Intereye Asymmetry Detected by Scheimpflug Imaging in Subjects With Normal Corneas and Keratoconus

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Purpose: To report the intereye asymmetry with regard to pachymetry and corneal elevation variables in subjects with normal corneas and in those with keratoconus.

Methods: This is a prospective study that included 151 patients who had Pentacam imaging in both eyes: 53 subjects with bilateral normal corneas and 98 with bilateral keratoconus. Central corneal thickness (CCT), pachymetry at the thinnest point (TP), posterior elevation at the thinnest point of the cornea (PETP), distance, volume, and differential pachymetry were measured. Intereye asymmetry was determined by subtracting the lowest value from the highest value for each variable. The degree of asymmetry between each subject's eyes was calculated with intraclass correlation coefficients for all the variables. Receiver operating characteristic curve was used to determine predictive accuracy and to identify optimal cutoffs of these values.

Results: In the normal subjects, the mean intereye asymmetries in CCT, TP, and PETP were 10.28, 11.04, and 3.75 μm, respectively. In the keratoconic patients, the mean intereye asymmetries in CCT, TP, and PETP were 25.89, 30.15, and 20.08 μm, respectively. Normal eyes demonstrated the smallest difference between eyes, compared with the keratoconic eyes, in all of the variables analyzed ($P < 0.05$). A cutoff value of 6.5 μm in the mean intereye asymmetry at the posterior elevation had an area under the receiver operating characteristic curve of 0.91.

Conclusions: There is a greater intereye asymmetry in pachymetry and posterior corneal elevation variables in keratoconic patients than in subjects with normal corneas.

Key Words: intereye asymmetry, keratoconus, Scheimpflug imaging, posterior corneal elevation, pachymetry

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Keratoconus is a bilateral noninflammatory corneal ectasia.[1] The reported frequencies of unilateral keratoconus diagnosed with computerized videokeratography range from 0.5% to 4.5%.[2–6] However, previous studies have shown that patients with diagnoses of unilateral keratoconus, if observed for a sufficient period, commonly develop signs of keratoconus in the other eye as well.[4] Li et al[7] reported that ~50% of clinically normal fellow eyes progress to keratoconus within 16 years. This suggests that the majority of patients have bilateral disease, and its presentation is asymmetric between the 2 eyes.[8–10]

Some authors have reported asymmetry in keratoconic patients in terms of clinical signs, manifest refraction,[8] corneal curvature,[8] and topographic indices.[9] For many years, asymmetry in corneal curvature has been used as a diagnostic criterion of keratoconus. It is reasonable to think that by evaluating symmetry, we may be able to detect abnormalities and, by evaluating symmetry in corneal maps, to even detect subtle changes in elevation and pachymetry. Scheimpflug imaging measures 25,000 elevation points, in addition to anterior surface topography, posterior surface topography, and pachymetry measurements from limbus to limbus, that are highly reproducible and repeatable.[11,12] Hence, the purpose of this study was to describe the intereye asymmetry in normal subjects and in keratoconic patients using data provided by Scheimpflug imaging.

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MATERIALS AND METHODS

This study was part of a larger prospective study evaluating clinical, demographic, tomographic, and topographic characteristics of patients with keratoconus at the Oftalmosalud Instituto de Ojos in Lima, Peru. The study followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all subjects before the study.

Selection Criteria

A diagnosis of bilateral keratoconus (keratoconus group) was defined as keratoconus in both eyes, with the presence of ≥1 clinical signs (corneal stromal thinning, Vogt striae, Fleischer ring, scissoring of the red reflex, or oil droplet sign identified by retinoscopy) and topographic evaluation (an increased area of corneal power surrounded by concentric areas of decreasing power, inferior–superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian[13]). Subjects who had normal corneas in both eyes (normal group), with no ocular pathology, no irregular corneal pattern, no previous ocular surgery, no significant refractive error, and no clinical signs of keratoconus or scissoring on retinoscopy, were included in the study.

Statistical Analysis

Statistical analysis was performed using SPSS version 17 (SPSS Inc, Chicago, IL). Data were represented as mean ± SD. A P value of <0.05 was considered as statistically significant. The Mann–Whitney test was used to compare the results between keratoconic and normal subjects. An unpaired t test was used to determine whether the difference between eyes in keratoconic patients and normal subjects was significantly different. The Kruskal–Wallis test was used as a nonparametric alternative.

To quantify the degree of asymmetry between eyes, an intraclass correlation coefficient was calculated for each quantitative descriptor of paired eyes. Asymmetry was determined by subtracting the lowest value from the highest value for each variable [eg, a patient with a central corneal thickness (CCT) of 550 μm in the right eye and 545 μm in the left eye would have an intereye asymmetry of 5 μm].

The receiver operating characteristic (ROC) curve was obtained with SPSS 15.0 (SPSS Inc) and was used to determine the intereye asymmetry predictive accuracy and to identify cutoff points with maximum sensitivity and specificity. An area under the ROC (AUROC) curve of 1 implies that the test perfectly discriminated normal subjects from keratoconic patients.

Pentacam Analysis and Data Calculation

For the Pentacam measurements, data were collected using Pentacam Comprehensive Eye Scanner software, version 1.17r37 (Oculus GmBH, Wetzlar, Germany). For posterior corneal elevation measurements, a best-fit sphere was used as a reference surface, with the float option over an 8-mm fit. On these maps, posterior elevation at the thinnest point of the cornea (PETP) was measured as the maximum value above the best-fit sphere at the thinnest point (TP) of the cornea. A pachymetry map was recorded, and we obtained the CCT (pachymetry at the apex of the cornea), TP (pachymetry at the thinnest point of the cornea), volume (corneal volume within 3 mm central), distance (distance of the TP from the geometric center was calculated as the hypotenuse of x and y),[13] and differential pachymetry (defined as CCT minus the pachymetry measurement at the TP of the cornea). Finally, from the refractive maps on the sagittal curvature (cornea front), we obtained the flat and steep keratometric values reported in the 3-mm central zone.

RESULTS

A total of 151 subjects (302 eyes) were analyzed with the Pentacam: 53 bilateral normal eyes and 98 with bilateral keratoconus. The mean age in the normal group was 28.4 ± 5.3 years and 29.29 ± 8.33 years in the keratoconus group. The male/female relation was 25/28 in the normal group and 40/58 in the keratoconus group ($P > 0.05$ for sex and age).

Table 1 presents the between-eyes asymmetry, range, and SDs in all the indices analyzed in subjects with bilateral normal eyes and in patients with bilateral keratoconus. The mean between-eyes differences were statistically significant for all of the variables when comparing the normal eyes with the keratoconic eyes (unpaired t test, $P < 0.05$).

Table 2 presents the mean value for each variable of each eye analyzed in both groups. P values show that there was no statistically significant difference between the better and worse eyes in flat keratometry, steep keratometry, posterior elevation, distance, or differential pachymetry ($P > 0.05$) in the normal group, whereas there were statistically significant differences in CCT, TP, and volume ($P < 0.05$). In the keratoconus group, there were statistically significant differences between the worse and better eyes in all the variables except for distance ($P = 0.22$).

Table 3 shows the sensitivities and specificities of the intereye asymmetry value for each variable. An intereye asymmetry in the posterior elevation of 6.5 μm had 85% sensitivity and 88% specificity, discriminating normal subjects from keratoconic patients. In normal eyes, the mean intraclass correlation coefficients for CCT, TP, and PETP were 0.96, 0.96, and 0.85, respectively; in keratoconic eyes, the mean intraclass correlation coefficients for CCT, TP, and PETP were 0.73, 0.64, and 0.39, respectively.

DISCUSSION

Corneal symmetry is common in normal eyes. In normal myopic subjects, the difference in the spherical equivalent

TABLE 1. Distribution of the Intereye Asymmetry in the Normal and Keratoconus Groups

	Normal Group			Keratoconus Group			
Parameter	Mean Intereye Asymmetry (SD)	Range	Average + 2 SD/3 SD	Mean Intereye Asymmetry (SD)	Range	Average + 2 SD/3 SD	P*
Flat keratometry	0.29 (0.22)	0–1.2	0.73/0.66	2.73 (3.31)	0–18.8	9.35/9.93	0.00
Steep keratometry	0.33 (0.31)	0–1.8	0.95/0.93	3.82 (4.18)	0–27.7	12.18/12.54	0.00
CCT	10.28 (7.89)	0–33	26.06/23.67	25.89 (24.10)	0–169	74.09/72.3	0.00
TP	11.04 (8.22)	0–34	27.48/24.66	30.15 (29.05)	0–177	88.25/87.15	0.00
PETP	3.75 (2.85)	0–11	9.45/8.55	20.08 (20.59)	1–153	61.26/61.77	0.00
Distance	0.27 (0.17)	0–0.57	0.61/0.51	0.22 (0.21)	0–0.98	0.64/0.63	0.04
Volume	0.07 (0.07)	0–0.30	0.21/0.21	0.15 (0.13)	0–0.8	0.41/0.39	0.00
Differential pachymetry	2.21 (1.39)	0–7	4.99/4.17	6.94 (14.52)	0–136	35.98/43.56	0.00

*Normal group versus keratoconus group.

TABLE 2. Mean Value for Each Variable in the Normal and Keratoconus Groups

Variable	Normal Group, Mean (SD)		Keratoconus Group, Mean (SD)		P*
	Better Eye	Worse Eye	Better Eye	Worse Eye	
Flat keratometry†	42.32 (1.38)	42.28 (1.34)	44.72 (3.03)	46.97 (4.72)	0.44/0.00
Steep keratometry†	43.53 (1.44)	43.52 (1.38)	48.60 (3.75)	52.26 (5.42)	0.89/0.00
CCT‡	547.66 (34.59)	543.34 (33.83)	487.14 (35.68)	468.89 (39.03)	0.01/0.00
TP‡	544.26 (34.97)	539.72 (33.66)	479.79 (34.59)	457.10 (42.89)	0.01/0.00
PETP†	4.62 (3.32)	5.51 (3.56)	29.32 (16.29)	46.68 (26.13)	0.14/0.00
Distance†	0.64 (0.29)	0.72 (0.21)	0.74 (0.27)	0.80 (0.32)	0.11/0.22
Volume‡	3.96 (0.25)	3.92 (0.24)	3.56 (0.24)	3.47 (0.24)	0.01/0.00
Differential pachymetry†	3.40 (2.31)	3.62 (1.99)	7.36 (5.65)	11.79 (15.98)	0.53/0.01

*Better eye versus worse eye in the normal group/better eye versus worse eye in the keratoconus group.
†Worse eye is the eye with the highest value.
‡Worse eye is the eye with the lowest value.

between eyes is ~0.50 to 0.75 diopters (D), ~0.33 D in cylinder power,[8] and the mean difference between eyes in CCT (measured by manual ultrasonic pachymetry) is 25 μm.[14]

Keratoconus is a "bilateral" noninflammatory disease[1] that, in the majority of the cases, is asymmetric[2]; the incidence of unilateral keratoconus is 0.5% to 4.5%.[2–6] This asymmetry between keratoconic eyes has been reported previously: the Rabinowitz and MacDonnell criteria for keratoconus included a difference between the right and left central corneal power.[1] According to our results, an intereye asymmetry of 0.75 D in steep keratometry had an AUROC value of 0.92, with 86% sensitivity and 90% specificity, discriminating normal subjects from keratoconic patients.Interestingly, we found that the intereye asymmetry at the posterior elevation (PETP) had a similar AUROC value (0.91), with 85% sensitivity and 88% specificity. Few other reports document asymmetry in keratoconic eyes.[8,9,15] Zadnik et al[8] reported mean differences between keratoconic eyes: spherical equivalent, 3.00 D; cylinder power, 1.50 D; and corneal curvature, 3.5 to 4.0 D.

Today, the use of corneal pachymetry maps and posterior elevation maps is almost mandatory for evaluating refractive surgery candidates and keratoconic patients. Researchers have reported statistically significant differences between normal eyes and keratoconic eyes with respect to parameters such as CCT, TP, PETP, distance, and volume.[13,16–23] Some suggest using these parameters to distinguish between normal eyes and keratoconic eyes.

It is evident from our data that the intereye asymmetry was greater among keratoconic patients than between eyes with normal corneas, in parameters derived from Scheimpflug imaging. The mean intereye asymmetry was statistically significant for all of the variables analyzed when comparing the normal subjects with the keratoconic patients. The mean intereye asymmetry in the normal group in pachymetry at the apex of the cornea was 10.28 μm, and at the TP was 11.04 μm, in accordance with those reported by Khachikian et al,[24] who reported 8.8 and 9.0 μm, respectively. Falavarjani et al[25] reported an intereye asymmetry of 8.42 μm at the TP for normal subjects. In contrast, our results show that the mean intereye asymmetry in the keratoconus group at the apex of the cornea was 25.89 μm and at the TP 30.15 μm. Based on our data, a greater than 26.06-μm difference in the apical thickness between eyes represents <3.8% of the normal population and 36.20% of the keratoconic population. A greater than 27.48-μm difference in the TP between eyes represents <3.8% of the normal population and 39.9% of the keratoconic population. Our results showed that an intereye asymmetry of 10.5 μm in the CCT had 78% sensitivity and 69% specificity, discriminating normal subjects from keratoconic patients.

When evaluating posterior elevation, the mean intereye asymmetry in the normal group at the posterior corneal elevation was 3.75 μm in accordance with 3.62 μm reported by Falavarjani et al,[25] at the maximum posterior elevation; and the mean intereye asymmetry in the keratoconus group

TABLE 3. Efficacy of the Intereye Asymmetry Values Discriminating Between Normal Subjects and Keratoconic Patients

Mean Intereye Asymmetry	AUROC	Cutoff	Sensitivity	Specificity	Standard Error	P
Flat keratometry	0.90	0.65	0.76	0.94	0.024	0.00
Steep keratometry	0.92	0.75	0.86	0.90	0.019	0.00
CCT	0.77	10.50	0.78	0.69	0.038	0.00
TP	0.78	24.50	0.46	0.94	0.037	0.00
PETP	0.91	6.50	0.85	0.88	0.026	0.00
Distance	0.402	0.25	0.316	0.434	0.050	0.04
Volume	0.686	0.1500	0.418	0.849	0.044	0.00
Differential pachymetry	0.666	3.50	0.510	0.868	0.043	0.00

was 20.08 μm. A cutoff value of 6.5 μm in the mean intereye asymmetry at the posterior elevation had an AUROC value of 0.91, with 85% sensitivity and 88% specificity, discriminating these 2 groups. Based on our results, a greater than 9.45-μm difference in the PETP represents <5.7% of the normal population and 66.9% of the keratoconic population.

In the normal subjects, there was no statistically significant difference in the posterior elevation between the better and worse eyes. This could be because this value is modified in abnormal corneas where the posterior surface is affected as it is in keratoconus. In contrast, the mean posterior elevation between eyes with keratoconus was statistically significant; evidence that keratoconus is an asymmetric disease and posterior elevation is modified according to severity of the cone.[26]

Our study does not attempt to establish the diagnosis based in this single metric but suggests that the evaluation of asymmetry in normal subjects and keratoconic patients should not be done only with anterior surface data; it should also include intereye asymmetry concerning pachymetry and posterior elevation data. When evaluating the distance and volume, the mean intereye asymmetry in distance from the TP to the apex of the cornea in the normal group was 0.27 mm and in the keratoconus group 0.22 μm. A greater than 0.61-mm difference in distance represents 0% of the normal population, but it also represents <5% of the keratoconic population. Distance was the only variable that did not show statistically significant difference between the better and worse eyes of the keratoconic patients ($P = 0.22$). The mean intereye asymmetry in volume at 3 mm central in the normal group was 0.07 mm^3, similar to 0.06 mm^3 reported in a previous study,[25] and in the keratoconus group 0.15 mm^3, demonstrating that there is a greater intereye asymmetry in the keratoconus group consistent with the characteristics of keratoconus as a bilateral, asymmetric, slowly progressive disorder in which the cornea has central or paracentral thinning,[1] resulting in asymmetry of the corneal volume.

A potential limitation of this study is that we did not include a group with a large amount of anisometropia. However, the incidence of anisometropia is between 7% and 13%,[27] and this will be the subject of further investigation. This study demonstrates that there is a greater intereye asymmetry in keratoconic patients than in subjects with normal corneas in pachymetry and posterior corneal elevation variables.

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