Corneal Biomechanical Metrics and Anterior Segment Parameters in Mild Keratoconus

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Purpose: To compare corneal hysteresis (CH), corneal resistance factor (CRF), spherical equivalent (SE), average central keratometry (K-Avg), corneal astigmatism (CA), corneal volume (CV), anterior chamber (AC) depth, and central corneal thickness (CCT) between patients with mild keratoconus and healthy controls and to estimate the sensitivity and specificity of CH and CRF in discriminating mild keratoconus from healthy corneas.

Design: Comparative case series.

Participants: Sixty-three eyes (40 patients) with mild keratoconus (group 1) and 80 eyes from 40 gender- and age-matched controls (group 2).

Methods: Patients underwent a complete clinical eye examination, corneal topography (Humphrey ATLAS; Carl Zeiss Meditec, Dublin, CA), tomography (Pentacam; Oculus, Wetzlar, Germany), and biomechanical evaluations (ocular response analyzer; Reichert Ophthalmic Instruments, Depew, NY). The receiver operating characteristic (ROC) curve was used to identify cutoff points that maximized sensitivity and specificity in discriminating mild keratoconus from normal corneas.

Main Outcome Measures: Corneal hysteresis, CRF, SE, K-Avg, CA, CV, AC depth, and CCT. The diagnostic performance of CH and CRF for detecting mild keratoconus was assessed using the ROC curve.

Results: In group 1 versus group 2, the SE values (mean$\pm$standard deviation) were –3.55$\pm$2.87 diopters (D) versus –1.46$\pm$3.09 D ($P = 0$); K-Avg, 45.09$\pm$2.24 versus 43.24$\pm$1.54 D ($P = 0$); CA, 3.15$\pm$1.87 versus 1.07$\pm$0.83 D ($P = 0$); CV, 57.3$\pm$2.12 versus 60.86$\pm$3.39 mm^3 ($P = 0$); AC depth, 3.19$\pm$0.35 versus 3.05$\pm$0.43 mm ($P = 0.0416$); CCT, 503$\pm$34.15 versus 544.71$\pm$35.89 μm ($P = 0$); CH, 8.50$\pm$1.36 versus 10.17$\pm$1.79 mmHg ($P = 0$); CRF, 7.85$\pm$1.49 versus 10.13$\pm$2.0 mmHg ($P = 0$). The ROC curve analyses showed a poor overall predictive accuracy of CH (cutoff, 9.64 mmHg; sensitivity, 87%; specificity, 65%; test accuracy, 74.83%) and CRF (cutoff, 9.60 mmHg; sensitivity, 90.5%; specificity, 66%; test accuracy, 76.97%) for detecting mild keratoconus.

Conclusions: The values for CH, CRF, CV, and CCT were statistically lower and those for SE, K-Avg, CA, and AC depth were statistically higher in patients with mild keratoconus compared with controls. Corneal hysteresis and CRF were poor parameters for discriminating between mild keratoconus and normal corneas.

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Keratoconus is an ectatic, noninflammatory disorder in which corneal thinning and protrusion cause the cornea to assume a conical shape. It most commonly is bilateral and asymmetric, with no gender or race predilection, and begins typically at puberty.[1–8] Detection of initial (mild) and subclinical (forme fruste) keratoconus is of paramount importance in the preoperative evaluation of refractive surgery candidates to avoid complications such as post-LASIK ectasia.[9–12] New corneal imaging technologies and indices were described recently, and further research is underway.[13–27]

Since the time Luce[28] developed the ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY), there has been increased interest in evaluating corneal biomechanics evaluation in vivo. The ORA records corneal inward and outward applanation after delivering a metered collimated air pulse and provides an indication of the viscosity and elastic properties of the cornea. Corneal hysteresis (CH) and corneal resistance factor (CRF), which are the corneal biomechanical metrics given by the ORA, have been the subjects of several recent publications.[29–54] Corneal biomechanical metrics may have great value in the preoperative screening of refractive surgery candidates, helping to differentiate between healthy and abnormal corneas.

This study compared anterior segment parameters, CH, and CRF between patients with mild keratoconus and control healthy subjects. The sensitivity and specificity of corneal biomechanical metrics for discriminating between mild keratoconus and normal corneas also were estimated.

Patients and Methods

The study constituted a comparative case series. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Federal University of São Paulo, Brazil (protocol 0123/06). All subjects were told of the purpose of the study and gave informed consent before inclusion. Patients were evaluated sequentially from October 2005 through December 2008. Demographic and clinical data were obtained, including date of birth, gender, and self-reported race or ethnicity.

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Table 1. Keratoconus Grading Scheme

	Normal	Mild Keratoconus
Corneal topography	Regular axial topography pattern (round, oval, symmetric bow tie, etc.)	Axial topography consistent with keratoconus (increased area of corneal power surrounded by concentric areas of decreasing power, inferosuperior power asymmetry, or skewing of the steepest radial axes above and below the horizontal meridian) and flat keratometry reading <51.00 D
Slit-lamp examination	Normal	Fleischer ring or Vogt striae
Visual acuity	Spectacle-corrected acuity ≥55 letters at 4 m on logMAR chart (with no other ocular pathologic features)	Reduced spectacle-corrected acuity (<55 letters at 4 m on logMAR chart with no other ocular pathologic features)

D = diopters; logMAR = logarithm of the minimum angle of resolution.
Adapted from McMahon et al.[5]

Each subject underwent a comprehensive ophthalmologic examination, which included a medical history review, best-corrected visual acuity, slit-lamp and fundoscopic examinations, Placido disc topography (Humphrey ATLAS; Carl Zeiss Meditec, Dublin, CA), Pentacam tomographic evaluation (Oculus, Wetzlar, Germany), and ORA measurements (Reichert Ophthalmic Instruments).

Mild keratoconus was defined using the grading scheme of the Collaborative Longitudinal Evaluation of Keratoconus Study Group[5] (Table 1). The criteria were axial topography consistent with keratoconus, which includes 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; a flat keratometry reading of less than 51.00 diopters (D); Fleischer ring or Vogt striae; no corneal scarring; and reduced spectacle acuity (with no other ocular pathologic features).

Cases were matched for gender and age with healthy subjects as controls. The subjects were divided in 2 groups: mild keratoconus (group 1) and control healthy eyes (group 2) for data comparison. Participant exclusion criteria were age younger than 18 years, any previous corneal or ocular surgery, any eye disease other than keratoconus, chronic or continuous use of topical medications, corneal scars or opacities, and declining informed consent. Contact lenses had to be removed at least 72 hours before the examination.

The patients underwent a clinical evaluation and testing with an ORA, corneal topography, and Pentacam tomography, all of which were performed by 2 trained ophthalmologists (RA and DJ) during the same visit. All measurements were obtained between 8 AM and 6 PM. Two consecutive ORA measurements were obtained from both eyes (only good-quality readings, as defined by the manufacturer, were stored), and the results were averaged. The spherical equivalent was obtained by dynamic refraction during the clinical examination. The average central keratometry, central corneal thickness, corneal volume, corneal astigmatism, and anterior chamber depth were assessed using the Pentacam system.

The Pentacam system was connected to a personal computer with automated software. The device had been calibrated by the manufacturer. The system uses a rotating Scheimpflug camera and a monochromatic slit light source (blue LED at 475 nm) that rotate together around the optical axis of the eye. After proper alignment of the face, the patient is shown a target to guide fixation. The examiner sees a real-time image of the patient's eye on the computer screen, and the image is focused and centered manually. The rotating camera was set to take 25 slit images of the anterior eye segment in approximately 2 seconds with 500 true elevation points incorporated into each slit image. Minute eye movements were captured by a second camera and were corrected simultaneously. Single-point pachymetric measurements of the entire cornea were determined by separating of the calculated front and back corneal surfaces. All data were measured in each of the single images of a scan, giving very accurate and precise values.[14,15,18,24,25,55]

An ORA determines corneal biomechanical properties using an applied force-displacement relationship, and the details have been described previously.[28,35,44–46,48,49,56–62] 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 adsorption 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. 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 (Luce D. Methodology for cornea compensated IOP and CRF for the Reichert ocular response analyzer. Invest Ophthalmol Vis Sci 2006;47:E-Abstract 2266), and it can be considered as weighted by the elastic resistance because of its stronger correlation with 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.

The receiver operating characteristic (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.

The cases were gender- and age-matched with control subjects for data comparison, because relationships between these 2 variables with CH and CRF were found previously.[52] Data are expressed as the mean±standard deviation.

Table 2. Summary Data from the Studied Population

	Group 1: Mild Keratoconus	Group 2: Control	Statistical Analysis
Male/female	18/22	18/22	
Mean age±SD (range), yrs	34.98±12.4 (18–73)	35.23±12.6 (18–72)	P = 1
Spherical equivalent (range), D	–3.55±2.87 (–10.25 to 3.75)	–1.46±3.09 (–9.25 to 8.00)	P = 0*
Average central keratometry (range), D	45.09±2.24 (40.40–50.85)	43.24±1.54 (39.90–46.75)	P = 0† (95% CI, –2.48 to –1.23)
Corneal astigmatism (range), D	3.15±1.87 (0.70–9.50)	1.07±0.83 (0–4.90)	P = 0*
Anterior chamber depth (range), mm	3.19±0.35 (2.41–5.21)	3.05±0.43 (2.08–3.80)	P = 0.0416† (95% CI, –0.27 to –0.01)
Corneal volume (range), mm^3	57.3±2.12 (49.5–66.9)	60.86±3.39 (53.7–68.5)	P = 0† (95% CI, –4.45 to –2.21)
Central corneal thickness (range), μm	503±34.15 (414–568)	544.71±35.89 (457–627)	P = 0† (95% CI, 30.01–53.41)
Corneal hysteresis (range), mmHg	8.50±1.36 (5.71–11.80)	10.17±1.79 (5.95–14.58)	P = 0† (95% CI, 1.13–2.20)
Corneal resistance factor (range), mmHg	7.85±1.49 (5.01–11.20)	10.13±2.0 (5.45–15.10)	P = 0† (95% CI, 1.68–2.88)

CI = confidence interval; D = diopters; SD = standard deviation.
Data are expressed as mean±standard deviation (where applied).
*Wilcoxon rank-sum test.
†Standard 2-sample *t* test.

Results

Group 1 consisted of 63 eyes from 40 patients with mild keratoconus (defined in Table 1). Group 2 included 80 eyes from 40 healthy participants, who were gender- and age-matched with the cases. Each group comprised 18 females and 22 males. The mean age±standard deviation was 34.98±12.4 years in group 1 and 35.23±12.6 years in group 2. The results are summarized in Table 2.

The spherical equivalent was –3.55±2.87 D (range, –10.25 to 3.75 D) in group 1 and –1.46±3.09 D (–9.25 to 8.00 D) in group 2 (P = 0, Wilcoxon rank-sum test). The average central keratometry values were 45.09±2.24 D (range, 40.40–50.85 D) and 43.24±1.54 D (range, 39.90–46.75 D) in groups 1 and 2, respectively (P = 0; 95% confidence interval, –2.48 to –1.23; standard 2-sample *t* test). Corneal astigmatism (given by corneal topography) was significantly higher in group 1 (mean, 3.15±1.87 D; range, 0.70–9.50 D) than in group 2 (1.07±0.83 D; range, 0–4.90 D; P = 0, Wilcoxon rank-sum test).

The corneal volume was 57.3±2.12 mm^3 (range, 49.5–66.9 mm^3) in group 1 and 60.86±3.39 mm^3 (range, 53.7–68.5 mm^3) in group 2 (P = 0; 95% confidence interval, –4.45 to –2.21; standard 2-sample *t* test). Anterior chamber depth was significantly greater in group 1 (mean, 3.19±0.35 mm; range, 2.41–5.21 mm) compared with that of group 2 (mean, 3.05±0.43 mm; range, 2.08–3.80 mm; P = 0.0416; 95% confidence interval, –0.27 to –0.01; standard 2-sample *t* test). The central corneal thickness measurements were 503±34.15 μm (range, 414–568 μm) and 544.71±35.89 μm (457–627 μm) in groups 1 and 2, respectively (P = 0; 95% confidence interval, 30.01–53.41; standard 2-sample *t* test).

Corneal hysteresis was 8.50±1.36 mmHg (range, 5.71–11.80 mmHg) in group 1 and 10.17±1.79 mmHg (range, 5.95–14.58 mmHg) in group 2 (P = 0; 95% confidence interval, 1.13–2.20; standard 2-sample *t* test). The distribution of CH in each group is shown on Figure 1. Corneal resistance factor was 7.85±1.49 mmHg (range, 5.01–11.20 mmHg) and 10.13±2.0 mmHg (range, 5.45–15.10 mmHg) in groups 1 and 2, respectively (P = 0; 95% confidence interval, 1.68–2.88; standard 2-sample *t* test), and their distributions are shown in Figure 2.

The ROC curve analysis (Fig 3) showed a poor overall predictive accuracy of CH for detecting mild keratoconus. The optimal cutoff point was 9.64 mmHg, with 87% sensitivity and 65% specificity (test accuracy, 74.83%). The sensitivity and specificity of other CH cutoff points are shown in Table 3.

The ROC curve analysis (Fig 4) also showed a poor overall predictive accuracy of CRF for detecting mild keratoconus; the

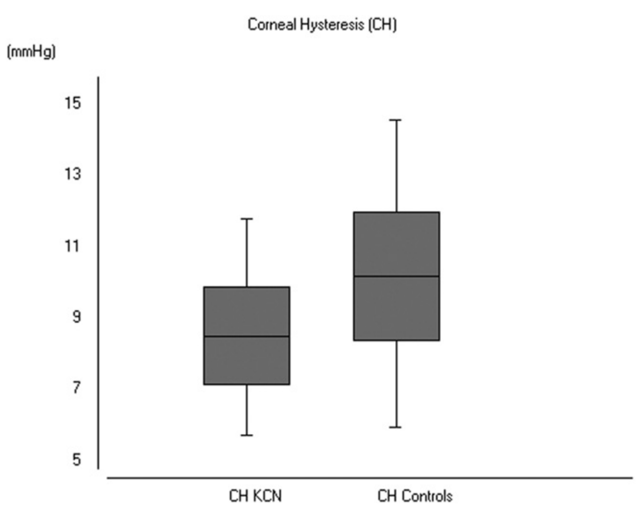

Figure 1. Box plot showing corneal hysteresis (CH) distribution in both groups. KCN = keratoconus.

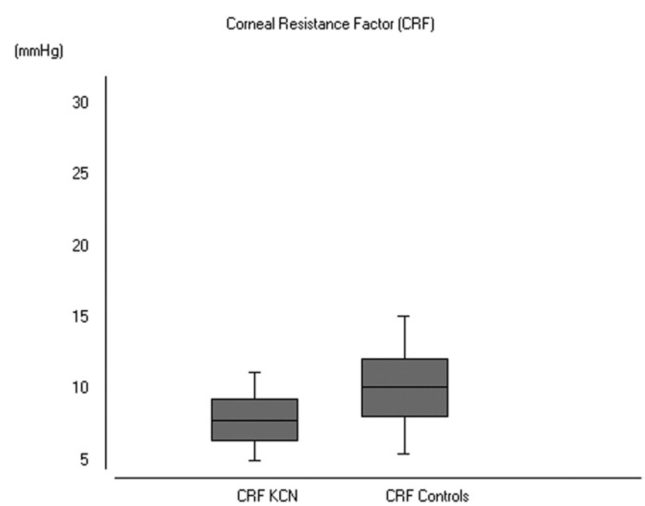

Figure 2. Box plot showing corneal resistance factor (CRF) distribution in both groups. KCN = keratoconus.

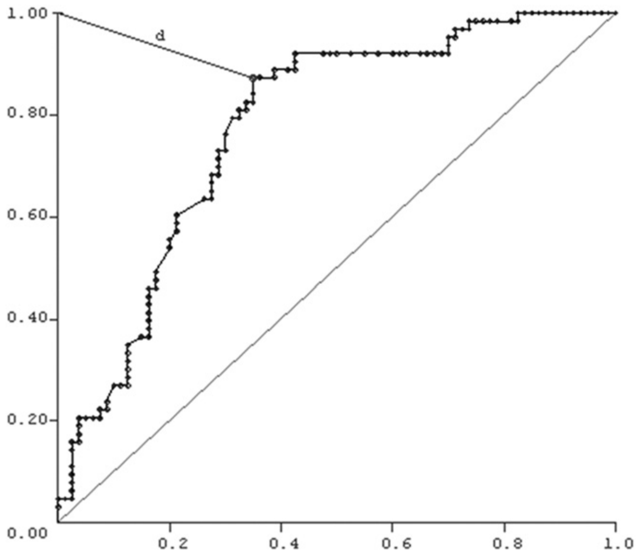

Figure 3. Receiver operating characteristic (ROC) curve (graphical plot of the sensitivity vs. 1–specificity) for corneal hysteresis (CH) data. The cutoff was 9.64 mmHg, with 87% sensitivity and 65% specificity (test accuracy, 74.83%). d = distance from cutoff point to the upper left corner or coordinate (0,1) of the ROC space (the best possible prediction point that represents 100% of sensitivity and specificity, also called a perfect classification).

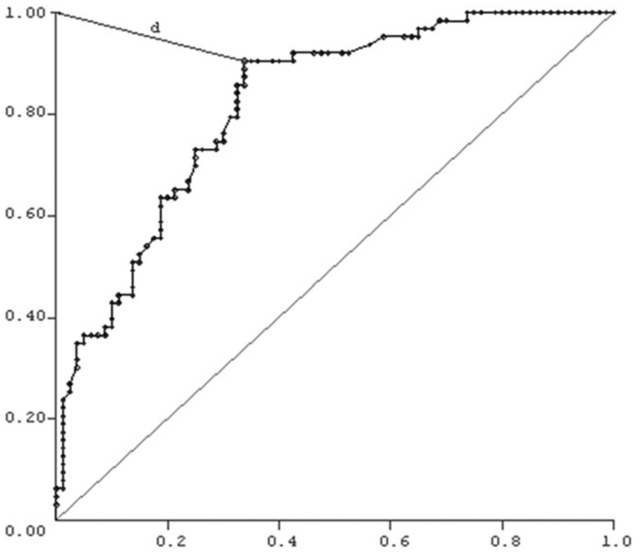

Figure 4. Receiver operating characteristic (ROC) curve (graphical plot of the sensitivity vs. 1–specificity) for corneal resistance factor (CRF) data. The cutoff was 9.60 mmHg, with 90.5% sensitivity and 66% specificity (test accuracy, 76.97%). d = distance from cutoff point to the upper left corner or coordinate (0,1) of the ROC space (the best possible prediction point that represents 100% of sensitivity and specificity, also called a perfect classification).

best cutoff point was 9.60 mmHg, with 90.5% sensitivity and 66% specificity (test accuracy, 76.97%). The sensitivity and specificity of other CRF cutoff points are shown in Table 4.

Discussion

The ability to detect mild and subclinical (forme fruste) forms of keratoconus has improved greatly in recent years. Although Placido disc-based corneal topography remains the most widely used tool, new tomographic indices such as corneal pachymetric progression and elevation analysis have helped in identifying subtle abnormalities in corneal anatomic features.[3,9,15,16,18,22,23,25,27,63,64] Nevertheless, new cases of corneal ectasia occurring after refractive surgery still are reported quite often.[9–12,65] A test that could classify the corneal biomechanical strength consistently to predict the response after surgery would have great usefulness.

Healthy human corneal tissue is composed mainly of heterotypic collagen type I fibrils and is an anisotropic, biocomposite structure with high tensile strength that provides the globe with a resilient layer.[66–72] It is considered a viscoelastic material with measurable properties.[28,37,46,48,52,62,70,73–77] In a pioneering study, Luce[28] proposed that CH, determined using an ocular response analyzer, could be an independent indicator or corneal biomechanical measurement in vivo, with probable practical applications in

Table 3. Sensitivity and Specificity for Different Cutoff Points of Corneal Hysteresis

Mild Keratoconus vs. Controls		
Cutoff Point (mmHg)	*Sensitivity (%)*	*Specificity (%)*
CH≤7.0	16	98
CH≤7.5	22	91
CH≤8.0	35	88
CH≤8.25	35	84
CH≤8.5	46	84
CH≤8.75	57	79
CH≤9.0	67	73
CH≤9.25	73	70
CH≤9.5	79	66
CH≤9.75	89	58
CH≤10	92	58

CH = corneal hysteresis.

Table 4. Sensitivity and Specificity for Different Cutoff Points of Corneal Resistance Factor

Mild Keratoconus vs. Controls		
Cutoff Point (mmHg)	*Sensitivity (%)*	*Specificity (%)*
CRF≤7.0	35	95
CRF≤7.5	37	91
CRF≤8.0	49	86
CRF≤8.25	59	81
CRF≤8.5	65	76
CRF≤8.75	73	71
CRF≤9.0	79	70
CRF≤9.25	83	68
CRF≤9.5	89	66
CRF≤9.75	90	61
CRF≤10	92	49

CRF = corneal resistance factor.

preoperative screening for refractive surgery. Several studies have reported interesting results for refractive surgery candidates as well as for healthy persons and those with glaucoma or ectasia.[28–32,34–49,51–54,56–62,66,73–75,78–85]

Previously, the authors' group found that both CH and CRF had a negative relationship with age, a positive relationship with corneal thickness, and no correlation with spherical equivalent, anterior chamber depth, or central keratometry.[52] An ongoing study is being conducted with pachymetry-matched subjects to determine whether ORA helps to differentiate abnormalities such as thin or thick corneas in special cases. In addition, Luce presented new data (Luce D. ORA Waveform Analysis and beyond. Presented at: American Society of Cataract and Refractive Surgery Annual Meeting, April 3–8, 2009; San Francisco, California) regarding waveform parameters provided from the ORA signal that may be more sensitive than CH or CRF in discriminating abnormal corneas.

In this study, the corneal biomechanical metrics were statistically lower in patients with mild keratoconus compared with those in healthy controls. However, no cutoff value could be established with high sensitivity and specificity for the diagnosis of mild keratoconus, based on the diagnosis determined with Placido disc-based corneal topography. As expected, the spherical equivalent measurements revealed that the keratoconic patients were significantly more myopic than the control subjects. Keratoconic patients also had significantly steeper corneas of less volume and significantly higher corneal astigmatism, based on the central keratometric, corneal volume, and corneal astigmatism measurements. In addition, the central corneal thickness was statistically lower in the mild keratoconus group compared with the control group. An interesting finding was the difference in anterior chamber depth, showing that corneal protrusion makes the anterior chamber wider in keratoconus patients compared with normal subjects.

Corneal biomechanical metrics may prove to be useful for the preoperative screening of refractive surgery candidates and may help clinicians choose between surface ablation techniques such as photorefractive keratectomy and incisional procedures such as LASIK. Based on the present findings, CH and CRF should not be used as the sole criteria in the diagnosis of mild keratoconus. Additional research on this new technology is warranted to elucidate its full usefulness in daily practice.

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