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Biomechanical properties of early keratoconus: Suppressed deformation signal wave

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Purpose: To examine the diagnostic validity of different corneal biomechanical parameters for the detection of early keratoconus
Methods: Sixty-one eyes with a diagnosis of early keratoconus and 61 topographically normal eyes were enrolled in the study. All participants underwent testing with the Ocular Response Analyzer (ORA), and 40 indices from each cornea were included in the analysis.
Results: The mean (standard deviation: SD) of keratometry and central corneal thickness in keratoconic corneas was 46.9 (2.5) diopter (D) and 473 (31) μm, respectively. Of the 40 evaluated indices, 32 showed a significant difference between the two groups using *t*-test ($p < 0.05$). According to the results of logistic regression, the indices of height from the lowest to the highest point in peak 2 ($H2^1$) and corneal resistance factor (CRF) with $R^2 = 0.79$ were the best predictors of early keratoconus ($p < 0.001$). $H2^1 \leq 190$ with a sensitivity and specificity of 87% and 91.8%, respectively, and CRF ≤ 8.6 with sensitivity and specificity of 87% and 85.3%, respectively, yielded an overall diagnostic accuracy of 97.3%.
Conclusion: This study results point to the important role of novel waveform-derived indices measured by ORA, along with conventional biomechanical indices, for the early diagnosis of keratoconus. The best predictors of keratoconus in its early stages are $H2^1$ and CRF which showed very high sensitivity and specificity for the detection of early keratoconus.

1. Introduction

Corneal biomechanical examinations consist of the two components of viscosity and elasticity, and they characterize certain corneal properties that are influenced by the structure of the corneal collagen in the stroma [1]. Since about 90% of the corneal thickness is composed of stroma, a strong association between elasticity and corneal thickness is quite expected [2]. However, there are still unknown facts, especially in regard to cases of post-surgical ectasia who had a residual stromal bed (RSB) >250 μm after keratorefractive procedures [3,4]. On the other hand, there have also been cases with RSB less than 250 μm who did not develop any post-operative complications [5,6]. Current protocols for the preoperative evaluation of surgical candidates includes special attention to their corneal topography and thickness. In particular, care is taken to make sure that RSB estimates are accurate when photoablative techniques are used. However, it seems that all these measures cannot guarantee that postoperative ectasia does not develop. Biomechanical properties of the cornea could resolve this ambiguity, and their evaluation, along with corneal topographic and thickness data, may improve surgical safety.

Keratoconus, as an ectatic disorder of the cornea, is of particular interest in studies of corneal biomechanics. In keratoconus, the diameter of collagen fibrils is decreased, and fibril layers, especially in the central cornea, lose their normal orientation. These changes, which can cause corneal deformation, result in the loss of corneal rigidity [7–9]. Common biomechanical indices, namely the CRF and corneal hysteresis (CH), have not shown agreeable levels of sensitivity and specificity for the diagnosis of ectasia. [10–12] However, recent versions of the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Buffalo, NY) software provide data on changes in the corneal shape during applanation in the

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form of 34 indexes which are recommended for the diagnosis of keratoconus eyes and keratoconus suspects.

A number of studies have compared these indices between keratoconus and normal eyes, and some have found that these new waveform-derived biomechanical parameters are more useful than CRF and CH in predicting and detecting early keratoconus [10–12]. This is while some other recent studies suggest that conventional indices, i.e. CRF and CH, are better predictors and perform better in the early diagnosis of keratoconus [13]. They also suggest that even combining these novel indices with conventional factors does not improve their diagnostic ability [13].

In light of the inconsistencies in the literature in this regard, it seemed necessary to conduct further studies. The present study was designed to perform a complete assessment of the diagnostic ability of new waveform-derived and conventional ORA indices for the early and accurate detection of early keratoconus.

2. Materials and methods

In this cross-sectional study, subjects were selected from patients examined at the Cornea Clinic of Noor Eye Hospital (Tehran, Iran) enrolled using a database of patients with normal corneas who were candidates for refractive surgery and a database of cases diagnosed with early keratoconus.

The two groups were similar in terms of age and gender. All participants had complete eye examinations including visual acuity, refraction, retinoscopy, and slit-lamp examination. They also had corneal topography (Pentacam HR, Oculus, Germany), and the diagnosis of early keratoconus was based on the ophthalmologist's interpretation of the four topography and pachymetry maps and the Belin/Ambrósio display along with keratoconus indices based on McMahon criteria.

The inclusion criteria of this study were:

1. A definite diagnosis of keratoconus by an ophthalmologist based on topographic maps and Pentacam numerical data
2. Compatibility with McMahon criteria of mild keratoconus
3. No history of ocular surgery

The inclusion criteria for the control group were:

1. No sign of corneal disease on slit lamp examination
2. No suspicion of keratoconus in corneal topographic maps
3. No history of ocular surgery
4. Match a keratoconus patient in terms of age (±5 years) and gender

The study was approved by the Institutional Review Board of Noor Ophthalmology Research Center. All cases and controls signed informed consents before participation in the study.

All participants were tested twice with the ORA (software version 3.01), and the one with a better waveform score (WS) was recorded.

The ORA applies a dynamic bi-directional applanation process for the assessment of corneal biomechanical properties. A rapid air puff causes the cornea to move backward, past applanation, and into concavity. After the initial applanation, as the air force reduces, the cornea returns from concavity to its normal configuration and passes through a second applanation. Viscous damping in the cornea results in an offset between the backward and forward pressure values. The difference between these motion applanation pressures is the CH which indicates viscous damping in the cornea. CRF is a measure of both the viscous and elastic resistance of the corneal surface [12,14,15].

The new version of the ORA device provides 34 new indices in addition to CRF and CH, which are derived from waveform data.

Table 1 presents the descriptions of the indexes evaluated in this study. Fig. 1 illustrates these indices in the deformation profile of a healthy cornea. In the control group, one eye was randomly selected in each participant. In keratoconus patients, the data of the eye with a diagnosis of mild keratoconus was used for analysis. Independent-samples *t*-test was used to compare the mean values of the indexes between the two groups. To identify the best predictors of early keratoconus, 40 biomechanical indices were evaluated in a stepwise logistic regression model (P removal = 0.05).

3. Results

Sixty one keratoconic patients with a mean (SD) age of 23.9 [4] years and 61 controls with a mean age of 22.1 [7] years were

Table 1
Characterization of corneal deformation signal indices.

Parameter	Description
CRF	Corneal resistance factor
CH	Corneal hysteresis
p1area,p2area	Upper 75% area of peak
p1 area1,p2area1	Upper 50% area of peak
Aspect1, Aspect 2	Aspect ratio of peak height/width
Uslope1, Uslope 2	Rate of increase from 25% point to peak
Uslope11,Uslope21	Rate of increase from 50% point to peak
Dslope1,Dslope2	Rate of increase from peak to 25% point
Dslope11,Dslope21	Rate of increase from peak to 50% point
H1, H2	Height from lowest to highest point in peak
H11, H21	Height from 50% point to highest point in peak
Dive1, Dive2	Backside of down slope of peak (absolute value of peak until the first break)
Mslew1,Mslew2	Maximum single increase in the rise of peak (longest continuous line without a break)
Slew1,Slew2	Aspect ratio of dive1 where dive is divided by width
aplhf	High frequency noise in regions between peaks normalized by product of average of heights*width of region
Bindex	Number of breaks in the peak2
Aindex	Number of breaks in the peak1
TFI	Tear film index
Aspect11, Aspect21	Aspect ratio of peak height/width from 50% point
Path1, Path2	Absolute value of path length around peak
Path11, Path21	Upper 50% of absolute value of path length around peak
W11, W21	Width of peak 1/2 at point of 50% of the base region
w1,w2	Width of peak 1/2 at point of 25% of the base region

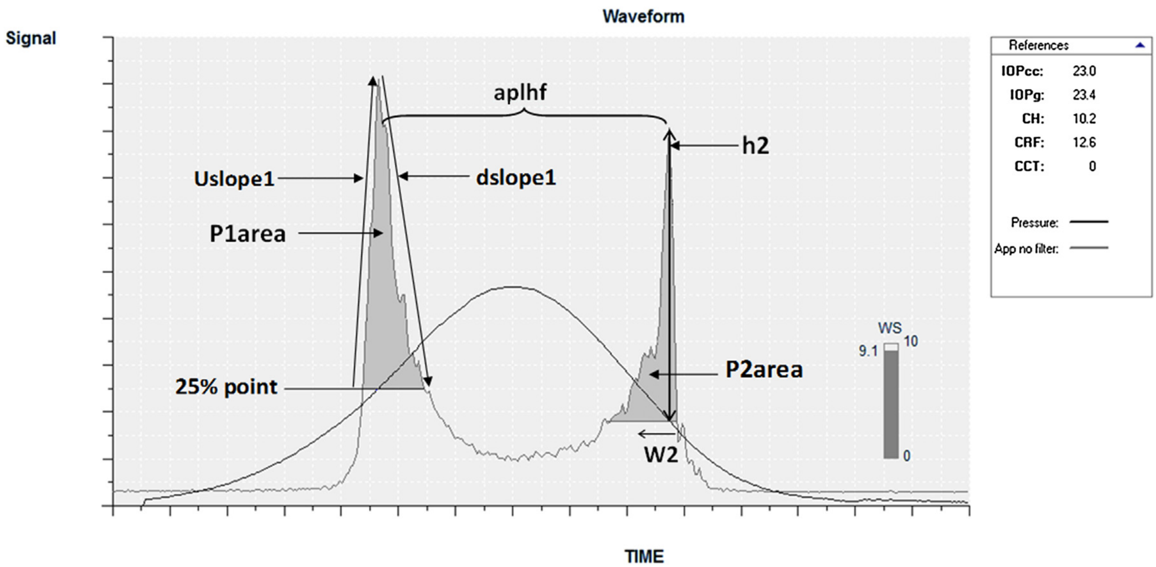

Fig. 1. Illustration of certain parameters measured with the Ocular Response Analyzer.[1]

included in the study (P = 0.106). There was no significant difference in male/female ratio between the two groups (P = 0.705). The mean keratometry and central corneal thickness was 46.9 (2.5) diopters (D) and 473 (31) μm in keratoconic corneas, respectively.

Table 2 shows mean values of ORA indexes in keratoconic and healthy groups. Of the 40 evaluated indexes, 32 showed a significant difference between the two groups in the *t*-tests ($P < 0.05$). According to the results of the logistic regression model, H2[1] and CRF with $R^2 = 0.79$ were the best predictors of early keratoconus ($P < 0.001$). Table 3 presents the cutoff points of these indexes and their diagnostic sensitivity and specificity relative to clinical diagnosis.

4. Discussion

In this study, the sensitivity was examined and specificity of corneal biomechanical indexes for detecting early keratoconus. This evaluation of new ORA indexes showed that H2[1], in addition to CRF, was an efficient index. H2[1], which represents the height from the 50% point to the highest point of the second peak, shows the height of the rebounding signal after decreasing the air puff pressure. This finding somehow shows the increased viscosity of the corneal tissue which is expected in such cases. In addition to this index, CRF shows a significant decrease in keratoconic patients. Although decreased corneal thickness can result in lower CRF, increased viscosity indicates undesirable corneal structural changes which might originate from changes in the corneal tissue [1,16]. This highlights the importance of assessing both the corneal thickness and viscoelasticity in these patients [17]. When combined, CRF and H2[1] indexes offer a sensitivity of 86% and specificity of 100% which can win the trust of surgeons to rely on biomechanical data for differential diagnosis.

Since most studies evaluated CH and CRF, in this study the differences of these indexes were investigated as well [18–20]. Similar to some previous studies, this study showed that CH and CRF were different in keratoconic corneas when compared to

Table 2
values of biomechanic indices in normal and mild keratoconic corneas.

	Mean ± SD		
Parameter	Normal eyes	keratoconus	Pvalue
H21	227 ± 33	105 ± 57	<0.001
H2	340 ± 49	157 ± 85	<0.001
CRF	10.85 ± 2.5	6.84 ± 1.6	<0.001
P2area	2804 ± 671	1339 ± 712	<0.001
Dive2	279 ± 76	100 ± 64	<0.001
Bindex	9.53 ± 0.5	6.45 ± 2.8	<0.001
CH	10.24 ± 2.3	7.53 ± 1.6	<0.001
Aindex	9.26 ± 1.0	6.37 ± 2.8	<0.001
P2area1	1206 ± 323	568 ± 354	<0.001
Aspect2	17.76 ± 4.5	7.87 ± 5.9	<0.001
Dslope2	23.73 ± 6.3	10.45 ± 8.2	<0.001
H11	278 ± 47	196 ± 67	<0.001
H1	417 ± 70	295 ± 101	<0.001
Aspect21	23.92 ± 7.2	11.18 ± 7.5	<0.001
P1area	3883 ± 819	2565 ± 953	<0.001
Dslope21	37 ± 14	17 ± 11	<0.001
P1area1	1700 ± 397	1100 ± 427	<0.001
Uslope21	66 ± 25	30 ± 21	<0.001
Uslope2	77.62 ± 28.8	34.92 ± 26.4	<0.001
Slew2	77 ± 29	36 ± 25	<0.001
aplhf	1.27 ± 0.2	1.92 ± 0.8	<0.001
Mslew2	121 ± 31	64 ± 44	<0.001
Dive1	349 ± 100	211 ± 123	<0.001
Mslew1	122 ± 31	94 ± 30	0.002
W2	19.94 ± 3.8	23.50 ± 6.6	0.001
Uslope1	78 ± 27	56 ± 34	0.004
Uslope11	68 ± 28	48 ± 30	0.007
Path1	21.35 ± 3.5	25.21 ± 7.7	0.008
Slew1	77 ± 28	58 ± 34	0.014
Aspect1	19.89 ± 4.6	16.35 ± 11.4	0.016
Aspect11	25.21 ± 7.4	21.30 ± 11.6	0.021
Dslope1	27.89 ± 7.1	23.47 ± 16.5	0.032
W21	10.07 ± 2.3	10.75 ± 3.4	0.092
Path11	29 ± 6	33 ± 9	0.114
Path21	34 ± 9	38 ± 9	0.173
Dslope11	41 ± 16	37 ± 20	0.200
TFI	4.65 ± 3.4	3.82 ± 3.1	0.213
Path2	23.62 ± 5.35	25.16 ± 5.5	0.439
W11	11.60 ± 2.4	10.81 ± 3.6	0.549
W1	21.46 ± 3.1	21.31 ± 5.9	0.840

Parameters are sorted by most absolute difference they make between keratoconus vs. healthy corneas from up to down.

[1] *In this figure, unnecessary repetition of same parameters at both signal peaks has been avoided. Furthermore, indices which need to be calculated are not illustrated here (e.g. Mslew, slew, etc).

Table 3
Cut off points of ORA indices for detection of mild keratoconus cases.

	Cut off	Sensitivity (%)	Specificity (%)	Correctly classified (%)	AUC
$H2^1$	<= 190	87	91.8	90.8	0.94
CRF	<= 8.6	87	85.3	86.0	0.92
Total		86	100	97.3	0.98

AUC: Area Under Curve.

healthy corneas [21,22], while only CRF remained among the predictor variables of the model with an acceptable sensitivity and specificity. Due to their overlap in keratoconic and healthy corneas in previous studies, they did not provide acceptable diagnostic efficiency, although CRF is a better index for detecting keratoconus when compared to CH [17]. In line with these findings, Mikielewicz et al. reported that CRF was the best index for detecting mild keratoconus [23]. Given how CRF is calculated and influenced by corneal thickness, CRF is expected to be a better predictor in comparison with CH. Some studies have even stated that CH and CRF are not different between early keratoconus and normal corneas [24]. The point is that these two indexes have little diagnostic accuracy and validity per se, and other parameters are required to increase the diagnostic sensitivity and specificity.

This data showed that $H2^1$ was an appropriate index for differentiating cases of mild keratoconus from healthy cases. Mikielewicz et al. evaluated biomechanical changes of the cornea after corneal cross-linking, and reported that CRF and p2area (upper 75% area of peak 2) were correlated with the severity of keratoconus [23]. Luz et al. also reported better predictive performance for keratoconus with the p2area index [12]. As shown in Fig. 1, it is clear that the area under the curve in rebound (p2area) is correlated with the height of the applanation signal (H2). According to Table 2, p2area was also among the variables that showed a significant difference between the two groups in this study. Therefore, all three studies share the emphasis on the importance of the height of the second peak. Although it has been empirically mentioned that the applanation signal graph is suppressed in keratoconic cases [25], it was quantitatively confirmed in this study with $H2^1$.

In addition to a decrease in the curve height in keratoconic patients, a wider pressure curve was observed (Fig. 2). These

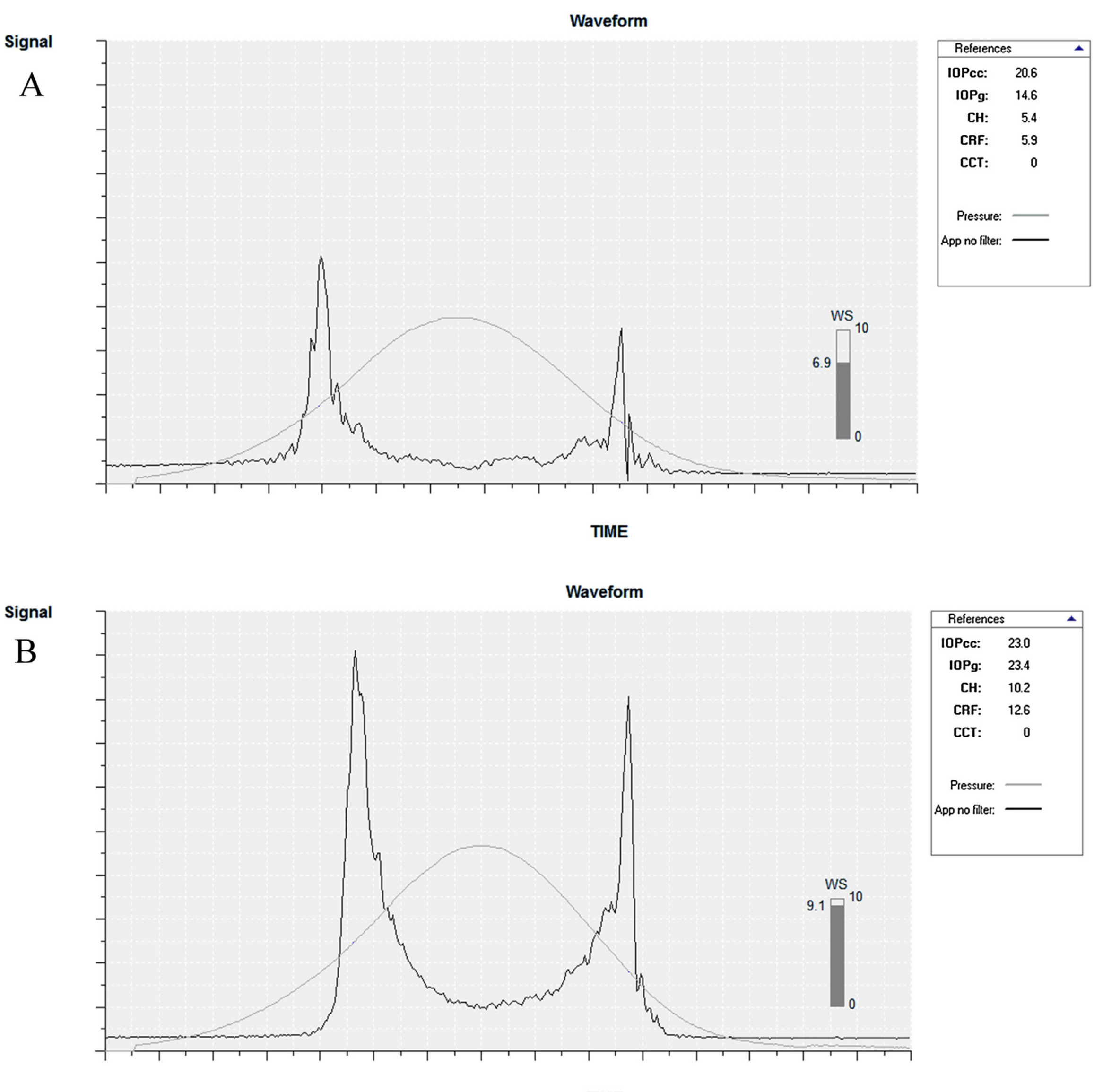

Fig. 2. The waveform in a keratoconus patient (A) and a normal eye (B).

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changes, which are observed in the horizontal axis of time, are reflected in the aphlf index. According to Table 2, this index was significantly higher in keratoconic versus healthy corneas. A review of the variables in Table 2, which are sorted by the absolute inter-group difference, shows that peak 2 parameters showed far more differences between the two groups. This data clearly indicates delayed return to the baseline configuration in keratoconic versus healthy corneas. Moreover, the signal intensity is less than healthy corneas at the time of rebound, as discussed above. This is in line with decreased corneal elasticity in these patients.

Wolffsohn et al. [26] evaluated all ORA indexes to determine keratoconus severity and reported that dive1 (the backside of the down slope of peak 1), slew2 (the aspect ratio of dive1 where dive is divided by width) and path1 (the absolute value of the path length around peak 1) along with keratometry and central corneal thickness were efficient in keratoconus grading with a sensitivity and specificity of 93%. However, the mean age of the participants should be considered when comparing the results of the two studies; it seems that in patients evaluated by Wolffsohn et al. [26] (mean age of 36 years) keratoconus was more severe than the patients of this study (mean age of 24 years). Moreover, patients were evaluated with mild keratoconus; therefore, inter-study differences should not be interpreted as inconsistencies, but rather complementary results. In other words, CRF and H2[1]are important indexes for diagnosis in the early stages, while in more advanced stages, indexes like dive1, slew2, and path1 can determine the trend of keratoconus progression. Displaying the values of such indexes in routine reports of corneal biomechanical examinations and their use in artificial intelligence diagnostic systems would better demonstrate their clinical value.

In conclusion, the findings of this study highlighted the importance of the height of the applanation signal curve and CRF $\leq$ 8.6 among different corneal deformation signal parameters. These parameters can help identify corneas with no suspicious evidence in topographic and central thickness examinations, but are likely to develop post-LASIK ectasia, and therefore, can play an important role in completing the work-up before refractive surgery. Further longitudinal studies on refractive surgery candidates are required to present more accurate cutoff points for these parameters.

Conflict of interest

No conflicting relationship exists for any author.

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