# Ocular Response Analyzer Measurements in Keratoconus With Normal Central Corneal Thickness Compared With Matched Normal Control Eyes

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## ABSTRACT

**PURPOSE:** To compare corneal hysteresis (CH) and corneal resistance factor (CRF) in eyes with keratoconus with a central corneal thickness (CCT) ⩾520 μm with CH and CRF in matched controls, and to estimate the sensitivity and specificity of these parameters for discriminating between the two groups.

**METHODS:** This prospective, comparative case series comprised 19 eyes of 19 patients with keratoconus with CCT ⩾520 μm and 19 eyes of 19 healthy sex-, age-, and CCT-matched patients who underwent a complete clinical eye examination, corneal topography, tomography, and biomechanical evaluation. The receiver operating characteristic (ROC) curve was used to identify cutoff points that maximized the sensitivity and specificity for discriminating between groups.

**RESULTS:** Central corneal thickness was 543.1±13.9 μm (range: 520 to 568 μm) in the keratoconus group and 545±12.5 μm (range: 527 to 575 μm) in the control group ($P$=.6017). Corneal hysteresis was 9.22±1.44 mmHg (range: 6.2 to 11.35 mmHg) in the keratoconus group and 10.58±1.91 mmHg (range: 7.34 to 13.53 mmHg) in the control group ($P$=.0075). Corneal resistance factor was 8.62±1.52 mmHg (range: 5.60 to 11.20 mmHg) in the keratoconus group and 10.30±1.92 mmHg (range: 6.95 to 14.12 mmHg) in the control group ($P$=.0049). The ROC curve analyses showed a poor overall predictive accuracy of CH (cutoff, 9.90 mmHg; sensitivity, 78.9%; specificity, 63.2%; test accuracy, 71.05%) and CRF (cutoff, 8.90 mmHg; sensitivity, 68.4%; specificity, 78.9%; test accuracy, 73.65%) for detecting keratoconus in the eyes studied.

**CONCLUSIONS:** Corneal hysteresis and CRF were statistically lower in the keratoconus group compared with the control group. Given the large overlap, both CH and CRF had low sensitivity and specificity for discriminating between groups. [*J Refract Surg.* 2010;xx(x):xxx-xxx.] doi:10.3928/1081597X-20100415-02


Corneal thickness is not only an indicator of endothelial function, but also is considered a biometric entity.[1,2] Its biologic variability in healthy eyes is believed to result from different amounts of collagen fibrils and interfibrillary substance in the corneal stroma.[3,4] Therefore, it is a measure of tissue mass and possibly a good estimator of corneal biomechanical parameters such as rigidity.[3]

As expected, tomographic studies show that the corneal volume is reduced in eyes with keratoconus,[5-10] as keratoconic eyes generally present with corneal thinning and reduced tissue mass.[10-17] Similarly, reduced corneal thickness and volume are found in patients undergoing ablative corneal refractive surgery with an excimer laser, reflecting the redistribution and loss of corneal tissue.[18-22]

Healthy patients can present with thin corneas (⩽500 μm), and keratoconic eyes can have a "normal" (⩾520 μm) central corneal thickness (CCT).[1,3,23-25] In addition, corneal biomechanical metrics (ie, corneal hysteresis [CH] and corneal resistance factor [CRF]) have shown disparity in different age groups, among diabetics, and with diverse ocular pathologies.[26-41] Therefore, corneal rigidity and resistance to deformation are likely affected by unknown factors in addition to corneal thickness.[42]

The development of a test for "pre-clinical" keratoconus diagnosis, with greater accuracy than corneal mapping and clinical examination, would be of importance when considering refractive surgery.[6,12-14,16,18,21,43-46]

In vivo measurement of corneal resistance to deforma-

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tion was enabled by the development of the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY) by Luce.[47] The ORA determines corneal biomechanical properties (CH and CRF) using an applied force-displacement relationship.[48,49]

In a previous study,[37] our group found a strong direct association between corneal biomechanical metrics and CCT, an inverse relation with older age, and higher values in females in a population of healthy individuals. Many other studies by different investigators[39,47,50-52] have found lower values for keratoconic eyes, but none used controls that were matched using known variables. Therefore, we investigated the corneal biomechanical metrics in a population of eyes with keratoconus with "normal" central corneal thickness (≥520 µm) with age-, sex-, and CCT-matched healthy controls.

## PATIENTS AND METHODS

A prospective, comparative case series design was used. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Federal University of Sao Paulo, Brazil (protocol 0123/06). Study participants were informed of the purpose of the study, and all gave informed consent before inclusion.

Patients underwent a comprehensive ophthalmologic examination, including a review of their medical history, corrected visual acuity, slit-lamp microscopy, funduscopic examination, Placido disk topography (Humphrey ATLAS; Carl Zeiss Meditec, Dublin, Calif), Pentacam tomographic evaluation (Oculus Optikgeräte GmbH, Wetzlar, Germany), and ORA measurements.

Diagnosis of keratoconus was made by clinical (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[6,10,11,13,43,53,54]).

Keratoconic eyes with CCT ≥520 µm were matched with healthy controls according to CCT (±8 µm), age (±2 years), and sex. Only 1 eye per patient was considered. For analysis, CCT was used instead of the thinnest point (given by the Pentacam) because the air-jet delivered by the ORA is directed at the corneal center. In addition, a CCT match of ±8 µm was chosen based on the work by Khachikian et al,[2] which showed that the average pachymetric difference between fellow healthy eyes was 8.8±7.2 µm at the corneal apex and 8.9±8.3 µm at the pupil center. Patients were divided in two groups for data comparison: the keratoconus group and healthy-eye control group.

Exclusion criteria were age <18 years, previous corneal or ocular surgery, eye disease other than keratoconus (especially endothelial dysfunction or dystrophy), chronic or continuous use of topical medications, corneal scars or opacities, and refusal to sign informed consent. Contact lenses had to be removed at least 72 hours before the examination.

Patients underwent testing with the ORA, corneal topography, and Pentacam during the same visit. All measurements were made between 8 AM and 6 PM. Two consecutive ORA measurements were made (only good-quality readings, as defined by the manufacturer, were stored), and the results were averaged. Central corneal thickness was determined using the Pentacam rotating Scheimpflug camera.

Previously, we published a detailed description of the Pentacam system,[37] as have other investigators.[7,8,10,17,20,55,56] Briefly, a rotating camera is set to take 25 slit images of the anterior eye segment in approximately 2 seconds with 500 true elevation points incorporated in each slit image. Central corneal thickness is measured in each of the single images of a scan giving accurate, repeatable, and reproducible measurements.

Details of the ORA have been described extensively.* 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. The energy absorbed during the 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 corneal hysteresis and is an indication of viscous damping in the cornea, reflecting the capacity of corneal tissue to absorb and dissipate energy. 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 CCT,[63] and it can be considered as weighted by the elastic resistance because of its stronger correlation with the CCT than with CH. Although CH and CRF are related, they can differ significantly in some instances, and each provides distinct information about the cornea.

*7, 30-32, 35, 37-40, 47-49, 52, 57-62

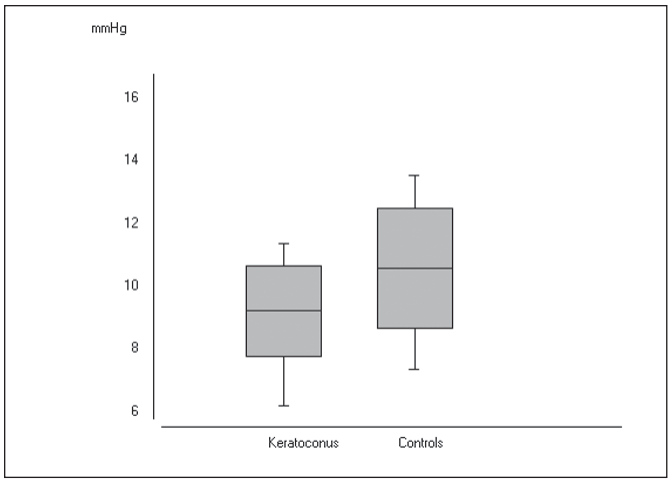


**Figure 1.** Corneal hysteresis (CH) distribution in the keratoconus and control groups (n=19 eyes in each group). Error bars indicate standard deviation.

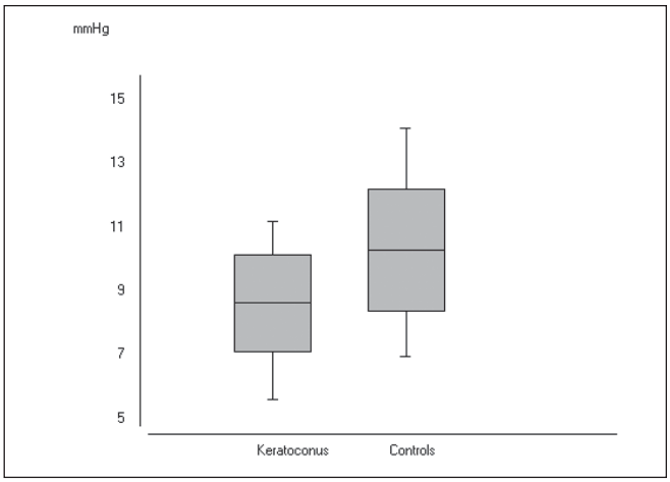


**Figure 2.** Corneal resistance factor (CRF) distribution in the keratoconus and control groups (n=19 eyes in each group). Error bars indicate standard deviation.

Statistical analysis was performed using BioEstat 5.0 software (Federal University of Belém, Pará, Brazil). The ROC curve was used to identify the best CH and CRF cutoff points to maximize the sensitivity and specificity for discriminating mild keratoconus from normal corneas. The ROC curve was obtained by plotting sensitivity against 1−specificity, calculated for each value observed. Ideally, an area of 100% implies that the test perfectly discriminates between groups. Logistic regression was used to support the cutoff point identified in the ROC curve analysis. Differences between data were evaluated using the paired *t* test. Data are expressed as the mean±standard deviation.

## RESULTS

Each group comprised 19 eyes of 19 patients (12 men and 7 women). Central corneal thickness was 543.1±13.9 µm (range: 520 to 568 µm) in the keratoconus group and 545±12.5 µm (range: 527 to 575 µm) in the control group (*P*=.6017).

Corneal hysteresis was 9.22±1.44 mmHg (range: 6.2 to 11.35 mmHg) in the keratoconus group and 10.58±1.91 mmHg (range: 7.34 to 13.53 mmHg) in the control group (*P*=.0075). Corneal resistance factor was 8.62±1.52 mmHg (range: 5.60 to 11.20 mmHg) in the keratoconus group and 10.30±1.92 mmHg (range: 6.95 to 14.12 mmHg) in the control group (*P*=.0049). The data are summarized in Table 1. Box-plot distributions of CH and CRF are shown in Figures 1 and 2, respectively.

The ROC curve analysis showed a poor overall predictive accuracy of both CH and CRF for detecting keratoconus in eyes with CCT ⩾520 µm. Regarding CH, the optimal cutoff point was 9.90 mmHg, with 78.9% sensitivity and 63.2% specificity (test accuracy, 71.05%). The best cutoff point for CRF was 8.90 mmHg, with 68.4% sensitivity and 78.9% specificity (test accuracy, 73.65%). The data from the ROC curves are presented in Table 2.

TABLE 1

**Summarized Data of Eyes With Keratoconus and Control Eyes**

| Demographic | Mean±SD (Range) Keratoconus Group | Mean±SD (Range) Control Group | *P* Value* |
|---|---|---|---|
| Sex (M/F) | 12/7 | 12/7 | 1.0 |
| Age (y) | 30.8±12.1 (18 to 64) | 30.5±12.0 (18 to 65) | .86 |
| CCT (µm) | 543.1±13.9 (520 to 568) | 545±12.5 (527 to 575) | .6017 |
| CH (mmHg) | 9.22±1.44 (6.2 to 11.35) | 10.58±1.91 (7.34 to 13.53) | .0075 |
| CRF (mmHg) | 8.62±1.52 (5.60 to 11.20) | 10.30±1.92 (6.95 to 14.12) | .0049 |

*CCT = central corneal thickness, CH = corneal hysteresis, CRF = corneal resistance factor*
**Paired* t *test.*

Clinical (spherical equivalent refraction) and topographic (corneal astigmatism and average central keratometry) data are summarized in Table 3. Spherical equivalent refraction was −3.18±3.10 diopters (D) (range: −0.50 to −9.75 D) in the keratoconus group and −2.02±2.27 D (range: 1.25 to −6.50 D) in the control group (*P*=.3163). Corneal astigmatism (given by corneal topography) was 3.14±1.73 D (range: 0.70 to 6.40 D) in the keratoconus group and 1.18±0.99 D (range: 0.20 to 4.60 D) in the control group (*P*=.0007).

TABLE 2

**Data From the Receiver Operating Characteristic Curves* for Corneal Hysteresis and Corneal Resistance Factor in Eyes With Keratoconus and Healthy Matched Control Eyes**

| | Sensitivity (%) | Specificity (%) | Test Accuracy (%) |
|---|---|---|---|
| CH | 78.9 | 63.2 | 71.05 |
| CRF | 68.4 | 78.9 | 73.65 |

*CH = corneal hysteresis, CRF = corneal resistance factor*
**Plots of the sensitivity vs 1−specificity.*

TABLE 3

**Clinical and Topographic Data From Eyes With Keratoconus and Healthy Matched Control Eyes**

| | Mean±SD (Range) (D) | | |
|---|---|---|---|
| | Keratoconus Group (n=19) | Control Group (n=19) | *P* Value* |
| Spherical equivalent refraction | −3.18±3.10 (−0.50 to −9.75) | −2.02±2.27 (1.25 to −6.50) | .3163 |
| Corneal astigmatism | 3.14±1.73 (0.70 to 6.40) | 1.18±0.99 (0.20 to 4.60) | .0007 |
| Average central keratometry | 44.28±2.35 (40.40 to 51.70) | 43.33±1.57 (39.90 to 46.15) | .0849 |

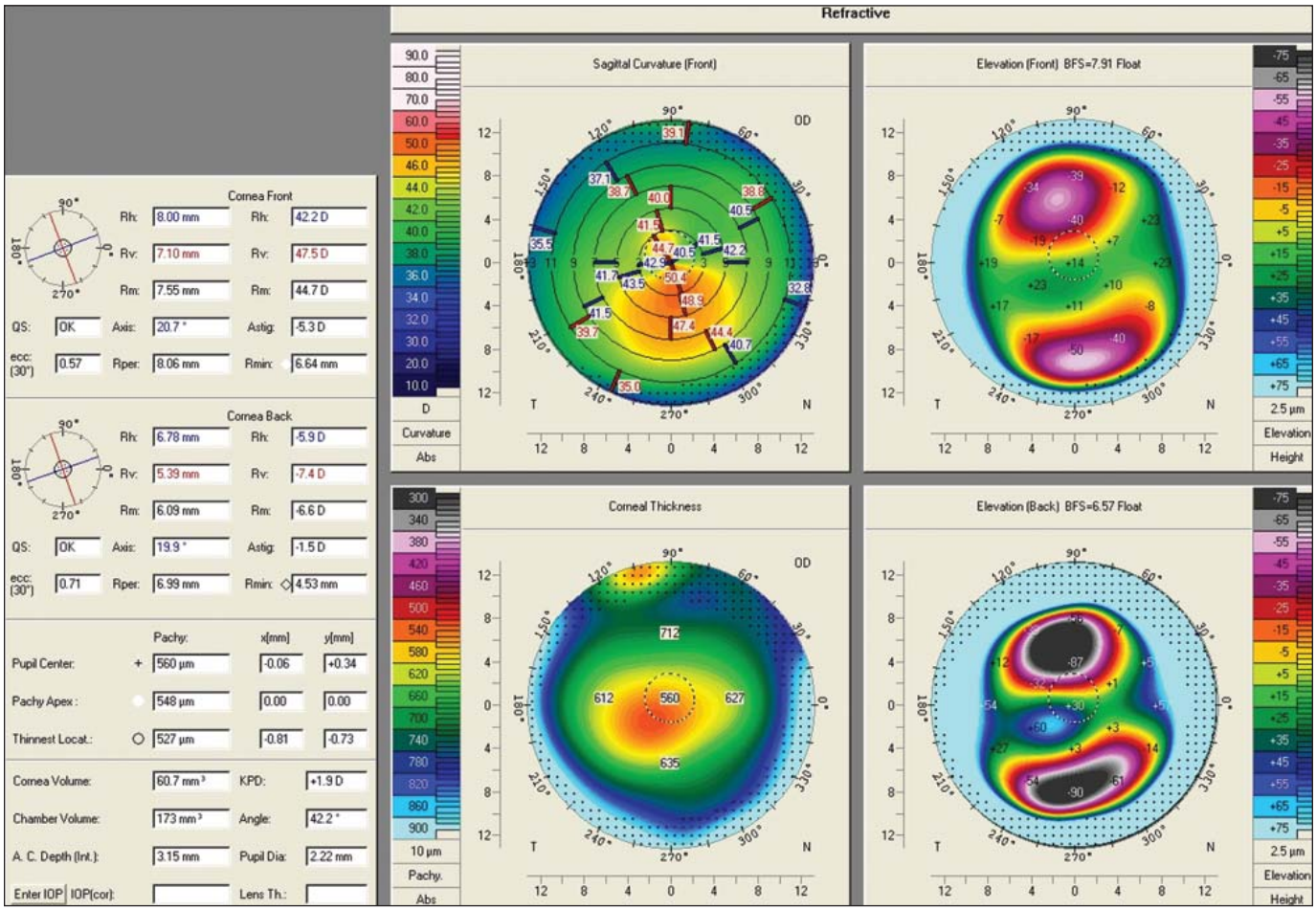


**Figure 3.** Pentacam examination of a patient with keratoconus and central corneal thickness ⩾520 µm.

Average central keratometry was 44.28±2.35 D (range: 40.40 to 51.70 D) in the keratoconus group and 43.33±1.57 D (range: 39.90 to 46.15 D) in the control group (*P*=.0849).

## DISCUSSION

Increased knowledge of corneal biomechanics, behavior, and the response to deformation is of great importance. Data generated from the ORA may expand

our understanding and perhaps help with preoperative refractive surgery screening, glaucoma treatment, Fuchs dystrophy counseling, and other ocular conditions.

Keratoconic eyes have a low tensile strength, thinning, and protrusion.* Our findings show that the lower resistance to deformation is due not only to thinning, as the groups were matched by thickness. Figure 3 is an example of a keratoconic eye with CCT ⩾520 µm. The corneal stromal collagen fibrils of keratoconus patients are probably more fragile and may be thinner than those of normal individuals.

We found a large overlap in the values of CH and CRF between groups, as seen in Figures 1 and 2. New data presented by Luce[66] indicate that the waveform parameters provided by the ORA signal may contain additional important information, which could be more sensitive than CH or CRF in discriminating abnormal corneas. Figure 4 shows an interesting example of two patients with the same CH (9.1 mmHg) and completely different waveforms given by the ORA. Additional studies are warranted to help elucidate whether signal analysis is important in biomechanical studies of the cornea.

Corneal hysteresis and CRF were statistically lower in eyes with keratoconus with CCT ⩾520 µm in comparison with healthy matched control eyes. However, because of the large overlap between groups, both CH and CRF had low sensitivity and specificity for discriminating between the two groups.

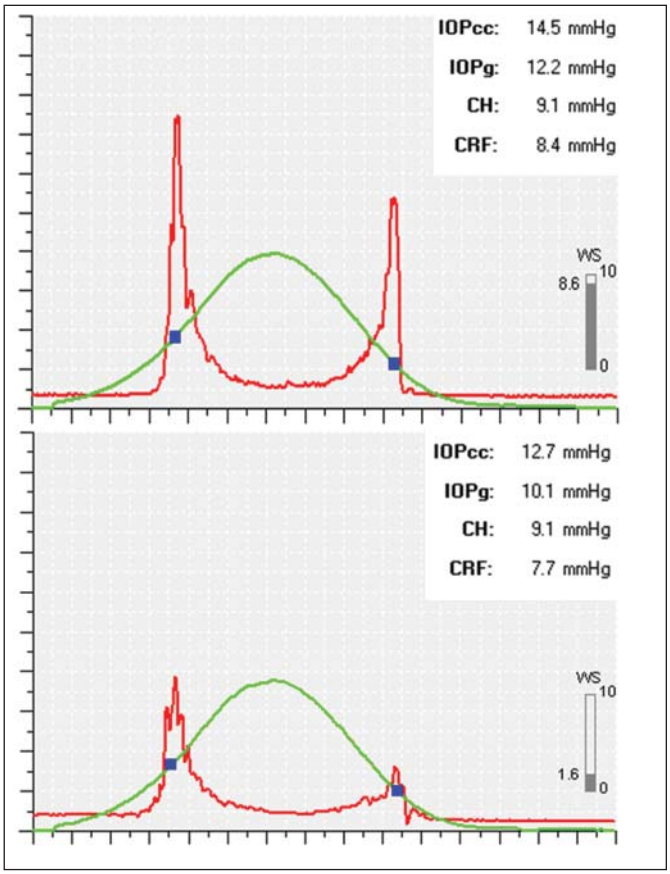


**Figure 4.** Corneal hysteresis of 9.1 mmHg in two healthy patients with completely different waveform signals.

### AUTHOR CONTRIBUTIONS

*Study concept and design (B.M.F., R.A.) ; data collection (B.M.F., R.A.); analysis and interpretation of data (B.M.F., R.A., G.C.V., W.N.); drafting of the manuscript (B.M.F., R.A.); critical revision of the manuscript (B.M.F., R.A., G.C.V., W.N.); statistical expertise (B.M.F., G.C.V.); administrative, technical, or material support (B.M.F., R.A., W.N.); supervision (R.A., W.N.)*

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