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Astigmatic Vector Analysis of Posterior Corneal Surface; Healthy versus Keratoconic Corneas

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Short title: Astigmatic Vector Analysis of Posterior Corneal Surface

Abstract

Purpose: To define an unconventional diagnostic factor for keratoconus.

Design: Observational descriptive comparative cross sectional study

Method: This study included two hundred and forty-four eyes of 244 patients divided into groups; normal corneas, or controls (C, n [100]), fruste (FFKc, n [28]) and manifest keratoconus (Kc, n [116]). Full Ophthalmic examination was performed. All candidates were examined using a rotating Scheimpflug corneal tomographer (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany) to obtain corneal measurements. Astigmatic vector analyses were carried out according to the method proposed by Thibos.

Results: The area under receiver operating characteristic curve (AUC) for posterior corneal APV between normal and manifest keratoconus was 0.73 (95% confidence interval): 0.66 - 0.80. By using ROC curve Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy at cutoff 0.30 were (65.0%, 80.0%, 78.9%, 66.1% and 73.1% respectively). As regard posterior corneal Blur; the AUC between normal and manifest keratoconus was 0.92 (95% confidence interval): 0.88 - 0.96. By using ROC curve Sensitivity, Specificity, PPV, NPV and accuracy at cutoff 6.65 were (85.3%, 89.0%, 90.0%, 84.0% and 86.1%) respectively.

Conclusion: Vector analysis of posterior corneal astigmatism; APV and Blur, is a simple, unbiased and complementary way in the differentiation of normal from manifest keratoconus.

Keyword: vector analysis, astigmatism, keratoconus, cornea.

INTRODUCTION:

Keratoconus is characterized by non-inflammatory advancing thinning and steepening resulting in an apical cone-shaped corneal bulging[1-8]. It starts usually within the first or second decade of life, with no sex preference, and advances gradually till the third decade[5,9,10]. Visual acuity deterioration occur in the form of irregular myopic astigmatism[1,11].

Diagnosis of keratoconus depends firstly on the suspicion of the condition and then on precise assessments utilizing different accessible diagnostic tools including slit-lamp biomicroscopy, keratoscopy, pachymetry, and computer-assisted topography[12-16].

Iatrogenic ectasia has been excessively recorded in eyes with subclinical keratoconus that underwent refractive surgery[4,17-19]. This made the detection of keratoconus at early stages of particularly increasing importance to prevent ectasia formation[3,20-26].

The diagnosis of early keratoconus with a corneal shape analyzer including corneal topography or tomography is crucial as slit-lamp microscopy findings may be absent[28-30].

Vectors are mathematical descriptors of the physics of motion which combine values for magnitude and direction[31]. Astigmatism can be considered as a vector with an axis and a magnitude[32]. Full precise analysis of any procedure that targets ameliorating astigmatism would necessitate evaluation of

changes in both axis and magnitude of cylinder, i.e., vectorial character of astigmatism[5].

The aim of this study was to assess the sensitivity and specificity of posterior vector parameters in differentiating normal corneas from keratoconic ones.

PATIANT AND METHOD

This is an observational comparative descriptive cross sectional study conducted at Mansoura ophthalmic center at the period between September 2017 and August 2018. It followed the declaration of Helsinki and was approved by the Institutional Review Board IRB: MS/17.04.151 and the Committee of Ethics at Mansoura University.

Two hundred and forty four eyes of 244 patients attending the Mansoura Ophthalmic Center outpatient clinic were enrolled into this study. Normal corneas or controls (C, n = 100) were compared to keratoconus patients, furthermore categorized into manifest keratoconus (KC, n = 116) and forme fruste (FFKc, n = 28).

Keratoconus diagnosis depended on the characteristic clinical signs, including examination by slit lamp, e.g.: Vogt striae, Fleisher ring, retinoscope; scissoring reflex, distorted ophthalmoscopic red reflex (oil droplet) and evaluation of the corneal topography by Pentacam for KC - suggestive topographic features, such as: corneal steepness higher than 48.00 diopters (D), superior-inferior asymmetry higher than 1.40 D and thinnest pachymetric reading lower than 470 μm.

Forme fruste keratoconus (FFKc) group included the asymptomatic eye of patients with unilateral keratoconus.

To preclude any possible correlation between the eyes of a single participant; one eye was randomly chosen for the normal and keratoconic group, while for the forme fruste group; only the uninfluenced eyes were selected in the study (the fellow eye of a patient with unilateral keratoconus).

Contact lens wear was stopped before assessment. Rigid contact lenses were stopped for at least 3 weeks while soft contact lenses were stopped for only one week.

Corneal measurements were acquired using a rotating Scheimpflug corneal tomographer (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany). Positioning of the participant comfortably at appropriate height. Ask the patient to put his chin on the chin rest, while placing the forehead against the forehead strap with the lateral canthus meeting the marker on the side of the chin rest / forehead apparatus. After blinking a few times, the patient was asked to open both eyes and stare at the blue light with the eye to be measured and not to blink. This ensure good fixation for accurate scans to be obtained. After making appropriate height adjustments, fine adjustments were made to bring the patient's eye to a sharp focus in the center. The joystick was used to gain proper alignment. The automatic release mode starts the scan. 25 single Scheimpflug images is captured for each eye within 2 seconds.

Only patients with Scheimpflug scans of good-quality were selected. Good quality images are labeled ‘‘OK’’ by the device in the ‘‘Examination Quality Specification’’

For each group (Control, manifest Kc, and FFKc), corneal astigmatism values were obtained:

a) Anterior corneal astigmatism

b) Posterior corneal astigmatism

c) For both anterior and posterior surfaces, astigmatism alignment (α) coincides with the steepest meridian of that surface.

Vectorial analyses was carried on as stated by Thibos for both corneal surfaces depending on these equations:

i) Average keratometric reading (M) = $(K_{steep} + K_{flat})/2$

ii) Vector along the 0-degree meridian (J_0) = $[-(K_{steep} - K_{flat})/2] \times \cos 2\alpha$

iii) Vector along the 45-degree meridian (J_{45}) = $[-(K_{steep} - K_{flat})/2] \times \sin 2\alpha$

iv) Astigmatic power vector (APV) = $(J_0^{\,2} + J_{45}^{\,2})^{1/2}$

v) Overall blur vector (Blur) = $(M^2 + J_0^{\,2} + J_{45}^{\,2})^{1/2}$

Microsoft Excel 2013 (version 15.0.5241.1000; part of Microsoft Office Professional Plus 2013) was used to carry out these calculations. IBM SPSS (version 24) for Windows was used to perform the statistical analysis. Descriptive evaluation of data was performed using the mean and median, standard deviation and 95% confidence interval (95% CI). Normality of all data samples was checked by the Shapiro-Wilk test. The Mann-Whitney U test was used for comparisons between

groups. The Spearman correlation coefficient (r) was used to assess the strength of the correlations between pairs of variables. A P value of less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were used to determine the overall predictive accuracy of test parameters, as described by the area under the curve (AUC), to calculate the sensitivity and specificity rates.

RESULTS

Normal or control group (C) included 100 participants; 39 male and 61 female. Keratoconus group included 144 patients furthermore subdivided into 116 manifest keratoconus (KC) group; 43 male and 73 female and 28 forme fruste keratoconus (FFKc) group; 6 male and 22 female. The study groups and their corresponding demographic data are presented in Table 1.

TABLE 1: Demographic Data of the patient enrolled in the study A comparison among healthy, forme fruste, and overt keratoconus corneas

Parameters	Normal N = 100	Keratoconus N = 144		Test of significance
		KC N = 116	FFKc N = 28	
Age				P = 0.1
➢ **(Mean ± SD)**	30.0 ± 9.2	32.2 ± 10.1	28.9 ± 9.7	
➢ **Median**	29	31	29	
(min – max)	(16 – 50)	(16 – 55)	(16 – 52)	
Sex				P = 0.22
➢ **Male**	39 (39%)	43 (37.1%)	6 (21.4%)	
➢ **Female**	61 (61%)	73 (62.9%)	22 (78.6%)	
Family History				P = 0.03*
➢ **Positive**	2 (2%)	13 (11.2%)	2 (7.1%)	
➢ **Negative**	98 (98%)	103 (88.8%)	26 (92.9%)	
Eye				P = 0.44
➢ **Right**	47 (47%)	58 (50%)	17 (60.7%)	
➢ **Left**	53 (53%)	58 (50%)	11 (39.3%)	

C = Control **KC** = manifest keratoconus **FFKc** = Forme Fruste Keratoconus

SD = standard deviation **min** = minimum **max** = maximum

Data expressed as mean ± SD, median (minimum – maximum) or number (%)

***:** significant $p \leq 0.05$

Table 2 compares posterior corneal surface parameters among the study groups. Most of the assessed parameters exhibited a statistically significant difference among the different groups (P value ≤ 0.05) except for the alignment of the steepest meridian (α_{steep}) and vector among J_0 and J_{45} meridians were no statistically significant difference was detected.

TABLE 2: Vector Parameters of the Posterior Corneal surface A comparison among healthy, forme fruste, and overt keratoconus corneas

Parameters	Normal N = 100	Keratoconus N = 144		Test of significance
		KC N = 116	FFKc N = 28	
K_{steep}	- 6.6 ± 0.27	- 7.9 ± 1.02	- 6.8 ± 0.39	**P ≤ 0.001***
(D)	*- 6.6*	*- 7.8*	*- 6.7*	
	[(- 7.3) – (- 5.7)]	*[(-11.4) – (- 6.1)]*	*[(- 7.7) – (- 6.1)]*	
α_{steep}	89.2 ± 15.5	90.5 ± 32.1	98.8 ± 19.3	P = 0.2
(°)	*91.1 (15.4 – 126.3)*	*91.5 (2.6 – 175.1)*	*94 (74.7 – 157)*	
ΔK	- 0.4	- 0.8	- 0.7	**P ≤ 0.001***
(D)	[(- 1.2) – (0.0)]	[(- 3.5) – (0.0)]	[(- 0.9) – (0.0)]	
M	- 6.4 ± 0.26	- 7.5 ± 0.98	- 6.5 ± 0.35	**P ≤ 0.001***
(D)	*- 6.3*	*- 7.2*	*- 6.47*	
	[(- 5.5) – (- 6.9)]	*[(- 5.7) – (- 11.6)]*	*[(- 5.95) – (-7.3)]*	
J_0	- 0.2	- 0.28	- 0.29	P = 0.12
(D)	[(- 0.6) – (0.1)]	[(- 1.75) – (0.9)]	[(- 0.4) – (0.01)]	
J_{45}	- 0.01	- 0.004	- 0.02	P = 0.85
(D)	[(- 0.21) – (- 0.22)]	[(- 0.44) – (0.7)]	[(- 0.2) – (0.15)]	
APV	0.2	0.4	0.32	**P ≤ 0.001***
(D)	(0 – 0.6)	(0 – 1.75)	(0 – 0.45)	
Blur	6.4 ± 0.26	7.49 ± 0.98	6.5 ± 0.35	**P ≤ 0.001***
(D)	*6.35*	*7.3*	*6.3*	
	(5.5 – 6.9)	*(5.8 – 11.6)*	*(5.95 – 7.36)*	

C = Control **KC** = manifest keratoconus **FFKc** = Forme Fruste Keratoconus **K_{steep}** = steepest keratometric reading

ΔK = toricity (the difference between the steepest and the flattest corneal keratometric readings)

M = average keratometric reading **APV** = astigmatic power vector **J_0** = Vector along the 0-degree meridian

Blur = overall blur vector **J_{45}** = Vector along the 45-degree meridian **D** = Diopter

α_{steep} = meridian of the steepest keratometric reading

Data expressed as mean ± SD, median (minimum – maximum) or number (%)

*: significant p ≤ 0.05

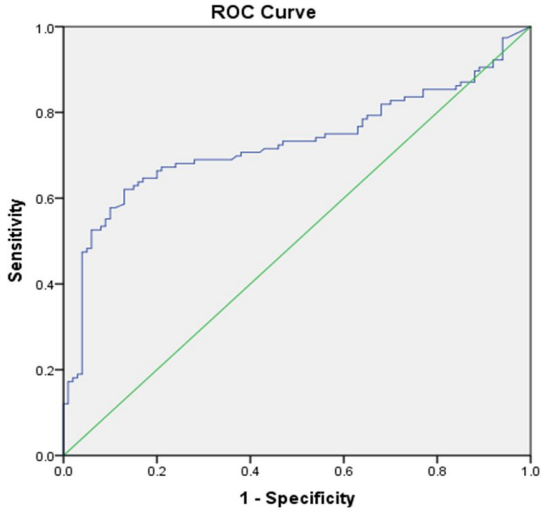

FIGURE 1 Receiver operating characteristic (ROC) curve for posterior corneal APV between Normal and Manifest KC.

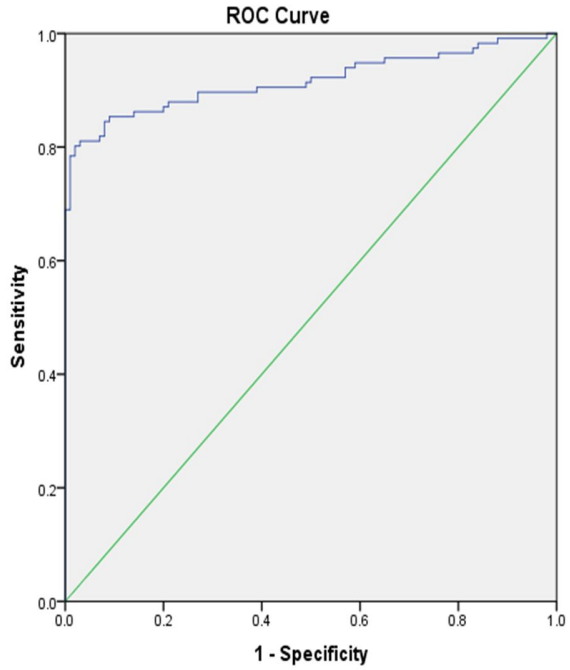

FIGURE 2 Receiver operating characteristic (ROC) curve for posterior corneal Blur between Normal and Manifest KC.

The area under receiver operating characteristic curve (AUC) for posterior corneal APV between normal and manifest keratoconus; shown in Figure 1, was 0.73 (95% confidence interval): 0.66 - 0.80. By using ROC curve Sensitivity, Specificity. PPV, NPV and accuracy at cutoff 0.30 were (65.0%, 80.0%, 78.9%, 66.1% and 73.1% respectively). As regard posterior corneal Blur; the AUC between normal and manifest keratoconus; shown in Figure 2, was 0.92 (95% confidence interval): 0.88 - 0.96. By using ROC curve Sensitivity, Specificity. PPV, NPV and accuracy at cutoff 6.65 were (85.3%, 89.0%, 90.0%, 84.0% and 86.1% respectively).

Vector analysis of the astigmatism of the anterior corneal surface was also conducted for each study group. Results were compared to the posterior astigmatism to evaluate any possible correlation between both surfaces.

Within each group; analysis of non-parametric correlation was carried out between the posterior and anterior astigmatism of the corneal surface. Correlation coefficient values are shown in Table 3.

TABLE 3 Correlation between Vector Parameters of Anterior and Posterior Corneal Surfaces in Control (C), FFCK and Manifest KC groups

Item	r in C group	r in FFKc group	r in KC group
M (D)	- 0.86 [a]	- 0.79 [a]	- 0.95 [a]
J_0 (D)	- 0.85 [b]	- 0.85 [b]	- 0.80 [b]
J_{45} (D)	- 0.72 [b]	- 0.79 [b]	- 0.78 [b]
APV (D)	0.69 [b]	0.89 [b]	0.75 [b]
Blur (D)	0.86 [a]	0.79 [a]	0.95 [a]

C = Control **KC** = manifest keratoconus

FFKc = Forme Fruste Keratoconus

M = average keratometric reading

J_0 = Vector along the 0-degree meridian

J_{45} = Vector along the 45-degree meridian

APV = astigmatic power vector **Blur** = overall blur vector

a: Pearson correlation **b:** Spearman's correlation

r: correlation coefficient **D** = Diopter

Keratoconus group showed constantly elevated values of the correlation coefficient compared to the other two groups. M and Blur parameters recorded respectively, - 0.95 and 0.95. Correlation coefficients were of lower values among the control group corneas with a lowest recorded value of 0.69.

DISCUSSION

The detection of subclinical keratoconus, unfortunately is significantly more complex. It could be considered a very early stage of keratoconus, characterized by normal appearance of the

cornea on the slitlamp. For detecting such cases; the definitive factor is the thorough analysis of corneal topography. There are other complementary techniques that enhance subclinical keratoconus identification, as asphericity, pachymetry, corneal aberrations and biomechanical properties analysis. Vector analysis could be considered another important useful tool for keratoconus detection[32].

Recently, the posterior corneal astigmatism is gaining importance. This is due to both its effect over the total astigmatism and to the alterations that seem to occur at the posterior surface at keratoconic corneas at earliest stages. Recent techniques, as Scheimpflug tomography, are able to assess both corneal surfaces. This permit calculation of many secondary parameters that improve sensitivity and specificity in the detection of keratoconus at earliest stages[18].

Power vectors are considered a way of converting the conventional refractive errors and the keratometric data, into reciprocally independent, orthogonal components, more appropriate for statistical analysis. Vector analysis allow perfect characterization of astigmatism[18].

The present study analyzed the posterior corneal astigmatism. Vector analysis was applied among normal, forme fruste, and manifest keratoconus in a comparative manner.

Neither the patients' age, sex nor eyes (left or right) enrolled in the study presented statistically significant differences between groups, as shown in Table 1.

Comparing vector parameters of the posterior corneal surface between the different study groups; toricity (ΔK) exhibited a statistically significant difference between groups ($P \leq 0.05$) except for the FFKc group compared to the KC group. On the contrary, *(Freitas Gde et al.)* [18] study exhibited a statistically significant difference between groups except for the FFKc group compared to the C group.

As regarding vector along 0 and 45 degree meridians (J_0 and J_{45}) of the posterior corneal surface. Median value of J_0 was – 0.2 for control group, – 0.29 for FFKc and – 0.28 for the KC group with no statistically significant difference among various study groups. Median value of J_{45} was – 0.01 for control group, – 0.02 for FFKc and – 0.004 for the KC group with no statistically significant difference among various study groups. These results were consistent with *(Freitas Gde et al.)* [18] results that showed a median value of J_0 – 0.14 for control group, – 0.12 for FFKc and – 0.12 for the KC group and a median value of J_{45} – 0.01 for control group, – 0.01 for FFKc and 0.00 for the KC group with no statistically significant difference for both J_0 and J_{45} among various study groups.

A regular pattern became evident regarding the APV and Blur of the posterior surface. APV showed a median value of 0.2 for control group, 0.32 for the FFKc group and 0.4 for the KC group. Blur showed a median value of 6.35 for control group, 6.3 for the FFKc group and 7.3 for the KC group. *Freitas Gde et al.* [18] recorded similar results with APV showed a median value of 0.15 for control group, 0.15 for the FFKc group and 0.35 for the KC group. Blur showed a median value of 6.3 for control group, 6.2 for the FFKc group and 6.85 for the KC group.

The current study showed a statistically significant difference between the study groups regarding the APV and Blur (P value was close to zero). These was slightly different from *(Freitas Gde et al.)* [18] study that showed a statistically significant difference between the study groups regarding the APV and Blur (P value was close to zero) except for APV for the control group compared to the FFKc group.

The differences between normal and keratoconic groups were fortunately extremely considerable to the extent that permit obvious discrimination between them, based on posterior M, APV, and Blur analyses.

Moreover, each of these parameters was analyzed using a receiver operating characteristic (ROC) curve and the resulting area under the curve (AUC). Posterior APV and Blur ROC curves exhibited significant AUC: 0.73 and 0.92 respectively. The ROC curve for posterior M exhibited an AUC of 0.62, hence considered insignificant.

The current study showed a statistically significant difference between the study groups regarding the APV and Blur (P value was close to zero). These was slightly different from *(Freitas Gde et al.)* [18] study that showed a statistically significant difference between the study groups regarding the APV and Blur

(P value was close to zero) except for APV for the control group compared to the FFKc group.

According to the present data, any cornea could be virtually considered as keratoconic one, if the posterior APV measured equal to or greater than 0.30 D owing to the test's specificity and sensitivity rates of 80% and 65% respectively with an accuracy of 73.1%. Such rates would result in a PPV of 78.9 and a NPV of 66.1, thus increasing the probability of KC for a positive test and decreasing the probability of KC roughly by the same rate for a negative test.

A posterior Blur cutoff measurement of 6.65 D also defines a cornea as keratoconic (rates of 89.0% and 85.3% for specificity and sensitivity, respectively) with an accuracy of 86.1%. Compared to an APV cutoff value of 0.3 D, a Blur cutoff value of 6.65 D yielded a slightly more powerful differentiating approach.

(Freitas Gde et al.) [18] study showed that any cornea might virtually be considered as keratoconic, if its posterior APV measured equal to or greater than 0.23 D owing to the test's specificity and sensitivity rates of 77% and 81% respectively with an accuracy of 73.1%, while a posterior Blur cutoff measurement of 6.45 D defines a cornea as keratoconic (rates of 72% and 75% for specificity and sensitivity, respectively).

Conclusion

Evaluation of the corneal posterior APV and Blur measurements could represent an unbiased, complementary and amiable method for the ophthalmologist in order to discriminate normal and keratoconic corneas.

According to the present findings, any posterior APV value above 0.3 D or Blur above 6.65 D might raise the ophthalmologist's suspicion toward a likely diagnosis of a keratoconic eye.

DATA AVAILABILITY

All data are included in this article.

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None

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Ethics declarations

Conflict of interest

Sally G. Emarah, Eman Azmy, Walid Abu Samra, Mohammad Khalaf all authors have no conflicts of interest that are directly relevant to the content of this review.

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