Best waveform score for diagnosing keratoconus

Técnica para diagnosticar o ceratocone

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Abstract

Purpose: To test whether corneal hysteresis (CH) and corneal resistance factor (CRF) can discriminate between keratoconus and normal eyes and to evaluate whether the averages of two consecutive measurements perform differently from the one with the best waveform score (WS) for diagnosing keratoconus. **Methods:** ORA measurements for one eye per individual were selected randomly from 53 normal patients and from 27 patients with keratoconus. Two groups were considered the average (CH-Avg, CRF-Avg) and best waveform score (CH-WS, CRF-WS) groups. The Mann–Whitney U-test was used to evaluate whether the variables had similar distributions in the Normal and Keratoconus groups. Receiver operating characteristics (ROC) curves were calculated for each parameter to assess the efficacy for diagnosing keratoconus and the same obtained for each variable were compared pairwise using the Hanley–McNeil test. **Results:** The CH-Avg, CRF-Avg, CH-WS and CRF-WS differed significantly between the normal and keratoconus groups (p<0.001). The areas under the ROC curve (AUROC) for CH-Avg, CRF-Avg, CH-WS, and CRF-WS were 0.824, 0.873, 0.891, and 0.931, respectively. CH-WS and CRF-WS had significantly better AUROCs than CH-Avg and CRF-Avg, respectively (p=0.001 and 0.002). **Conclusion:** The analysis of the biomechanical properties of the cornea through the ORA method has proved to be an important aid in the diagnosis of keratoconus, regardless of the method used. The best waveform score (WS) measurements were superior to the average of consecutive ORA measurements for diagnosing keratoconus.

Keywords: Cornea/physiopathology; Keratoconus/diagnosis; Biomechanics/physiology; Dilatation, pathologic; Diagnostic techniques, ophthalmologic

Resumo

Objetivo: Testar se a histerese corneana (CH) e o fator de resistência corneano (CRF) podem discriminar olhos com ceratocone e avaliar se a média de duas medidas consecutivas apresenta desempenho diferente da medida única com a melhor *waveform score* para diagnósticar o ceratocone. **Métodos**: Foram realizadas medidas do ORA de um olho por indivíduo, selecionados aleatoriamente a partir de 53 pacientes normais e de 27 pacientes com ceratocone. Dois grupos foram considerados: a média (CH-médio, o CRF-médio) e melhor *waveform score* (CH-WS, CRF-WS). O teste de *Mann-Whitney U-teste* foi utilizado para avaliar se as variáveis apresentaram distribuições semelhantes entre os grupos. As curvas (ROC) foram calculadas para cada parâmetro para avaliar eficácia no diagnóstico e as obtidas para cada variável foram comparadas usando o teste de *Hanley-McNeil*. **Resultados**: CH-médio, CRF-médio, CH-WS e CRF-WS diferiram significativamente entre os grupos (p<0,001). Já as áreas sob a curva ROC para CH-médio, CRF-médio, CH-WS, e CRF-WS foram 0,824, 0,873, 0,891, 0,931, respectivamente. CH-WS e CRF-WS obtiveram AUROCs significativamente melhores do que CH-médio e CRF-médio (p=0,001 e 0,002). **Conclusão**: A análise das propriedades biomecânicas da córnea através do ORA demonstrou ser um método auxiliar importante no diagnóstico de ceratocone, independente do método utilizado. As melhores medidas *waveform score* foram superiores à média das medições consecutivas para o diagnóstico de ceratocone.

Descritores: Córnea/fisiopatologia; Ceratocone/diagnóstico; Biomecânica/fisiologia; Dilatação patológica; Técnicas de diagnóstico oftalmológico

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Introduction

Keratoconus is a non-inflammatory condition of unknown etiology affecting the central cornea and is characterized by thinning and ectasia of the cornea [1]. Keratoconus generally starts at puberty and progresses until the third or fourth decade of life [2], after which it usually stabilizes.

Keratoconus eyes are more elastic and less rigid than normal eyes. One measure of ocular rigidity is hysteresis [3]. Biomechanical metrics (corneal hysteresis and corneal resistance factor) may be useful when determining corneal stiffness by indicating 'more fragile' tissue [4].

The ocular response analyzer (ORA; Reichert Technologies, Depew, New York) was launched as the first commercial device claiming to provide *in vivo* measurements of corneal biomechanics [5]. It utilizes a dynamic bi-directional applanation process in which two applanation pressure measurements are recorded: the first, while the cornea is moving inward (P1); and the second, while the cornea returns [6].

Recently, a new version of the software (version 2.04) has incorporated an index called the waveform score on a scale of 0 to 10. The higher the number, the more reliable the measurement data will be [7].

We tested whether corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated intraocular pressure (IOPg) and corneal compensated intraocular pressure (IOPcc), determined using the ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY) could discriminate between keratoconus and normal eyes and evaluated whether the averages of two consecutive measurements were better than the measurement with the best waveform score for diagnosing keratoconus.

Methods

The study was a retrospective comparative case series. One eye from each individual was selected randomly from 53 patients with normal corneas and 27 patients with bilateral keratoconus. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Universidade Federal de São Paulo, Brazil (protocol 1210/10).

Patients examined at the Instituto de Olhos Renato Ambrósio (Rio de Janeiro, Brazil) were enrolled retrospectively from a database of candidates for refractive surgery with normal corneas and one of individuals diagnosed with keratoconus in both eyes. Two groups were formed: average (CH-Avg, CRF-Avg, IOPg-Avg, and IOPcc-Avg) and best waveform signal (CH-WS, CRF-WS, IOPg-WS, and IOPcc-WS).

All eyes were examined by a refractive surgeon (R.A.). Along with a comprehensive ocular examination, all eyes were examined using Placido-disk–based corneal topography (Atlas Corneal Topography System; Humphrey, San Leandro, CA) and rotating Scheimpflug corneal tomography (Pentacam HR, Oculus, Wetzlar, Germany). The diagnosis of keratoconus was based on clinical data, including Placido disk-based axial topography corneal curvature maps and Pentacam corneal tomography[8] criteria used in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study [9]. Keratoconus cases with a history of corneal surgery or extensive corneal scarring were excluded from the study.

All patients underwent a clinical evaluation and testing with the ORA during the same visit. All measurements were obtained between 8 AM and 6 PM. The average of two consecutive measurements was determined. Additionally, the measurement with the best waveform score (WS) was selected for analysis.

An ORA determines corneal biomechanical properties using an applied force-displacement relationship; the details have been described previously [10-12].Briefly, a precisely-metered air pulse is delivered to the eye, causing the cornea to move inward, past applanation, and into slight concavity. Milliseconds after the initial applanation, the air pump generating the air pulse is shut off and the pressure applied to the eye decreases in an inverse-time, symmetrical fashion. As the pressure decreases, the cornea passes through a second applanated state while returning from concavity to its normal convex curvature. Energy absorption during rapid corneal deformation delays the occurrence of the inward and outward applanation signal peaks, resulting in a difference between the applanation pressures. The difference between these inward and outward motion applanation pressures is the CH and is an indication of viscous damping in the cornea, reflecting the capacity of corneal tissue to absorb and dissipate energy. The corneal resistance factor is a measure of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface; it is an indicator of the overall resistance of the cornea. The CRF was derived empirically to maximize the correlation with the central corneal thickness [13] and it can be considered to be weighted by the elastic resistance because of its stronger correlation with the central corneal thickness than with CH. Although CH and CRF are related, they can differ significantly in some instances, and each provides distinct information about the cornea.

A graphic representation of the corneal response after each ORA measurement is displayed. The manufacturer defines good-quality measurements as both push-in and bounce-back signal peaks on the ORA waveform being fairly symmetrical in height. The best Waveform Score represents the most perfect signal which intended to give clinicians some guideline to the reliability of the measured.

BioEstat 5.0 (Instituto Mamirauá, Amazonas, Brazil) and MedCalc 11.1 (MedCalc Software, Mariakerke, Belgium) were used for the statistical analyses. The non-parametric Mann–Whitney *U*-test (Wilcoxon rank-sum test) was used to assess whether the variables had different distributions between the keratoconic and normal eye groups.

Receiver operating characteristic (ROC) curves were calculated for all parameters to determine the test's overall predictive accuracy (area under the curve or AUROC). The standard error of the AUROC was assessed using the DeLong method[14]. The binomial exact method was used to calculate the confidence interval (CI) for the AUROC. Nonparametric pairwise comparisons of the ROC curves were performed to test whether significant differences were present between the areas for each parameter using the Hanley–McNeil method for calculating the standard error [15]. A p-value <0.05 was considered statistically significant.

Results

Single eyes selected randomly from 53 patients with normal eyes and 27 patients with bilateral keratoconus were analyzed. The average patient age was 34.2±15.7 (range 15-80) and 25.3±07.8 (range 10-42) years, and the male/female ratio was 41.6/58.4 and 63.0/37.0 in the normal and keratoconic groups, respectively.

Table 1

ORA parameters measured in normal and keratoconic eyes

	Normal				Keratoconus				
	Mean	SD	Max	Min	Mean	SD	Max	Min	*p*-value
CH Ave	10.58	2.00	15.00	5.85	8.43	1.43	11.55	4.55	<0.0001
CH WS	10.88	1.95	15.90	6.40	8.20	1.40	10.30	4.20	<0.0001
CRF Ave	10.45	2.29	16.05	4.35	7.31	1.58	10.60	4.80	<0.0001
CRF WS	10.76	2.16	16.80	5.70	7.01	1.54	10.70	4.60	<0.0001
IOPg Ave	15.60	3.65	20.25	9.70	10.79	2.91	17.10	6.70	<0.0001
IOPg WS	15.29	3.79	24.00	9.30	10.42	2.67	16.70	6.20	<0.0001
IOPccAve	16.06	4.30	35.85	8.60	14.07	2.79	22.10	10.30	0.015
IOPccWS	15.27	3.58	23.10	7.40	14.00	2.55	21.20	10.30	0.071

Table 2

Data summary from receiver operating characteristic curves of pentacam parameters in normal and keratoconic eyes

	Cutoff	AUC	Sensitivity	Specificity	SE	95%CI	p-value
CH Ave	8.8	0.824	74.07	84.91	0.0456	0.723 to 0.900	<0.0001
CHWS	9.7	0.891	92.59	71.7	0.0353	0.801 to 0.950	<0.0001
CRF Ave	8.4	0.873	81.48	90.57	0.0383	0.780 to 0.937	<0.0001
CRF WS	8.2	0.931	81.42	92.45	0.0275	0.852 to 0.976	<0.0001
IOPg Ave	11.7	0.861	77.78	94.34	0.0403	0.765 to 0.928	<0.0001
IOPg WS	11.1	0.86	66.67	90.57	0.0405	0.764 to 0.927	<0.0001
IOPcc Ave	14.8	0.683	77.78	64.15	0.0643	0.569 to 0.782	0.0045
IOPcc WS	14.1	0.646	66.67	69.81	0.0637	0.532 to 0.750	0.0215

Table 3

Pairwise comparison of ROC curve

	CH WS	CRF Ave	CRF WS	IOPg Ave	IOPg WS
CH Ave	0.001	0.079	0.001	0.524	0.525
CH WS	-	0.516	0.057	0.560	0.528
CRF Ave	-	-	0.002	0.767	0.730
CRF WS	-	-	-	0.066	0.044
IOP g Ave	-	-	-	-	0.935

Significant differences were observed between normal and keratoconus eyes for all parameters except the IOPcc (p=0.071) (table 1).

Table 2 summarizes the best cutoff with optimal sensitivity and specificity for diagnosing keratoconus, AUROC, standard error, 95% CI, and significance level for each parameter tested. The AUROC of CRF-WS was 0.931 and CH-WS was 0.891. The AUROC of CRF-Avg and CH-Avg was 0.873 and 0.824, respectively. The corneal compensated intraocular pressure (IOPcc-WS and IOPcc-Avg) had the worst AUROC (0.646 and 0.683).

The pairwise comparison of the ROC curves of all parameters tested (table 3) revealed that CH-WS and CRF-WS differed statistically from CH-Avg and CRF-Avg (0.001 and 0.002), respectively. No significant differences were observed between the ROC curves obtained from CH-WS and CRF-WS (0.057).

In figure 1, the combined receiver operating curves for CH-WS, CH-Avg, CRF-WS, CRF-Avg, IOPg-WS, and IOPg-Avg reveal that CRF-WS had the best AUROC (0.931). Figures 2 and 3 present the ROC curves for CH-WS and CH-Avg and CRF-WS and CRF-Avg, respectively.

The best parameter identified was CRF-WS, which had an AUROC of 0.931 (95%CI 0.852-0.976). The sensitivity and specificity was 81.48 and 92.45, respectively, with the best cutoff of 8.2mmHg. Nevertheless, normal and keratoconus groups overlapped using CRF-WS (figure 4).

Discussion

This study evaluated a novel way to use the pressure parameters of the ocular responsive analyzer. Best waveform parameters were compared with the mean of two consecutive measurements.This is the first study that compares biomechanical data of the average of two consecutive measurements and data obtained from a single measurement the best waveform score.

To obtain representative findings, investigators obtain several readings to generate anaverage result for analysis. Previous investigators took two readings [16-17], three readings [18-19],

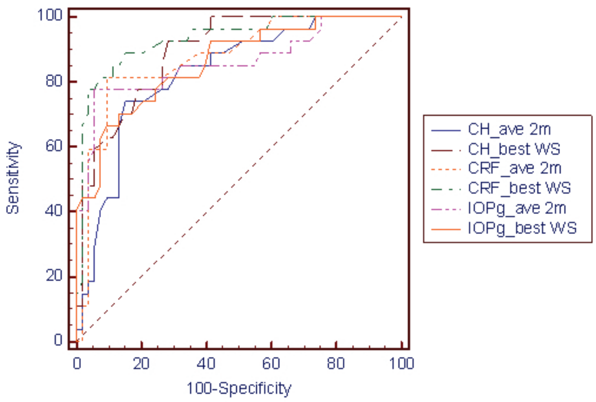

Figure 1: Combined receiver operating curves for CH -Ave, CH-WS, CRF-Ave, CRF-WS, IOPg-Ave and IOPg-WS

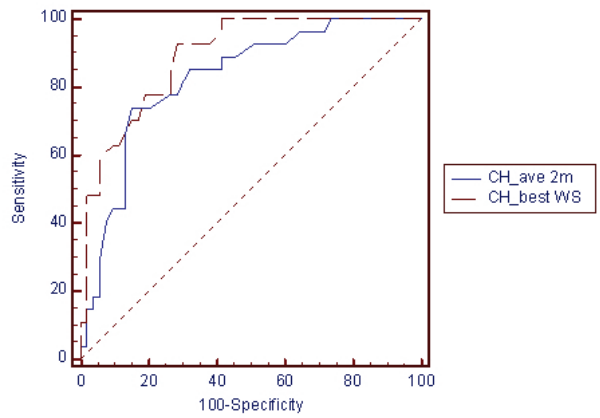

Figure 2: Combined receiver operating curves for CH-Ave and CH-WS

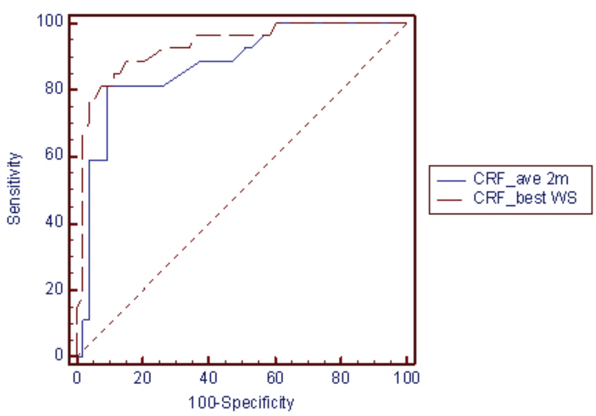

Figure 3: Combined receiver operating curves for CRF-Ave and CRF-WS

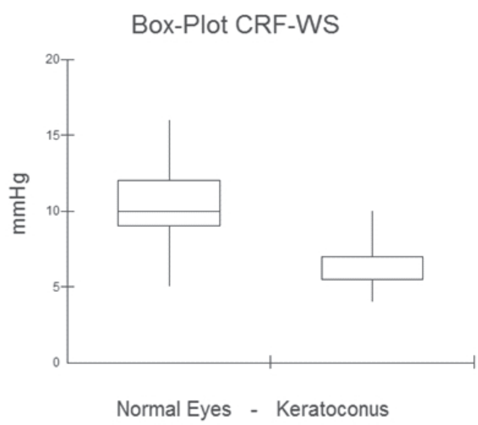

Figure 4: Normal and keratoconus groups overlapped using CRF-WS

and four readings [20-23] in their experimental protocols.

Is it worth use the average of two, three or four consecutive measurements if you can be used to measure the best score? The best waveform score refers to good-quality measurement was judged by the practitioner in terms of the waveform and symmetrical peaks and magnitude of good and the higher score, the more reliable the measurement date should be.

A previous study showed that ORA parameters were statistically similar whether we took the average from four measurement or just considered the best score waveform data [7]. In spite of that study recommend the use of three consecutive measures; it has been limited only to healthy young chinese patients while our study compared two populations - normal and keratoconus - finding greater sensitivity and specificity in separating groups of data from the best waveform score.

Accurate ORA measurement is crucial to determine the best waveform signal of pressure parameters (CH, CRF, IOPg, and IOPcc). At the beginning of the ORA measurement, the device carefully aligns the cornea automatically. This alignment is crucial to produce the maximum signal on the infrared detector during applanation. Closer examination of the signal morphology provides clues about the biomechanical behavior of the cornea. The width of the infrared signal peaks represents the speed at which the cornea is deforming. A wide spike indicates slow movement, while a narrow spike means that the cornea moved through applanation quickly. The amplitude of the peaks is a function of how much light hits the infrared detector during each applanation event. If the applanation area is large, the peak amplitude will be large; if it is small, the peak amplitude will be small. The timing of the spikes indicates when the applanation events occurred within the 25-millisecond measurement [24].

The ORA pressure parameters had significantly lower mean values in keratoconus compared to normal eyes, supporting the results of previous studies [25-26]. CH, CRF, and IOPg exhibited significantly different distributions in normal and keratoconic eyes (Mann–Whitney *U*-test, $p<0.0001$) in the analysis of the waveform signal and mean of consecutive measurements. Nevertheless, an overlap was observed. Receiver operating characteristic curves were calculated for all parameters. The areas under the curve of CH-WS and CRF-WS were statistically higher than in CH-Avg and CRF-Avg.

The pairwise comparison of the area under the curve of CRF-WS was statistically better than CRF-Avg ($p<0.001$). The best parameters were CRF-WS and CH-WS, with cutoffs of 8.2 and 9.7mmHg, respectively. CH and CRF values from the measurement with the best WS were superior to the average of consecutive ORA measurements for diagnosing keratoconus. The groups still overlapped significantly.

Conclusion

In conclusion, either through consecutive measurements or using a single measure best waveform score, the biomechanical data (CH and CRF) could be significantly different in normal and keratoconus groups. Have been observed greater accuracy in separating groups with best waveform score.

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