group, a separate analysis of subgroups according to the orientation of astigmatism was not done due to the limitation of the sample size (with-the-rule, against-the-rule and oblique), which should be also analyzed in future studies.

In conclusion, the results of our study suggest that the position of Kmax and MCT in healthy corneas can change significantly when presenting different accommodative stimuli using the accommodation mode of the Pentacam system, with different trends in these accommodation - related corneal changes between refractive errors. Likewise, the consistency of the measurements obtained with this tool has been confirmed. More studies with larger samples are needed to confirm the trends obtained in the current series and to investigate the potential diagnostic value of this option of measurement provided by the Pentacam system. Likewise, the correlation of the parameter "d" with corneal biomechanical data must be also confirmed.

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