Corneal Biomechanical Metrics in Eyes With Refraction of −19.00 to +9.00 D in Healthy Brazilian Patients

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ABSTRACT

PURPOSE: To evaluate corneal biomechanical metrics with tomographic parameters (given by the Oculus Pentacam) and refractive data in a population of healthy Brazilian patients.

METHODS: Observational, cross-sectional study of 150 consecutive patients (53 men and 97 women; 260 eyes). Age, gender, central keratometric readings (central K), central corneal thickness (CCT), anterior chamber depth (ACD), spherical equivalent refraction, corneal hysteresis, and corneal resistance factor (CRF) were assessed and analyzed.

RESULTS: Mean patient age was 46.5±21.04 years, average central K was 43.59±1.54 diopters (D), CCT was 545.05±35.41 μm, ACD was 2.96±0.52 mm, spherical equivalent refraction was −1.16±3.48 D, corneal hysteresis was 10.17±1.82, and CRF was 10.14±1.8 (range: 5.45 to 15.1). Mean CRF and corneal hysteresis were distinct among gender: CRF 10.326 in women and 9.810 in men (P=.0266); corneal hysteresis 10.421 in women and 9.727 in men (P=.0031). A negative correlation was found between both CRF and corneal hysteresis with age (r=−0.1255, P=.0434; and r=−0.2445, P=.0001, respectively). No association was found between CRF and average central K (r=0.0633, P=.3086), ACD (r=−0.0474, P=.4498), or spherical equivalent refraction (r=0.1028, P=.1061). Corneal hysteresis was not associated with age and average central K (r=0.0572, P=.3573), ACD (r=0.0060, P=.9236), or spherical equivalent refraction (r=0.0975, P=.1253). Corneal resistance factor and corneal hysteresis were positively associated with CCT (r=0.5760, P=0; and r=0.4655, P=0, respectively).

CONCLUSIONS: Corneal biomechanical metrics of healthy Brazilian patients were associated with CCT, gender, and age. Corneal steepness, ACD, and spherical equivalent refraction did not affect corneal hysteresis and CRF values in the studied population. [*J Refract Surg*. 2008;24:941-945.]

Since the first publication by Luce,[1] in vivo corneal biomechanics evaluation as provided by the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY) has gained increasing attention from the ophthalmic community. Corneal biomechanical metrics, namely corneal hysteresis and corneal resistance factor (CRF), have been the subject of several recent publications.[2-11]

Stress (applied force) and consequent strain (deformation in the material which stress has been applied) has a linear relation in an elastic material or tissue. When stress is removed, the original shape is recovered. Viscosity is the tendency of a liquid to resist flow, and in an ideal liquid stress–strain cycle is directly proportional.[12] The higher the viscosity, the slower the response to applied force; and viscous liquids do not regain their original shape.

The cornea is an example of a complex viscoelastic tissue (having both viscous and elastic properties).[12] However, corneal tissue is not linearly elastic: as applied stress increases, the cornea stiffens (less strain at higher stresses). Corneal biomechanics encompasses thickness, hydration, elasticity, viscosity, and possible other yet undefined factors.[12-19]

The ORA records corneal inward and outward applanation after delivery of a metered collimated air pulse, determining its viscoelastic properties. Hysteresis can be defined as a measure of the energy absorption during the stress–strain cycle of viscoelastic materials.[8] It has been previously shown that corneal hysteresis is lower in keratoconus, Fuchs' dystrophy, glaucoma patients, and after refractive surgery.[1-6,8] Also, it has been proven to be almost constant throughout the day.[7]

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The authors have no proprietary interest in the materials presented herein. Dr Ambrósio is a consultant for Oculus and Reichert.

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Received: March 15, 2007

Accepted: September 19, 2007

Posted online: April 30, 2008

For a new technology to become widely accepted and used on a clinical basis, it has to prove ability in diagnosing and/or altering physician behavior. Refractive surgeons and glaucoma specialists are thought to benefit the most from ORA, as the diagnosis, screening, and management of patients may be modified by corneal biomechanical metrics. However, these new diagnostic parameters (corneal hysteresis and CRF) should be tested by different, independent researchers and the "normal" values determined in different populations.

The majority of articles describe findings in Caucasian patients. The Brazilian population is highly heterogeneous, and miscegenation is common. This study aims to evaluate, determine, and correlate corneal biomechanical metrics (corneal hysteresis and CRF) with demographic, tomographic (Pentacam; Oculus Inc, Wetzlar, Germany), and refractive data in a population of healthy Brazilian patients.

PATIENTS AND METHODS

We conducted an observational, cross-sectional study. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee from Federal University of Sao Paulo. All patients were informed about the purpose of the study and gave informed consent before inclusion. Patients were sequentially evaluated from October 2005 to December 2006. Demographic and clinical data were obtained, including date of birth, gender, and self-reported race or ethnicity.

Each patient underwent a comprehensive ophthalmologic examination including review of medical history, best spectacle-corrected visual acuity, slit-lamp microscopy, funduscopic examination, Pentacam tomographic evaluation, and ORA measurements. Exclusion criteria were age <18 years, previous corneal or ocular surgery, eye disease that could possibly interfere with the readings/results (eg, glaucoma, uveitis, corneal ectatic disease, Fuchs' dystrophy, diabetic retinopathy, etc), chronic and/or continuous use of topical medications, corneal scars and/or opacities, irregular astigmatism, systemic collagen diseases, and refusal to sign an informed consent. Contact lenses had to be removed at least 72 hours before examination.

Patients underwent testing with the ORA and Pentacam by two trained ophthalmologists (R.S.A., D.J.) during the same visit. All measurements were taken between 8 AM and 6 PM. Two consecutive ORA measurements were performed on both eyes, and results were averaged. Only good quality readings (defined by the manufacturer as both force-in and force-out applanation signal peaks on the ORA waveform being fairly symmetrical in height[8]) were recorded. Spherical equivalent refraction was obtained by dynamic refraction during clinical examination. Central keratometry (average central K), central corneal thickness (CCT), and anterior chamber depth (ACD) were assessed by the Pentacam.

The Pentacam system is connected to a personal computer, with automated software. The manufacturer performed calibration of the device. The system uses a rotating Scheimpflug camera and a monochromatic slit light source (blue LED at 475 nm) that rotate together. After proper alignment of the patient's face, a fixation target is shown and guides the patient's look. A real-time image of the patient's eye is shown to the examiner 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 in each slit image. Minute eye movements are captured by a second camera and corrected simultaneously. Single point pachymetric measurements of the entire cornea are calculated from the calculated front and back corneal surfaces. The CCT, average central K, and ACD are measured in each of the single images of a scan.

The ORA determines corneal biomechanical properties using an applied force–displacement relationship. Details have been extensively described previously.[1,5-7,9,10] Briefly, a precisely metered air pulse is delivered to the eye, causing the cornea to move inward, past a first applanation, and into a slight concavity. Milliseconds after the first applanation, the air generating the air pump is shut down 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 called corneal hysteresis. Corneal hysteresis is an indication of viscous damping and elastic resistance, reflecting the capacity of corneal tissue to absorb and dissipate energy. Corneal resistance factor was empirically derived to maximize correlation to CCT,[20] and one can consider to be weighted by elastic resistance because it has a stronger correlation to CCT than corneal hysteresis. Although corneal hysteresis and CRF are related, in some instances they can be significantly different, each providing distinct information about the cornea.

The Kolmogorov-Smirnov test was used to check for a normal distribution of quantitative data, which

TABLE

Demographic and Clinical Characteristics of 150 Brazilian Patients (260 Eyes)

Characteristic	Mean±SD (Range)	Kolmogorov-Smirnov Test*
Age (y)	45.09±20.58 (18 to 90)	.00
Central K (D)	43.59±1.54 (38.1 to 46.75)	.0013
CCT (μm)	545.05±35.41 (454 to 640)	.30
ACD (mm)	2.96±0.52 (1.34 to 4.69)	.832
SE (D)	−1.16±3.48 (−19.75 to +9.50)	.00
Corneal hysteresis	10.17±1.82 (3.23 to 14.58)	.08
CRF	10.14±1.80 (5.45 to 15.10)	.363

Central K = average central keratometry, CCT = central corneal thickness, ACD = anterior chamber depth, SE = spherical equivalent refraction, CRF = corneal resistance factor
**Composite normality.*

are provided as the mean and standard deviation (SD). Differences between data were evaluated using the Student two-sample *t* test, whereas correlation coefficients (r) were established by Spearman's rank correlation or Pearson's product-moment correlation where appropriate. The level of significance for each parameter was set at $P<.05$.

RESULTS

The study included 260 eyes of 150 consecutive patients. Fifty-three (35.3%) patients were men, and 97 (64.7%) were women. Mean patient age was 46.5±21.04 years (range: 18 to 90 years). Average central K was 43.59±1.54 diopters (D) (range: 38.1 to 46.75 D), CCT 545.05±35.41 μm (range: 454 to 640 μm), ACD 2.96±0.52 mm (range: 1.34 to 4.69 mm), spherical equivalent refraction −1.16±3.48 D (range: −19.75 to +9.50 D), corneal hysteresis 10.17±1.82 (range: 3.23 to 14.58), and CRF 10.14±1.8 (range: 5.45 to 15.1). The Table shows patient demographic and clinical characteristics.

Mean CRF and corneal hysteresis were distinct among gender. Corneal resistance factor was 10.326 in women and 9.810 in men (*P*=.0266, Fig 1). Corneal hysteresis was 10.421 in women and 9.727 in men (*P*=.0031, Fig 2).

A negative correlation was found between CRF and age (r=−0.1255, *P*=.0434; Fig 3). There was no association between CRF and average central K (r=0.0633, *P*=.3086), ACD (r=−0.0474, *P*=.4498), or spherical equivalent refraction (r=0.1028, *P*=.1061). Corneal resistance factor was positively associated with CCT (r=0.5760, *P*=.00; Fig 4).

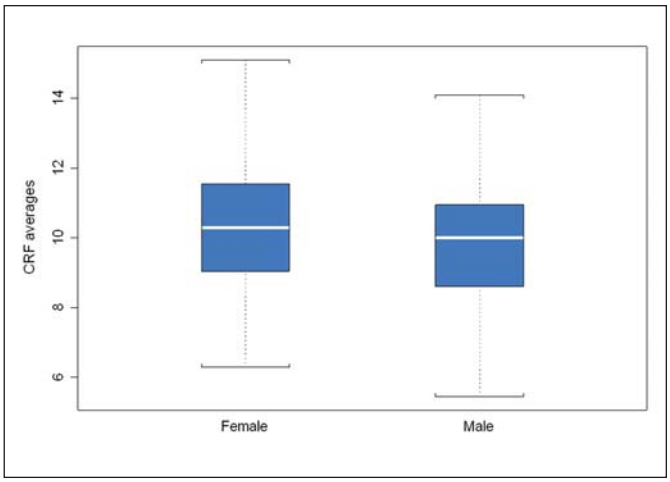

Figure 1. Corneal resistance factor (CRF) × gender. Mean value of 10.326 in women and 9.810 in men (*P*=.0266; 95% confidence interval 0.06043 to 0.97158; Standard two-sample *t* test).

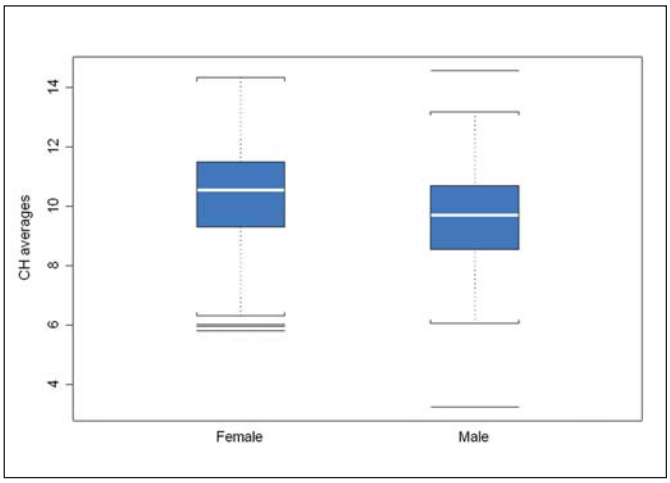

Figure 2. Corneal hysteresis × gender. Mean value of 10.421 in women and 9.727 in men (*P*=.0031; 95% confidence interval 0.235997 to 1.151652; Standard two-sample *t* test).

Corneal hysteresis was also associated with CCT (r=0.4655, *P*=.00; Fig 5) and negatively correlated with age (r=−0.2445, *P*=.0001; Fig 6). No association was found between corneal hysteresis and average central K (r=0.0572, *P*=.3573), ACD (r=0.0060, *P*=.9236), or spherical equivalent refraction (r=0.0975, *P*=.1253).

DISCUSSION

As Ethier et al[17] states, material properties of the cornea are heterogeneous, highly anisotropic, nonlinear, and viscoelastic. In an extensive review, Torres et al[14]

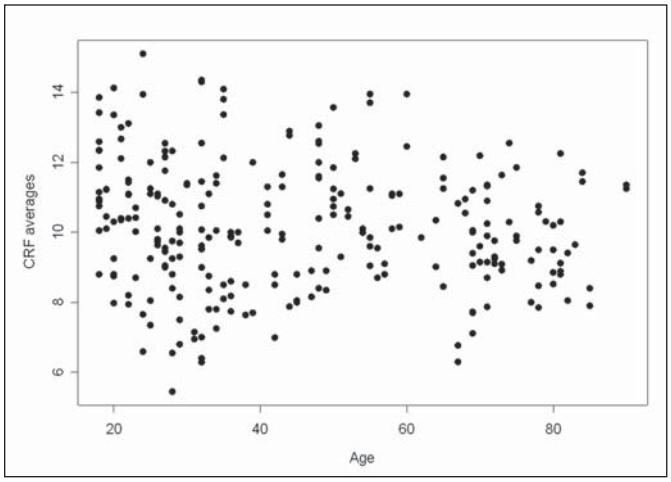

Figure 3. Negative correlation between corneal resistance factor (CRF) and age (r=−0.1255; *P*=.0434; Spearman's rank correlation).

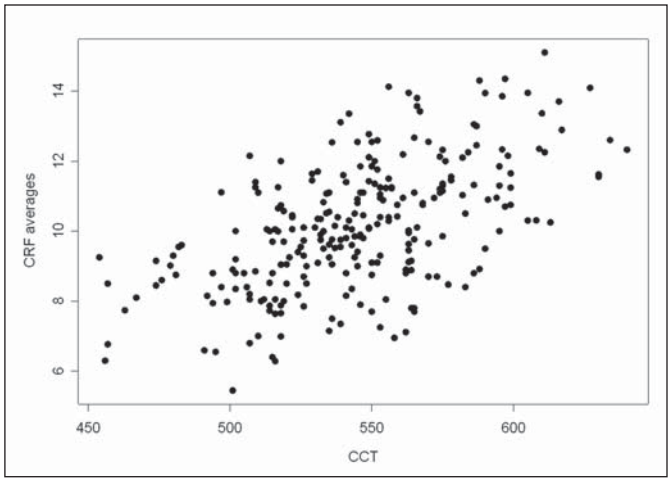

Figure 4. Positive association between corneal resistance factor (CRF) and central corneal thickness (CCT) (r=0.5760; *P*=.00; Pearson's product-moment correlation).

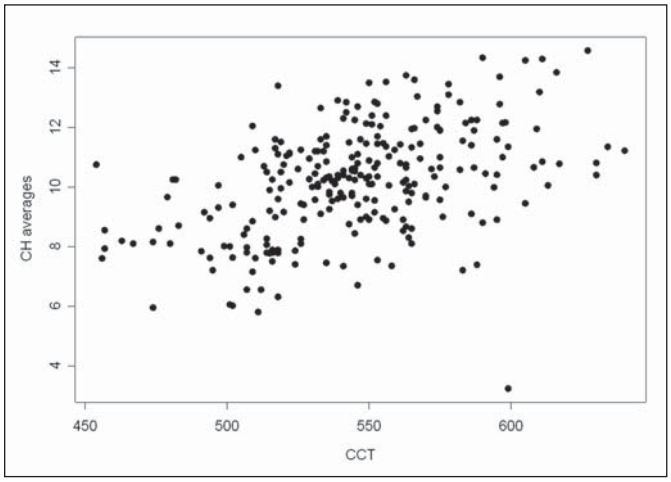

Figure 5. Corneal hysteresis (CH) was positively associated with central corneal thickness (CCT) (r=0.4655; *P*=.00; Pearson's product-moment correlation).

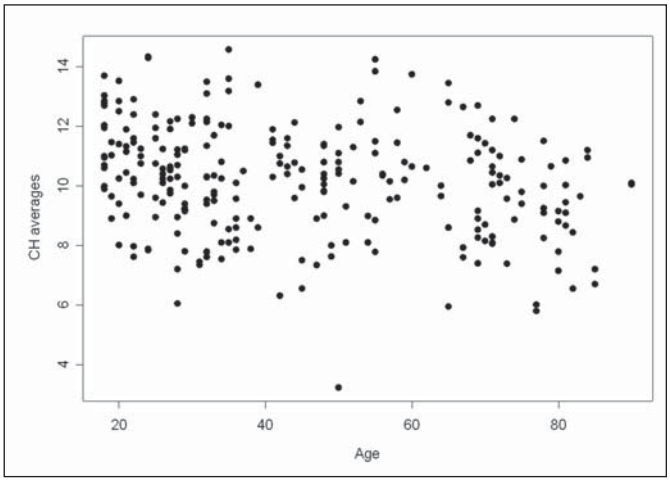

Figure 6. Corneal hysteresis (CH) was negatively correlated to age (r=−0.2445; *P*=.0001; Spearman's rank correlation).

described CCT and corneal collagen fibers density as the most important intrinsic factors determining corneal biomechanics. We would add to these, corneal hydration (and its control by the endothelium), corneal thickness regional variation,[18,21,22] and collagen fibril orientation and distribution.[18,23]

Studies by Kida et al[10] and Laiquzzaman et al[7] showed that corneal hysteresis remains almost constant throughout the day, whereas CCT and intraocular pressure showed statistically significant variations (higher values during nocturnal periods) in young adults. These interesting findings proved that corneal biomechanical metrics are independent of diurnal changes in CCT and corneal hydration. The small number of patients in both studies could restrict their findings to these specific populations. Our study indicates a relationship between CRF and corneal hysteresis with CCT, which is in agreement with previous studies.[4,6]

Luce,[1] in his pioneer study, found a mean corneal hysteresis of 9.6 in a population of healthy young patients (age range 23 to 38 years). Corneal hysteresis in children has been studied by Kirwan et al[9] who found a mean corneal hysteresis of 12.5 in healthy children, and no correlation with age. We found mean corneal hysteresis of 10.17±1.82 in a Brazilian population with a mean age of 46.5±21.04 years (range: 18 to 90 years). Our results complement these previous findings in an older population. Interestingly, in our study, age was inversely associated with corneal biomechanical metrics (see Figs 3 and 6).

We do not believe that the association between corneal biomechanical metrics and gender found in this study is clinically significant, and may be due to the

fact that more women were studied (97 women, 167 eyes; 53 men, 93 eyes). However, the numerical difference was small (10.326×9.810 for CRF; 10.421×9.727 for corneal hysteresis) and, most importantly, confidence interval has a wide range. Both groups had similar mean age (43.68±20.04 years for men and 48.04±21.52 years for women). We aim to continue evaluating corneal biomechanical metrics in healthy patients to confirm these data in a larger sample. In addition, our group is currently enrolling participants to study corneal biomechanical metrics in patients with ocular pathologies (such as keratoconus, Fuchs' endothelial dystrophy, and glaucoma) and its modifications after ocular surgery.

Our results of corneal hysteresis and CRF in a healthy Brazilian population were slightly lower than those previously published for healthy Caucasians.[1,4,7,8,10] Therefore, we can hypothesize that corneal biomechanical metrics may be influenced by race and/or ethnicity. Our study, however, has limitations. We chose to exclude patients with any ocular pathology other than cataract and previous corneal and/or ocular surgery. We do not know, for example, the effect of cataract wound in corneal biomechanics. Patients were not randomized; those seeking regular ocular examination, refractive surgery, and cataract candidates were included.

This study evaluated the corneal biomechanical metrics of healthy Brazilian patients, and an association with CCT, gender, and age was found. Average central K, ACD, and spherical equivalent refraction did not affect corneal hysteresis and CRF values in the studied population. Further studies are warranted to establish normal values of corneal hysteresis and CRF in different populations.

REFERENCES

1. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg*. 2005;31:156-162.
2. Pepose JS, Feigenbaum SK, Qazi MA, Sanderson JP, Roberts CJ. Changes in corneal biomechanics and intraocular pressure following LASIK using static, dynamic, and noncontact tonometry. *Am J Ophthalmol*. 2007;143:39-47.
3. Gatinel D, Chaabouni S, Adam PA, Munck J, Puech M, Hoang-Xuan T. Corneal hysteresis, resistance factor, topography, and pachymetry after corneal lamellar flap. *J Refract Surg*. 2007;23:76-84.
4. Shah S, Laiquzzaman M, Cunliffe I, Mantry S. The use of the Reichert ocular response analyser to establish the relationship between ocular hysteresis, corneal resistance factor and central corneal thickness in normal eyes. *Cont Lens Anterior Eye*. 2006;29:257-262.
5. Medeiros FA, Weinreb RN. Evaluation of the influence of corneal biomechanical properties on intraocular pressure measurements using the ocular response analyzer. *J Glaucoma*. 2006;15:364-370.
6. Martinez-de-la-Casa JM, Garcia-Feijoo J, Fernandez-Vidal A, Mendez-Hernandez C, Garcia-Sanchez J. Ocular response analyzer versus Goldmann applanation tonometry for intraocular pressure measurements. *Invest Ophthalmol Vis Sci*. 2006;47:4410-4414.
7. Laiquzzaman M, Bhojwani R, Cunliffe I, Shah S. Diurnal variation of ocular hysteresis in normal subjects: relevance in clinical context. *Clin Experiment Ophthalmol*. 2006;34:114-118.
8. Kotecha A, Elsheikh A, Roberts CR, Zhu H, Garway-Heath DF. Corneal thickness- and age-related biomechanical properties of the cornea measured with the ocular response analyzer. *Invest Ophthalmol Vis Sci*. 2006;47:5337-5347.
9. Kirwan C, O'Keefe M, Lanigan B. Corneal hysteresis and intraocular pressure measurement in children using the reichert ocular response analyzer. *Am J Ophthalmol*. 2006;142:990-992.
10. Kida T, Liu JH, Weinreb RN. Effect of 24-hour corneal biomechanical changes on intraocular pressure measurement. *Invest Ophthalmol Vis Sci*. 2006;47:4422-4426.
11. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol*. 2006;141:868-875.
12. Brown KE, Congdon NG. Corneal structure and biomechanics: impact on the diagnosis and management of glaucoma. *Curr Opin Ophthalmol*. 2006;17:338-343.
13. Dupps WJ Jr, Wilson SE. Biomechanics and wound healing in the cornea. *Exp Eye Res*. 2006;83:709-720.
14. Torres RM, Merayo-Lloves J, Jaramillo MA, Galvis V. Corneal biomechanics [Spanish]. *Arch Soc Esp Oftalmol*. 2005;80:215-223.
15. Schmack I, Dawson DG, McCarey BE, Waring GO III, Grossniklaus HE, Edelhauser HF. Cohesive tensile strength of human LASIK wounds with histologic, ultrastructural, and clinical correlations. *J Refract Surg*. 2005;21:433-445.
16. Pallikaris IG, Kymionis GD, Ginis HS, Kounis GA, Tsilimbaris MK. Ocular rigidity in living human eyes. *Invest Ophthalmol Vis Sci*. 2005;46:409-414.
17. Ethier CR, Johnson M, Ruberti J. Ocular biomechanics and biotransport. *Annu Rev Biomed Eng*. 2004;6:249-273.
18. Anderson K, El-Sheikh A, Newson T. Application of structural analysis to the mechanical behaviour of the cornea. *Journal of the Royal Society, Interface*. 2004;1:3-15.
19. Roberts C. The cornea is not a piece of plastic. *J Refract Surg*. 2000;16:407-413.
20. Luce D. Methodology for cornea compensated IOP and corneal resistance factor for the Reichert Ocular Response Analyzer. *Invest Ophthalmol Vis Sci*. 2006;47:E-Abstract 2266.
21. Luz A, Ursulio M, Castañeda D, Ambrósio R Jr. Corneal thickness progression from the thinnest point to the limbus: study based on a normal and a keratoconus population to create reference values [Portuguese]. *Arq Bras Oftalmol*. 2006;69:579-583.
22. Ambrósio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. *J Cataract Refract Surg*. 2006;32:1851-1859.
23. Boote C, Hayes S, Abahussin M, Meek KM. Mapping collagen organization in the human cornea: left and right eyes are structurally distinct. *Invest Ophthalmol Vis Sci*. 2006;47:901-908.