Bruno Machado Fontes

AVALIAÇÃO DAS PROPRIEDADES BIOMECÂNICAS CORNEANAS EM PACIENTES COM CERATOCONE E EM CÓRNEAS NORMAIS

Tese apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina, para obtenção do Título de Doutor em Ciências pelo programa de Pós-graduação em Oftalmologia.

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Orientador:
Prof. Dr. Walton Nosé

Co-orientador:
Prof. Dr. Renato Ambrósio Jr.

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2010

Fontes, Bruno Machado

Avaliação das propriedades biomecânicas corneanas em pacientes com ceratocone e em córneas normais / Bruno Machado Fontes. – São Paulo, 2010.

xi, 76f.

Tese (Doutorado) – Universidade Federal de São Paulo. Escola Paulista de Medicina. Programa de Pós-Graduação em Oftalmologia.

Título em inglês: Corneal biomechanical evaluation in healthy and keratoconic eyes.

1. Biomecânica. 2. Ceratocone. 3. Córnea

UNIVERSIDADE FEDERAL DE SÃO PAULO

ESCOLA PAULISTA DE MEDICINA

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Dedicatória

Aos meus queridos e dedicados Professores (todos que tive, desde a alfabetização até a Pós-graduação). Essenciais no desenvolvimento e progresso, tão desprestigiados e desvalorizados em nosso país.

Aos meus amados avô (Wilson Machado) e avós (Lisete Mussi Machado e Ilza A. Silva Fontes), pelo amor e suporte incondicionais.

Agradecimentos

Ao amigo, professor e co-orientador, **Dr. Renato Ambrósio Jr.,** pelo apoio constante e incansável motivação na realização destes trabalhos. Serei eternamente grato. Ainda, pela liderança na formação de jovens pesquisadores no Rio de Janeiro.

Ao professor **Dr. Walton Nosé,** pela total confiança e apoio no desenvolvimento desta tese.

Aos professores e amigos, **Dr. Wallace Chamon, Dr. Hamilton Moreira** e **Dr. Mauro Campos**, pela ajuda direta e indireta ("conversa de corredor") na condução e aperfeiçoamento dos trabalhos referentes à esta tese.

Aos meus pais, **Dra. Mara Lucia Machado Fontes** e **Dr. Paulo Cesar Silva Fontes**, pelo amor, suporte e apoio incondicionais em todos os momentos da minha vida.

A minha esposa, **Tatiana Braga C. Ganem,** pelo companheirismo e apoio.

Aos professores **Dr. Rubens Belfort Mattos Jr, Dra. Marian S. Macsai, Dra. Denise de Freitas, Dra. Luciene Barbosa de Sousa,** e **Dr. Lenio S. Alvarenga,** pela inspiração, incentivo, confiança e motivação desde a Residência Médica.

A todos que direta ou indiretamente colaboraram com a pesquisa e possibilitaram a realização desta tese.

Este trabalho deu origem às publicações:

1. Fontes BM, Ambrósio R Jr, Alonso RS, Jardim D, Velarde GC, Nosé W. Corneal biomechanical metrics in eyes with refraction of -19.00 to +9.00 D in healthy Brazilian patients. J Refract Surg. 2008;24(9):941-5.

2. Fontes BM, Ambrósio Junior R, Jardim D, Velarde GC, Nosé W. Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas. Arq Bras Oftalmol. 2010;73(4):333-7.

3. Fontes BM, Ambrósio R Jr, Jardim D, Velarde GC, Nosé W. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. Ophthalmology. 2010;117(4):673-9.

4. Fontes BM, Ambrósio R Jr, Velarde GC, Nosé W. Ocular Response Analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes. J Refract Surg. 2010:1-7.

5. Fontes BM, Ambrósio R Jr, Salomão M, Velarde GC, Nosé W. Biomechanical and tomographic analysis of unilateral keratoconus. J Refract Surg. 2010;26(9):677-81.

6. Fontes BM, Ambrósio Jr R, Velard GC, Nosé W. Biomechanical evaluation of healthy thin corneas compared with matched keratoconus cases. Arq Bras Oftalmol. 2011;74(1):13-6.

Sumário

Lista de abreviaturas

ORA	(Ocular Response Analyzer ®)
KCN	(ceratocone, do inglês keratoconus)
CH	(histerese corneana, do inglês corneal hysteresis)
CRF	(fator de resistência corneana, do inglês corneal resistance factor)
mmHg	(milímetro de mercúrio)
µm	(micrômetro)

Resumo

Objetivo: Definir os parâmetros biomecânicos da córnea gerados pelo equipamento Ocular Response Analyzer (histerese corneana – CH e fator de resistência corneana – CRF) em pacientes saudáveis e estudar suas alterações em pacientes com diversas formas clínicas e classificações de ceratocone. **Métodos:** Estudo clínico observacional, tipo série de casos comparativa. A primeira etapa do estudo consistiu na aferição dos parâmetros biomecânicos (CH e CRF) em um grupo de 260 olhos de 150 pacientes com córneas normais, para determinação de valores da normalidade (grupo controle) e identificação de possíveis fatores influenciadores e associados aos mesmos. Estudos subsequentes trataram de determinar as diferenças entre os valores encontrados no grupo controle daqueles obtidos em pacientes com ceratocone, tentando estabalecer valores de corte para melhor diferenciação entre os grupos. **Resultados:** Em indivíduos saudáveis (grupo controle – primeiro estudo) os valores médios encontrados foram de 10,17±1,82 mmHg para CH e 10,14±1,8 mmHg para CRF, havendo correlação entre estes e espessura corneana central, gênero e idade. Comparando os achados de um grupo de 77 olhos (43 pacientes) com ceratocone e 86 olhos (43 pacientes) com córneas normais, observamos valores estatisticamente mais baixos no primeiro para CH (8,23±1,51 mmHg no grupo ceratocone, e 10,13±1,75 mmHg no grupo controle; $p<0,001$) e CRF (7,46±1,76mmHg e 10,06±1,97mmHg respectivamente; $p<0,001$). Em pacientes com ceratocone leve / inicial o valor de CH encontrada foi 8,50±1,36 mmHg e o de CRF 7,85±1,49 mmHg, valores estatisticamente mais baixos que os encontrados no grupo controle (pareado por espessura corneana central, gênero e idade): CH 10,17±1,79 mmHg e CRF 10,13±2,0 mmHg ($p<0,001$). Em dezenove casos de ceratocone com espessura corneana central (CCT) ≥ 520µm comparados com grupo controle (pareado por CCT, gênero e idade) obtivemos novamente valores estatisticamente mais baixos no primeiro grupo, com os seguintes resultados: CH 9,22±1,44 mmHg vs. 10,58±1,91 mmHg ($p=0,0075$); CRF 8,62±1,52 mmHg vs. 10,30±1,92 mmHg, ($p=0,0049$) respectivamente. Estudando quatro casos de ceratocone unilateral e dezesseis olhos saudáveis como controle, encontramos os valores de CH 8,13±2,0 mmHg nos olhos acometidos, 8,96±0,86 mmHg nos contralaterais e 9,89±1,33 mmHg no grupo controle ($p > 0,064$ em todas as comparações); e CRF de 7,96±2,43 mmHg, 8,92±1,39 mmHg e 9,90±2,24 mmHg respectivamente ($p > 0,335$ em todas as comparações). Em 46 olhos de 30 pacientes com córneas finas normais (CCT ≤ 505μm) os valores de CH e CRF foram, respectivamente, 8,63±1,23 mmHg e 8,43±1,29 mmHg; estatisticamente mais baixos quando comparados com os valores encontrados em 42 olhos de 30 pacientes com ceratocone (pareados por CCT, gênero e idade) de 8,07±1,17 mmHg ($p=0,0312$) e 7,22±1,34 mmHg ($p<0,001$). **Conclusões:** Os parâmetros biomecânicos estudados mostraram associação com a espessura corneana central, gênero e idade em indivíduos saudáveis. Pacientes com diferentes apresentações e classificações de ceratocone exibiram valores inferiores aos do grupo controle. No entanto, a grande interseção dos valores obtidos não permitiu a determinação de valores de corte para diferenciação entre os grupos com adequadas sensibilidade e especificidade.

1. INTRODUÇÃO

O estudo da biomecânica corneana trata do equilíbrio e deformação teciduais decorrentes de qualquer força aplicada.[1-5] Além do componente genético, diversos fatores atuam em conjunto no estabelecimento do equilíbrio dinâmico da arquitetura e funcionamento corneanos. Podemos dividi-los em fatores extra e intra-corneanos (Quadro 1).

Quadro 1. Fatores determinantes da biomecânica corneana

Fatores extra-corneanos
Pressão intraocular
Pressão atmosférica
Pressão exercida pelas pálpebras
Tensão exercida pelos músculos extraoculares
Tensão exercida pelo músculo ciliar
Fatores Intra-corneanos
Densidade, entrecruzamento, ligações químicas, distribuição, orientação e tipo das fibras colágenas
Espessura (central e variação regional)
Hidratação estromal e seu controle pelo endotélio
Outros, tais como idade e exposição solar

Dentre os fatores extra-corneanos a pressão intra-ocular é a mais importante, exercendo uma força contínua na face interna da córnea.[1] Alguns autores levantaram a hipótese de que o aumento da pressão intra-ocular seria capaz de acelerar o desenvolvimento de ectasia após LASIK, e seu controle (através de medicação hipotensora) poderia paralisar sua progressão ou até mesmo, ainda que temporariamente, revertê-la.[6-9]

Estudos da biomecânica corneana podem ajudar a compreender melhor esta condição, assim como detectar pacientes com maior risco de desenvolvê-la.

Os fatores intra-corneanos são inerentes à própria estrutura corneana, a qual possui capacidade de suportar as pressões citadas anteriormente, mantendo sua curvatura e propriedades ópticas. Das cinco camadas anatômicas da córnea somente o estroma e a canada de Bowman contém fibras colágenas, sendo consideradas por muito tempo as principais responsáveis pela resistência corneana [1]. No entanto, estudos recentes utilizando extensiometria sugerem que as propriedades biomecânicas da córnea não sofrem alterações significantes com a retirada da membrana de Bowman, o que torna o estroma a camada mais importante para a manutenção da integridade estrutural do tecido.[10-12] O estroma corneano é composto aproximadamente por 78% de água, 15% colágeno e 7% de proteínas não-colágenas, sais e proteoglicanos. Trezentas a quinhentas lamelas cruzam o tecido de limbo a limbo, com posicionamento e entrecruzamento variáveis.[3, 4, 13-15]

Tecidos ou materiais elásticos são aqueles com uma relação entre força aplicada e deformação: quando a força é retirada, o formato original é recuperado. Viscosidade se refere à tendência de um líquido resistir a fluir, com um ciclo força–deformação também proporcional. A córnea apresenta estas duas propriedades, sendo um exemplo de tecido viscoelástico. Ainda, apresenta propriedades materiais heterogêneas, não lineares e altamente anisotrópicas.[1-4, 16-21]

Evidências obtidas por meio da experiência com cirurgias incisionais, como a ceratotomia radial, mostraram que a córnea não é mecanicamente inerte.[1, 19] O aplanamento progressivo e irregular da córnea, que cursa com graus variáveis de hipermetropia e astigmatismo, ocorre em cerca de 40% dos casos em longo prazo e tornou-se um desafio para os cirurgiões refrativos.[22-24] Acredita-se que o aplanamento tardio, anos após ceratotomia radial, esteja relacionado com a não cicatrização total das incisões.

Em um artigo clássico ("*The cornea is not a piece of plastic*"), Roberts [19] sugere que a córnea seja considerada como uma séria de bandas elásticas (lamelas) com esponjas entre cada camada (espaços interlamelares preenchidos com matriz extracelular). As bandas elásticas estão tensionadas constantemente, uma vez que existe uma força as empurrando (pressão intra-ocular), e suas extremidades são unidas firmemente ao limbo. A quantidade de água que cada esponja é capaz de manter é determinada pelo quanto os elásticos estão tencionados. Quanto maior a força submetida aos elásticos, maior a tensão e mais água é "espremida" das esponjas, com resultante menor espaço interlamelar.

O estudo da biomecânica é crucial para entendermos melhor a resposta da córnea à cirurgia refrativa com o Excimer Laser.[25, 26] Os resultados refrativos e visuais dependem do perfil de ablação, processo cicatricial e resposta biomecânica corneana à mudança em sua estrutura. Sendo assim, se pudéssemos avaliar individualmente as propriedades biomecânicas de cada paciente, poderíamos escolher e ajustar o tratamento de maneira a atingir o melhor resultado para cada indivíduo. Da mesma maneira, o conhecimento adquirido serviria para uma melhor seleção pré-operatória e reconhecimento de pacientes com maior risco de resultado insatisfatório ou progressão para ectasia corneana. Técnicas de aferição das propriedades biomecânicas da córnea *in vivo* despertam, portanto, grande interesse e investimento.

Considerando o grande interesse e necessidade clínica, novos métodos propedêuticos são, cada vez mais, encontrados na literatura para a avaliação das propriedades biomecânicas da córnea.[1, 2, 18, 20, 27-34] Destaca-se com possível futuro de aplicação clínica interferometria, imagem corneana dinâmica (através de uma técnica de topografias seriadas com indentação corneana) e avaliação do comportamento da córnea frente a um jato de ar. Este último encontra-se disponível clinicamente, e proporciona novos parâmetros métricos nomeados histerese (CH) e fator de resistência corneana (CRF).

No ano de 2005 Luce [30] descreve o funcionamento de um novo aparelho, denominado "*Ocular Response Analyzer*" (ORA), desenvolvido para determinar propriedades biomecânicas da córnea e as correlacionar com a pressão intra-ocular. Este equipamento utiliza um jato de ar, semelhante ao utilizado em tonômetros de sopro, gerando uma força/pressão diretamente na córnea. Com isso são aferidos dois momentos de aplanação corneana em aproximadamente 20 milisegundos, um tempo suficientemente curto para minimizar a influência de fatores como pulso ocular ou posicionamento ocular no processo de mensuração.

Durante as medidas, um pulso de ar precisamente controlado é aplicado na córnea, fazendo com que a mesma se deforme, passe por uma primeira aplanação e por uma ligeira concavidade. Milisegundos após a primeira aplanação, a bomba de ar geradora do pulso é desligada, e a pressão aplicada ao olho diminui progressivamente. Para confiabilidade da aferição dos parâmetros biomecânicos, é fundamental que as fases ascendentes e descendentes da curva sejam simétricas (Figura 1, linha verde). Com a diminuição da pressão do ar contra a córnea, o tecido passa por um segundo estado de aplanação, durante o processo de recuperação de sua forma original (de concavidade para arquitetura convexa normal). Um sistema eletro-óptico monitora a curvatura corneana nos 3 mm centrais durante os cerca de 20 milisegundos da aferição (Figura 1, linha azul). As duas fases de aplanação, aferidas durante os movimentos de deformação para trás e para frente da córnea, são determinadas e correlacionadas com a pressão de ar aplicada. A diferença das pressões aferidas durante as aplanações é determinada pela capacidade do tecido absorver energia, e é chamada de histerese corneana (CH). O fator de resistência corneana (CRF) é uma medida derivada da diferença entre as pressões, com maior peso na primeira pressão de aplanação. Os valores de CH e CRF são independentes, cada um nos dando informações distintas.

A introdução destes novos parâmetros fornecidos pelo ORA na prática clínica tem despertado enorme interesse da comunidade científica em todo o mundo, com diversos artigos publicados recentemente. Dentre outras informações, os trabalhos mostram que os valores de CH e CRF mantêm-se constantes ao longo do dia, e apresentam valores mais baixos em casos de ectasia corneana, edema estromal, e após cirurgias refrativas. Ainda, tem-se postulado sobre a importância desses novos índices no manejo de pacientes com doenças oculares, tais como glaucoma e ceratocone.[21, 27, 28, 35-73]

Pelos motivos aqui expostos e discutidos, acreditamos que o estudo das propriedades biomecânicas da córnea poderá trazer grandes benefícios para a comunidade científica e sociedade em geral. Cirurgias e intervenções clínicas poderão ser modificadas e aprimoradas de acordo com a resposta individual de cada paciente. Resultados melhores e mais previsíveis, assim como a redução de efeitos adversos e complicações são esperados com o uso desse novo conhecimento.

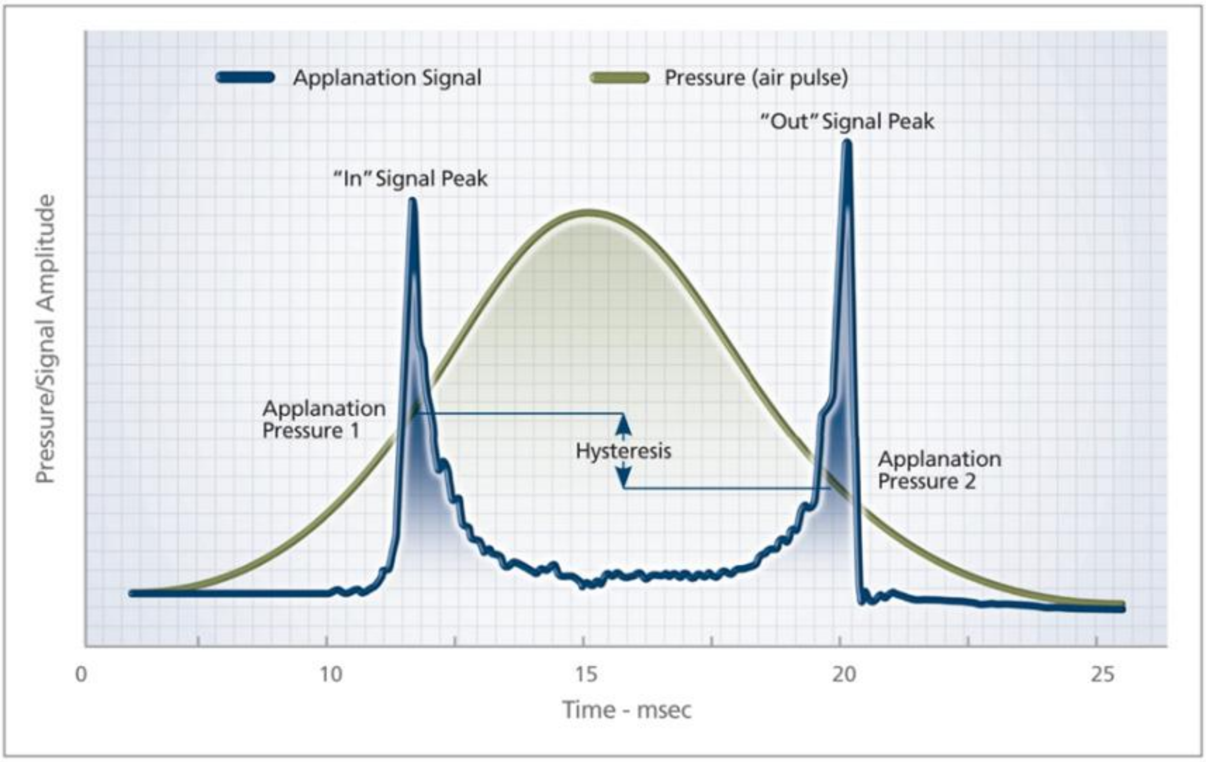

Figura 1. Representação gráfica da curva de pressão do jato de ar (linha verde) e resposta do tecido corneano à mesma (linha azul)

2. OBJETIVOS

Estudar os parâmetros biomecânicos da córnea aferidos pelo ORA e suas alterações em pacientes com ceratocone, correlacionando os valores encontrados em diversas apresentações da doença e comparando com os achados em indivíduos com córneas normais.

3. ARTIGOS

1. Fontes BM, Ambrosio R Jr, Alonso RS, Jardim D, Velarde GC, Nose W. Corneal biomechanical metrics in eyes with refraction of -19.00 to +9.00 D in healthy Brazilian patients. J Refract Surg. 2008 Nov;24(9):941-5.

2. Fontes BM, Ambrosio Junior R, Jardim D, Velarde GC, Nose W. Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas. Arq Bras Oftalmol. 2010 Aug;73(4):333-7.

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5. Fontes BM, Ambrosio R Jr, Salomao M, Velarde GC, Nose W. Biomechanical and tomographic analysis of unilateral keratoconus. J Refract Surg. 2010 Sep;26(9):677-81.

6. Fontes BM, Ambrosio R Jr, Velarde GC, Nose W. Biomechanical evaluation of healthy thin corneas compared with matched keratoconus cases. Arq Bras Oftalmol. 2011;74(1):13-6.

3.1 Corneal biomechanical metrics in eyes with refraction of -19.00 to +9.00 D in healthy Brazilian patients

BIOMECHANICS

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

Bruno M. Fontes, MD; Renato Ambrósio, Jr, MD, PhD; Ruiz S. Alonso, MD; Daniela Jardim, MD; Guillermo C. Velarde, DSc; Walton Nosé, MD

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]

From Federal University of Sao Paulo (Fontes, Nosé); Fluminense Federal University, Rio de Janeiro (Ambrósio, Alonso, Velarde); and Renato Ambrósio Eye Institute, Rio de Janeiro (Ambrósio, Alonso, Jardim), Brazil.

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).

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).

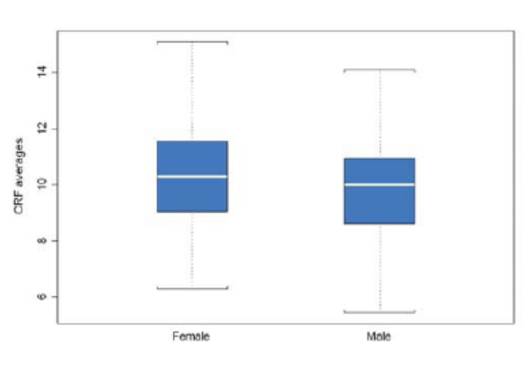

Figure 1. Corneal resistance factor (CRF) × gender. Mean value of 10.326 in women and 9.810 in men (*P*=.0266; 95% confidence interval 0.06043 to 0.97158; Standard two-sample *t* test).

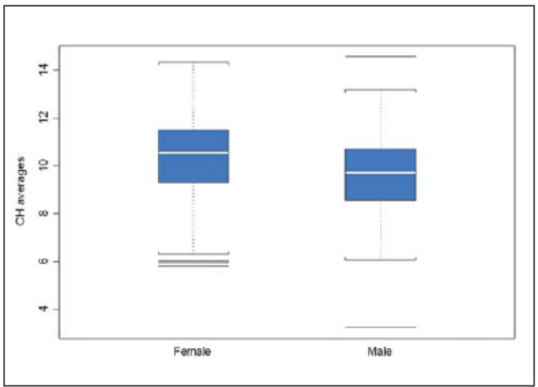

Figure 2. Corneal hysteresis × gender. Mean value of 10.421 in women and 9.727 in men (*P*=.0031; 95% confidence interval 0.235997 to 1.151652; Standard two-sample *t* test).

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]

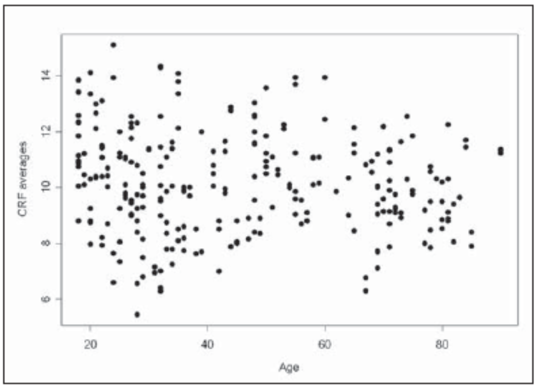

Figure 3. Negative correlation between corneal resistance factor (CRF) and age (r=−0.1255; *P*=.0434; Spearman's rank correlation).

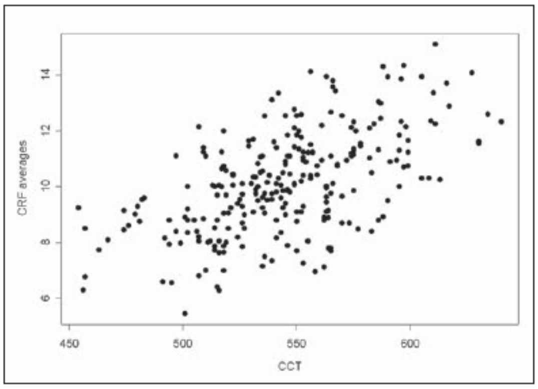

Figure 4. Positive association between corneal resistance factor (CRF) and central corneal thickness (CCT) (r=0.5760; *P*=.00; Pearson's product-moment correlation).

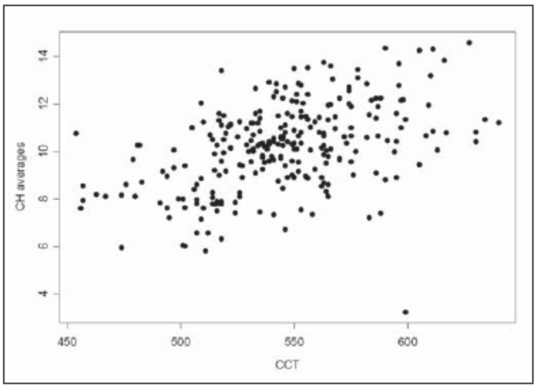

Figure 5. Corneal hysteresis (CH) was positively associated with central corneal thickness (CCT) (r=0.4655; *P*=.00; Pearson's product-moment correlation).

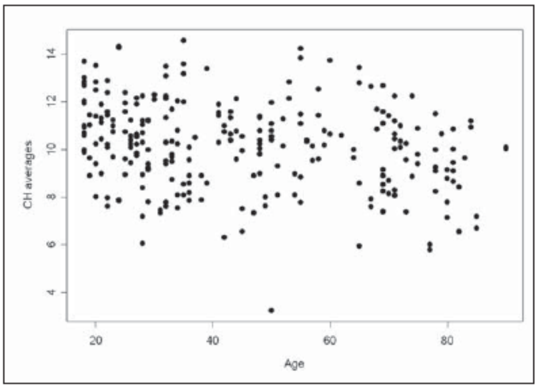

Figure 6. Corneal hysteresis (CH) was negatively correlated to age (r=−0.2445; *P*=.0001; Spearman's rank correlation).

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.

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3.2 Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas

ARTIGOS ORIGINAIS | *ORIGINAL ARTICLES*

Ability of corneal biomechanical metrics and anterior segment data in the differentiation of keratoconus and healthy corneas

Estudo da performance diagnóstica de parâmetros biomecânicos e dados anatômicos da câmara anterior na diferenciação de córneas saudáveis e com ceratocone

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ABSTRACT

Purpose: To evaluate the sensitivity, specificity, and test accuracy of corneal biomechanical metrics and anterior segment data in differentiating keratoconus from healthy corneas.

Methods: Comparative case series. Patients with and without keratoconus (gender and age-matched) were submitted for complete eye examinations including corneal hysteresis (CH) and corneal resistance factor (CRF) as measured by the Ocular Response Analyzer and anterior segment data as gathered through Pentacam assessments. The anterior segment data measurement included average central keratometric readings (K-Ave), corneal astigmatism (CA), central corneal thickness (CCT), anterior chamber depth (AC depth) and corneal volume (CV). All parameters were assessed, compared and analyzed. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point by which to maximize the sensitivity and specificity of discriminating keratoconus from normal corneas for each data category.

Results: Seventy seven eyes from forty three patients (24 male, 19 female) with keratoconus and eighty six eyes from forty three (24 male, 19 female) healthy controls were enrolled. ROC curve analysis showed poor overall predictive accuracy for all studied parameters in differentiating keratoconus from normal corneas. The highest sensitivity (79.2%) was obtained for both AC depth and CH (cutoff points 3.22 mm and 9.39 mmHg respectively). The best specificity (89.5%) and test accuracy (80.34%) were obtained for CA (cutoff point of 2.2 D).

Conclusion: When considered together, studied parameters showed statistical differences between groups. However, when considered independently they presented low sensitivity, specificity and test accuracy in differentiating keratoconus from healthy corneas.

Keywords: Cornea; Corneal diseases; Corneal topography; Biomechanics; Keratoconus.

RESUMO

Objetivo: *Avaliar a sensibilidade, especificidade e acurácia de parâmetros biomecânicos e anatômicos do segmento anterior isolados na diferenciação de córneas saudáveis e com ceratocone.*

Métodos: *Estudo tipo série de casos comparativa. Pacientes com ceratocone e controles saudáveis foram pareados (idade e sexo) e submetidos a exame oftalmológico completo, incluindo avaliação biomecânica (ORA) e tomográfica (Pentacam). Ceratometria central média, astigmatismo corneano, espessura corneana central, profundidade da câmara anterior, volume corneano, CH e CRF foram estabelecidos, avaliados e comparados. Curvas ROC (Receiver operating characteristic) foram utilizadas para identificar o melhor valor de corte que apresentasse a maior sensibilidade e especificidade na discriminação entre ceratocone e córneas saudáveis para cada dado estudado.*

Resultados: *Setenta e sete olhos de 43 pacientes com ceratocone (24 homens e 19 mulheres) e 86 olhos de pacientes saudáveis (24 homens e 19 mulheres) foram incluídos no estudo. Curvas ROC mostraram baixa acurácia na predição do diagnóstico de ceratocone em todos os parâmetros isolados estudados. Maior sensibilidade encontrada foi 79,2% para profundidade da câmara anterior e CH (ponto de corte 3,22mm e 9,39mmHg respectivamente); maior especificidade e acurácia foram encontradas na análise do astigmatismo corneano (ponto de corte 2,2 D; 89,5% e 80,34% respectivamente).*

Conclusão: *Todos os parâmetros estudados mostraram diferença estatisticamente significativa entre os grupos. No entanto, quando considerados isoladamente apresentaram baixas sensibilidade, especificidade e acurácia na diferenciação entre ceratocone e córneas saudáveis.*

Descritores: *Córnea; Doenças da córnea; Topografia da córnea; Biomecânica; Ceratocone*

Study carried out at Ophthalmology Department, Escola Paulista de Medicina, Universidade Federal de São Paulo - UNIFESP - São Paulo (SP), Brazil; Clínica Oftalmológica Renato Ambrósio - Rio de Janeiro (RJ), Brazil.

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Recebido para publicação em 30.07.2010
Última versão recebida em 07.05.2010
Aprovação em 12.07.2010

No financial support was available for this project.
Renato Ambrosio, MD is a consultant for Oculus and Reichert Companies.

Nota Editorial: Depois de concluída a análise do artigo sob sigilo editorial e com a anuência dos Drs. Luis Alberto Carvalho e Diane Ruschel Marinho sobre a divulgação de seus nomes como revisores, agradecemos sua participação neste processo.

INTRODUCTION

Keratoconus is an ectatic disease of the cornea, with progressive noninflammatory thinning and anterior protrusion that leads to an irregular conical shape[1-4]. It is usually a bilateral and asymmetric condition that manifests at puberty. Clinical (as corneal stromal thinning, conical protrusion, Vogt striae and Fleischer ring) and topographic (as irregular astigmatism, inferior steepening and inferior-superior asymmetry) findings are habitually combined for diagnosing and staging the disease[5-6].

Recently, new technology in eye imaging such as the Pentacam (Oculus Inc, Wetzlar, Germany) has revealed valuable information regarding corneal and anterior segment anatomy. These developments can be credited, primarily, to progress in refractive surgery and the need for better preoperative screening. Diagnosis of keratoconus has been improved by curvature (elevation) maps, corneal pachymetric distribution, corneal volume and anterior segment data, which have all been provided by a variety of currently available equipment[5-14]. However, accurate differentiation of keratoconus from healthy corneas is not yet sufficient, as there is a need to detect corneas with a higher susceptibility to becoming ectatic after laser photoablative surgery[15-16].

In vivo corneal biomechanical evaluation was first described by Luce[17] in 2005, with the development of the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Depew, New York, USA). A number of researchers published diverse and exciting new data regarding corneal hysteresis (CH) and corneal resistance factor (CRF) in healthy and pathological conditions[18-22]. If ORA proves that "fragile" corneas are more susceptible than "strong" corneas to developing ectasia in the future, then the best use for such data in refractive surgery would be in preoperative screening.

The present study compared the findings of biomechanical and anterior segment parameters in differentiating keratoconus from healthy corneas, and evaluated the ability of each individual parameter to differentiate them.

METHODS

This was 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 (protocol 0123/06). All subjects were informed about the purpose of the study and gave informed consent before inclusion. Patients were sequentially evaluated from October 2005 to December 2008. Demographic and clinical data were obtained, including date of birth, gender and self-reported race or ethnicity.

The keratoconus group consisted of 77 eyes from 43 patients (24 male, 19 female) with a mean age of 34.95 ± 11.95 years (ranging from 18 to 73 years). The control group consisted of 86 eyes from 43 (24 male, 19 female) gender- and age-matched healthy patients, with a mean age of 35.02 ± 12.19 years (ranging from 18 to 72 years-old) (p=1).

Each subject underwent a comprehensive ophthalmologic examination including review of medical history, best-corrected visual acuity, slit lamp biomicroscopy, fundoscopic examination, Placido disc topography (Humphrey ATLAS, Carl Zeiss Meditec Inc. Dublin, USA), Pentacam tomographic evaluation and ORA measurements.

Diagnosis of keratoconus was made by clinical (corneal stromal thinning, Vogt's striae, Fleischer ring, scissoring of the red reflex or oil droplet sign identified by retinoscopy) and topographic (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[2,5-6,10,23]) evaluation.

Cases were gender- and age-matched with controls for data comparison[21]. Exclusion criteria were: less than 18 years-old, any previous corneal or ocular surgery, any eye disease that could possibly interfere with the readings/results (e.g., glaucoma, uveitis, corneal ectatic disease, Fuch's 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 agreement. Contact lenses were required to be removed at least 72 h before examination.

Patients underwent testing with the ORA and Pentacam during the same visit. All measurements were taken between 8:00 AM and 6:00 PM. Two consecutive ORA measurements were performed on both eyes and the results were averaged. Only high-quality readings (defined by the manufacturer as both the force-in and force-out applanation signal peaks on the ORA waveform being fairly symmetrical in height) were stored. The Pentacam assessed central keratometry (K-Ave), corneal astigmatism (CA), central corneal thickness (CCT), anterior chamber depth (AC depth) and corneal volume (CV).

The Pentacam system was 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 (a blue light-emitting diode at 475 nm) that rotate together. After proper alignment of the patient's face, a fixation target is shown, which guides the patient's gaze. A real-time image of the patient's eye is shown to the examiner on the computer screen, and the image is manually focused and centered. The 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. Minute eye movements are captured by a second camera and corrected simultaneously. Single point pachymetric measurements of the entire cornea are calculated from the anterior and posterior corneal surfaces.

The ORA determines corneal biomechanical properties using an applied force-displacement relationship. Details have been extensively described in previous studies[17]. 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 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 (CH). 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 (CRF) was empirically derived to maximize correlation to CCT, and it can be considered to be weighted by elastic resistance since it has a stronger correlation to CCT than CH. Though CH 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 are provided as the mean and standard deviation (SD). Differences between data were evaluated using the Welch modified Student's two-sample *t*-test and Wilcoxon rank-sum test. The level of significance for each parameter was set at $p<0.05$. A receiver operating characteristic (ROC) curve was used to identify the cutoff point of studied parameters to maximize sensitivity and specificity in discriminating keratoconus from normal corneas. This curve is obtained by plotting sensitivity against 1- specificity, calculated for each value observed. An ideal area of 100% implies that the test perfectly discriminates between groups. Logistic regression was used to support the cutoff point identified with the ROC curve analysis.

RESULTS

K-Ave was 47.03 ± 5.22 diopters (D) (range 40.4 to 74.15 D) in keratoconus and 43.31 ± 1.53 D (range 39.9 to 46.75 D) in the control group (p=0). CA was 3.46 ± 2.20 D (range 0.7 to 10.9 D) in keratoconus and 1.08 ± 0.81 D (range 0 to 4.9 D) in the control group (p=0). CCT was 493.17 ± 42.84 µm (range 349 to 568 µm) in keratoconus and 543.90 ± 34.87 µm (range from 457 to 627 µm) in the control group (p=0) (Figure 1). AC depth was 3.25 ± 0.38 mm (range 2.41 to 5.21 mm) in keratoconus and 3.07 ± 0.42 mm (range 2.08 to 3.80 mm) in the control group (p=0.012). CV was 57.01 ± 3.53 mm^3 (range 49.5 to 66.9 mm^3) in keratoconus and 60.19 ± 3.40 mm^3 (range 53.7 to 68.5 mm^3) in the control group (p=0).

CH was 8.23 ± 1.51 mmHg (range 4.60 to 11.80 mmHg) in keratoconus and 10.13 ± 1.75 mmHg (range 5.95 to 14.58 mmHg) in the control group (p=0) (Figure 2). CRF was 7.46 ± 1.76 mmHg (range 2.80 to 11.20 mmHg) in keratoconus and 10.06 ± 1.97 mmHg (range 5.45 to 15.10 mmHg) in the control group (p=0) (Figure 3). The results are summarized in table 1.

ROC curve analyses showed poor overall predictive accuracy for all studied parameters in differentiating keratoconus from normal corneas. The results are summarized in table 2.

Higher sensitivity in differentiating keratoconus from healthy corneas was 79.2% for AC depth and CH (cutoff point 3.22 mm and 9.39 mmHg respectively); the best specificity and test accuracy for CA (cutoff point 2.2 D; 89.5% and 80.34% respectively). Lowest sensitivity was 62% for CV, with a specificity of 44.2% for AC depth and 69.93% test accuracy for K-Ave.

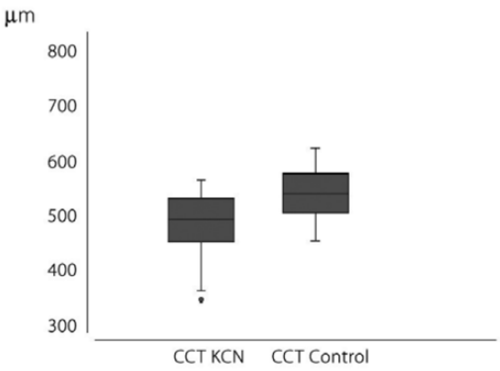
The cutoff point for K-Ave was 44.35 D with sensitivity of 74%, specificity of 66.3% and test accuracy of 69.93%. For CA, the cutoff point was 2.2 D with sensitivity of 70.1%, specificity of 89.5% and test accuracy of 80.34%. The cutoff point for CCT was 521 µm, with sensitivity of 77.9%, specificity of 80.2% and test accuracy of 79.11%. The cutoff point for AC depth was 3.22 mm, with sensitivity of 79.2%, specificity of 44.2% and test accuracy of 60.72%. The cutoff point for CV was 57.8 mm^3, with sensitivity of 62%, specificity of 77.9% and test accuracy of 70.71%. The cutoff point was 9.39 mmHg for CH, with sensitivity of 79.2%, specificity of 70.9% and test accuracy of 74.82% (ROC curve for CH is seen in Figure 4). The cutoff point was 8.68 mmHg for CRF, with sensitivity of 77.9%, specificity of 75.6% and test accuracy of 76.69%.

DISCUSSION

Biomechanical study of the cornea is crucial for refractive surgery progress not only for better preoperative screening, but also for prediction of individual outcomes. As Ethier et al.[24] stated, material properties of the cornea are heterogeneous, highly anisotropic, nonlinear, and viscoelastic. In a broad review, Torres et al.[25] described CCT and corneal collagen fiber density as the most important intrinsic factors determining corneal biomechanics. We would include corneal hydration (and its control by the endothelium), corneal thickness regional variation, collagen fibril orientation and distribution.

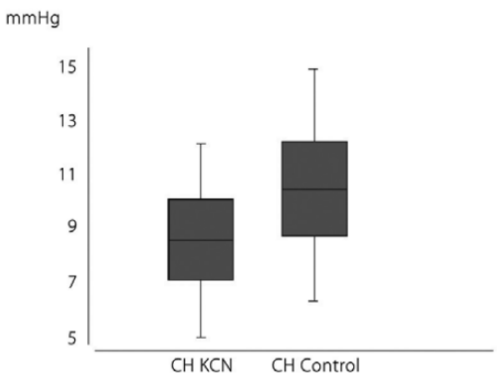
Kida et al.[26], and Laiquzzaman et al.[27] found that CH remained almost constant throughout the day, whereas CCT and intraocular pressure showed statistically significant variations (higher values during the nocturnal period) in young adults. The small number of patients in both studies might restrict their findings to these specific populations. Previous studies, including ours[21], indicate a through relation between CRF and CH with CCT and an inverse relation with age. The present data, in agreement with previous research[28-30], show that biomechanical metrics are statistically lower in keratoconus then in normal corneas. However, the big overlap of the results of both groups involves the issue of accuracy in discriminating normal from abnormal corneas. New data presented recently by David Luce (ASCRS 2009 meeting, San Francisco - CA) regarding waveform parameters provided from the ORA signal may turn out to be more sensitive than CH and CRF in discriminating abnormal corneas.

Anterior segment tomography has been the subject of several papers[5,7-8,31-32], and has shown its accuracy in corneal and anterior segment mapping. New parameters, such as corneal volume, pachymetric progression and elevation maps are of



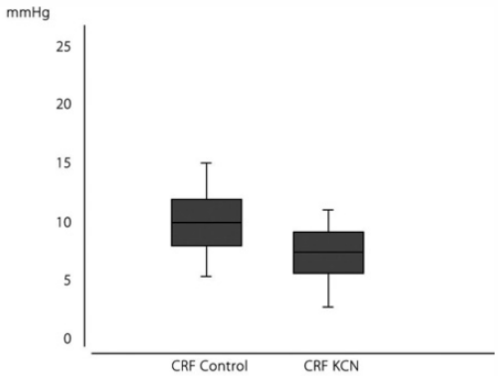
KCN= keratoconus

Figure 1. Central corneal thickness (CCT) distribution.



KCN= keratoconus

Figure 2. Corneal hysteresis (CH) distribution.



KCN= keratoconus

Figure 3. Corneal resistance factor (CRF) distribution.

Table 1. Summary of the anterior segment parameters and biomechanical metrics results of studied population

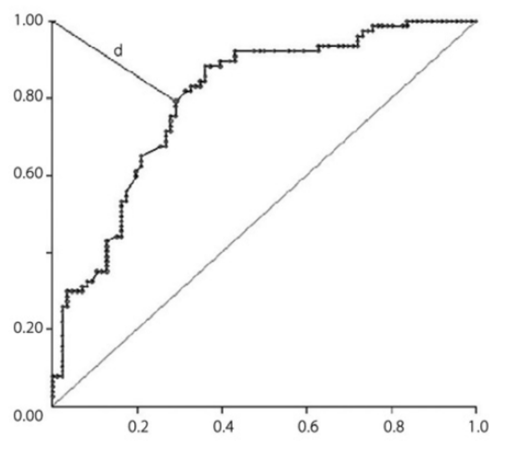
	K-Ave (D)	CA (D)	CCT (µm)	AC depth (mm)	CV (mm³)	CH (mmHg)	CRF (mmHg)
Keratoconus							
(mean ± SD)	47.03 ± 5.22	3.46 ± 2.20	493.17 ± 42.84	3.25 ± 0.38	57.01 ± 3.53	8.23 ± 1.51	7.46 ± 1.76
(min - max)	40.40 - 74.15	0.70 - 10.90	349.00 - 568.00	2.41 - 5.21	49.50 - 66.90	4.60 - 11.80	2.80 - 11.20
Controls							
(mean ± SD)	43.31 ± 1.53	1.08 ± 0.81	543.90 ± 34.87	3.07 ± 0.42	60.19 ± 3.40	10.13 ± 1.75	10.06 ± 1.97
(min - max)	39.90 - 46.75	0 - 4.90	457.00 - 627.00	2.08 - 3.80	53.70 - 68.50	5.95 - 14.58	5.45 - 15.10
Statistical analysis	Wilcoxon rank-sum test P=0	Wilcoxon rank-sum test P=0	Welch modified two-sample t-test P=0 (95% CI) 38.55 - 62.90	Wilcoxon rank-sum test P=0.012	Welch modified two-sample t-test P=0 (95% CI) 1.77 - 4.05	Welch modified two-sample t-test P=0 (95% CI) 1.39 - 2.40	Welch modified two-sample t-test P=0 (95% CI) 2.03 - 3.18

SD= standard deviation; min= minimum; max= maximum; D= diopters; µm= micrometers; mm= millimeters; mmHg= millimeters of mercury; K-Ave= central keratometry; CA= corneal astigmatism; CCT= central corneal thickness; AC depth= anterior chamber depth; CV= corneal volume; CH= corneal hysteresis; CRF= corneal resistance factor

Table 2. Receiver operating characteristic (ROC) identified the best cutoff point of studied parameters to maximize sensitivity and specificity in differentiating keratoconus and healthy corneas

	Cutoff point	Sensitivity (%)	Specificity (%)	Test accuracy
K-Ave	44.35 D	74.0	66.3	69.93
CA	2.2 D	70.1	89.5	80.34
CCT	521 µm	77.9	80.2	79.11
AC depth	3.22 mm	79.2	44.2	60.72
CV	57.8 mm³	62.0	77.9	70.71
CH	9.39 mmHg	79.2	70.9	74.82
CRF	8.68 mmHg	77.9	75.6	76.69

K-Ave= central keratometry; CA= corneal astigmatism; CCT= central corneal thickness; AC depth= anterior chamber depth; CV= corneal volume; CH= corneal hysteresis; CRF= corneal resistance factor



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 hysteresis (CH) data. Cutoff point was 9.39 mmHg, with sensitivity of 79.2%, specificity of 70.9% and test accuracy of 74.82%.

great utility in clinical practice[8-10,13-14,33-36]. In the present study, we were able to detect statistical difference in all anterior segment parameters given by the Pentacam rotating Scheimpflug camera. But, as in CH and CRF, a big overlap was found. The corneal color maps given by the Pentacam, as well as automated software for keratoconus screening and new indices such as the Belin/Ambrosio enhanced ectasia screening did not constitute a subject of our study. We studied only the isolated data given by the machine during anterior segment screening.

In conclusion, although all studied parameters showed statistical differences between the two groups, when considered individually they showed low sensitivity, specificity and test accuracy for keratoconus and healthy cornea differentiation. Corneal maps and automated software given by the Pentacam were not the subject of our study. New studies are warranted to expand the knowledge of corneal biomechanical metrics and anterior segment tomography.

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3.3 Corneal biomechanical metrics and anterior segment parameters in mild keratoconus

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±standard deviation) were –3.55±2.87 diopters (D) versus –1.46±3.09 D ($P = 0$); K-Avg, 45.09±2.24 versus 43.24±1.54 D ($P = 0$); CA, 3.15±1.87 versus 1.07±0.83 D ($P = 0$); CV, 57.3±2.12 versus 60.86±3.39 mm^3 ($P = 0$); AC depth, 3.19±0.35 versus 3.05±0.43 mm ($P = 0.0416$); CCT, 503±34.15 versus 544.71±35.89 μm ($P = 0$); CH, 8.50±1.36 versus 10.17±1.79 mmHg ($P = 0$); CRF, 7.85±1.49 versus 10.13±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.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
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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.

ISSN 0161-6420/10/$–see front matter
doi:10.1016/j.ophtha.2009.09.023

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

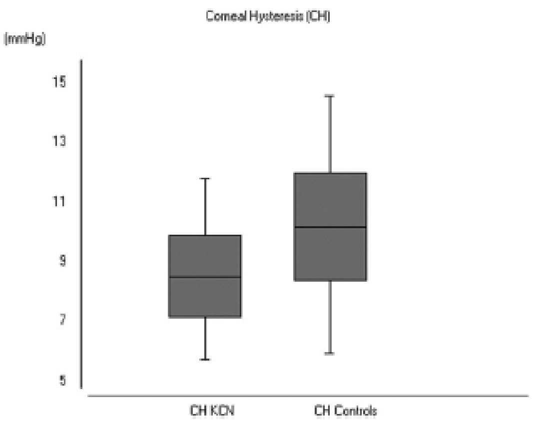

Figure 1. Box plot showing corneal hysteresis (CH) distribution in both groups. KCN = keratoconus.

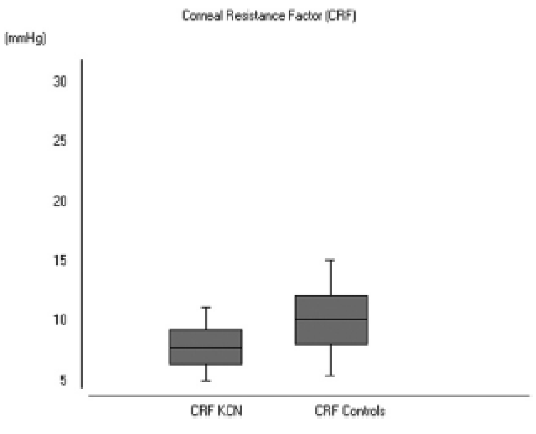

Figure 2. Box plot showing corneal resistance factor (CRF) distribution in both groups. KCN = keratoconus.

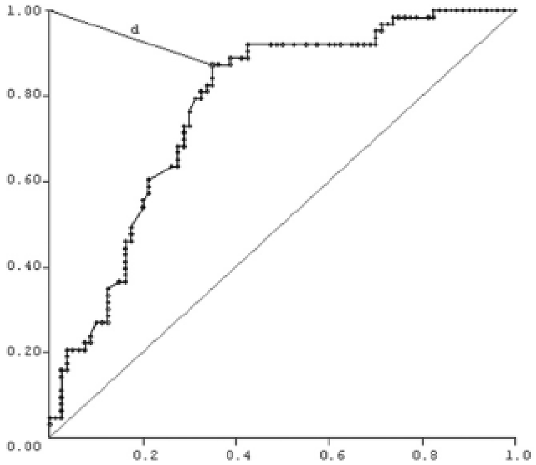

Figure 3. Receiver operating characteristic (ROC) curve (graphical plot of the sensitivity vs. 1–specificity) for corneal hysteresis (CH) data. The cutoff was 9.64 mmHg, with 87% sensitivity and 65% specificity (test accuracy, 74.83%). d = distance from cutoff point to the upper left corner or coordinate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

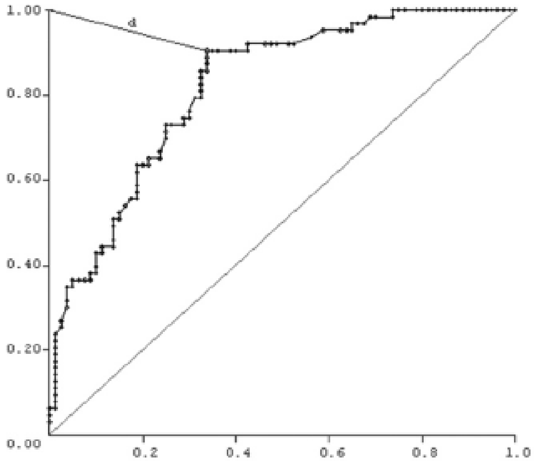

Figure 4. Receiver operating characteristic (ROC) curve (graphical plot of the sensitivity vs. 1–specificity) for corneal resistance factor (CRF) data. The cutoff was 9.60 mmHg, with 90.5% sensitivity and 66% specificity (test accuracy, 76.97%). d = distance from cutoff point to the upper left corner 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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Footnotes and Financial Disclosures

Originally received: February 23, 2009.
Final revision: August 29, 2009.
Accepted: September 14, 2009.
Available online: February 5, 2010. Manuscript no. 2009-262.

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Financial Disclosure(s):
The author(s) have made the following disclosure(s):
R. Ambrósio - Consultant - Oculus and Reichert.

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3.4 Ocular Response Analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes

BIOMECHANICS

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

Bruno M. Fontes, MD; Renato Ambrósio, Jr, MD, PhD; Guillermo Coca Velarde, DsC; Walton Nosé, MD

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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Received: November 12, 2009; Accepted: April 7, 2010

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

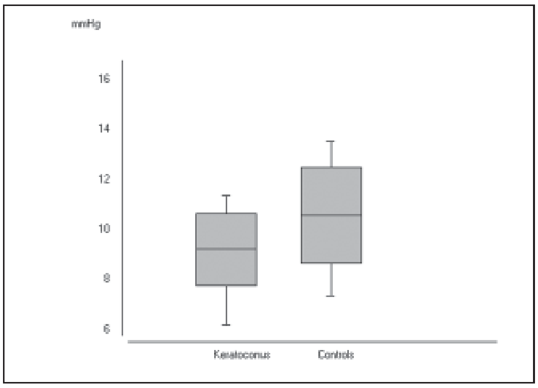

Figure 1. Corneal hysteresis (CH) distribution in the keratoconus and control groups (n=19 eyes in each group). Error bars indicate standard deviation.

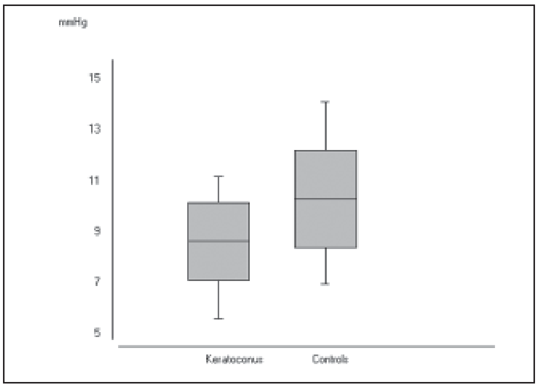

Figure 2. Corneal resistance factor (CRF) distribution in the keratoconus and control groups (n=19 eyes in each group). Error bars indicate standard deviation.

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.

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 1

Summarized Data of Eyes With Keratoconus and Control Eyes

	Mean±SD (Range)		
Demographic	**Keratoconus Group**	**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.*

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

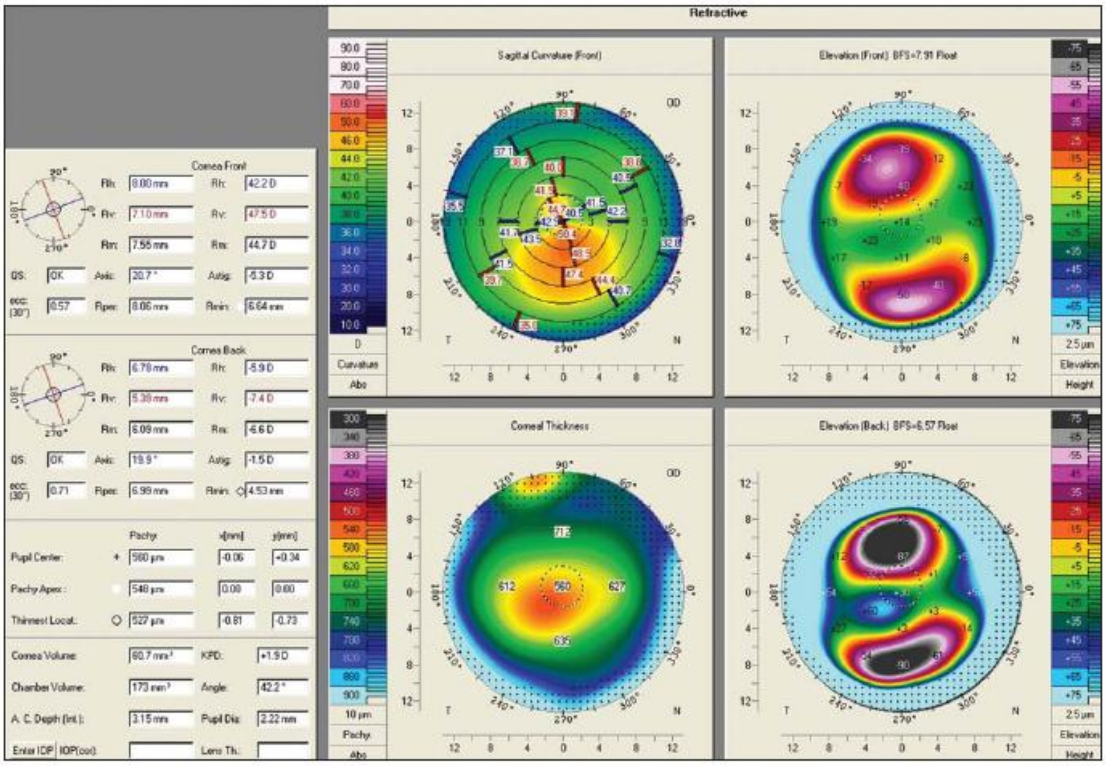

Figure 3. Pentacam examination of a patient with keratoconus and central corneal thickness ≥520 μm.

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.

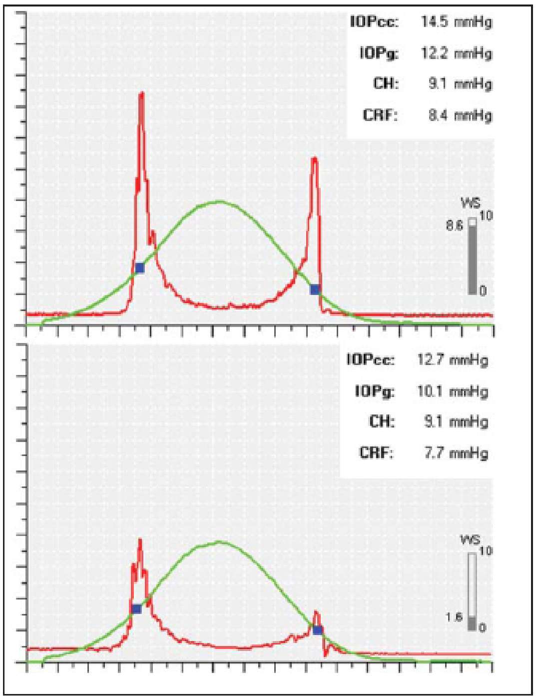

Figure 4. Corneal hysteresis of 9.1 mmHg in two healthy patients with completely different waveform signals.

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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3.5 Biomechanical and Tomographic Analysis of Unilateral Keratoconus

Biomechanical and Tomographic Analysis of Unilateral Keratoconus

Bruno M. Fontes, MD; Renato Ambrósio, Jr, MD, PhD; Marcella Salomão, MD; Guillermo C. Velarde, DSc; Walton Nosé, MD

ABSTRACT

PURPOSE: To evaluate and compare tomographic, clinical, and biomechanical data of patients with unilateral keratoconus and healthy controls.

METHODS: Observational, case-control study. Complete clinical eye examination was followed by topographic (ATLAS), tomographic (Pentacam), and biomechanical (Ocular Response Analyzer) evaluation. Cases were sex- and age-matched with healthy individuals for controls.

RESULTS: Four patients had unilateral keratoconus, and eight healthy patients served as controls. Central corneal thickness was 508±16 *µ*m in the keratoconus group, 531±12.7 *µ*m in the fellow eye group, and 528.6±40.7 *µ*m in the control group ($P>.125$, all comparisons). Central keratometry was 43.70±2.70 diopters (D) in the keratoconus group, 42.84±1.43 D in the fellow eye group, and 43.81±1.94 D in the control group ($P>.45$, all comparisons). Corneal astigmatism was 3.30±2.24 D in the keratoconus group, 1.38±1.49 D in the fellow eye group, and 1.34±1.13 D in the control group ($P=.037$ between the keratoconus and control groups; $P=.25$ between the keratoconus and fellow eye groups). Corneal hysteresis was 8.13±2 mmHg in the keratoconus group, 8.96±0.86 mmHg in the fellow eye group, and 9.89±1.33 mmHg in the control group ($P>.064$, all comparisons). Corneal resistance factor was 7.96±2.43 mmHg in the keratoconus group, 8.92±1.39 mmHg in the fellow eye group, and 9.90±2.24 mmHg in the control group ($P>.33$, all comparisons).

CONCLUSIONS: Corneal hysteresis and corneal resistance factor values were not statistically different among the groups; however, a trend for lower values was found for keratoconus and fellow eyes compared to controls. Data should be interpreted with caution because of the small sample. [*J Refract Surg*. 2010;26(9):677-681.]
doi:10.3928/1081597X-20091105-04

Keratoconus is an ectatic disorder in which thinning and protrusion of the cornea causes it to assume a conical shape. It is most commonly a bilateral and asymmetric condition with no sex or race predilection, with typical onset at puberty.[1] Unilateral cases are rarely described, with an estimated incidence of 1% to 4%.[2-7] A number of cornea specialists believe that patients initially diagnosed with unilateral keratoconus will develop the disease in the fellow eye over time. Currently, no test reliably detects anatomic or functional abnormality predicting disease progression in these eyes.

The ability to detect initial and subclinical (forme fruste) keratoconus has greatly improved with the use of new corneal imaging technology. The latest corneal topographers and tomographers are widely available, and new indices are described frequently.[8] Most improvements are due to the refractive surgery process, in which candidates are carefully screened preoperatively to avoid complications such as postoperative LASIK ectasia.[9,10] Corneal refractive surgery should not be performed in keratoconus suspects or on apparently normal corneas in cases of unilateral keratoconus.

Since the first publication by Luce in 2005,[11] in vivo corneal biomechanics evaluation using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, New York) has been the subject of several publications.[12-20] The ORA records corneal inward and outward applanation after delivery of a metered collimated air pulse and gives two

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

The authors thank Dan Z. Reinstein, MD, for his comments and input during the review process.

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Received: September 27, 2008; Accepted: October 6, 2009

Posted online: November 16, 2009

corneal biomechanic metrics: corneal hysteresis and corneal resistance factor. In the present study, we evaluated and compared tomographic, clinical, and biomechanical findings in patients with unilateral keratoconus and healthy control individuals.

PATIENTS AND METHODS

An observational, case-control study was performed. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee from Federal University of São Paulo. All study participants were informed about the purpose of the study and gave informed consent before inclusion. Patients were sequentially evaluated from October 2005 to December 2006.

Patients were diagnosed as having unilateral keratoconus during complete eye examination. Diagnosis of keratoconus (keratoconic eyes) was made by clinical (corneal stromal thinning, Vogt's 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[21]).

Each patient underwent a comprehensive ophthalmologic examination including review of medical history, corrected distance visual acuity, slit-lamp microscopy, funduscopic examination, Placido disk topography (Humphrey ATLAS; Carl Zeiss Meditec, Jena, Germany), Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) tomographic evaluation, and ORA measurements. Cases were sex- and age-matched with healthy individuals serving as controls. Patients were divided into three groups for data comparison: keratoconus group, fellow eye group, and control group.

Exclusion criteria were patient age <18 years, previous corneal or ocular surgery, eye disease other than keratoconus, chronic and/or continuous use of topical medications, corneal scars and/or opacities, and objection to signing 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.A., M.S.) during the same visit. All measurements were taken between 8 AM and 6 PM. Two consecutive ORA measurements were performed on both eyes (only good quality readings, as defined by the manufacturer, were recorded), and results averaged. Spherical equivalent refraction was obtained by dynamic refraction during the clinical examination. Central keratometry (average central K), central corneal thickness, corneal astigmatism, and anterior chamber depth were assessed by the Pentacam.

A detailed description of the Pentacam system was published in a previous study by our group[12] and other investigators.[22-24] Briefly, a 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. The central corneal thickness, average central keratometry, corneal astigmatism, and anterior chamber depth 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 described previously.[11,13,14,16,18] Corneal hysteresis 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 measurement of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface, and is an indicator of the overall resistance of the cornea. Although corneal hysteresis and corneal resistance factor are related, in some instances they can be significantly different, each providing distinct information about the cornea.

Statistical analysis was performed with BioEstat 5.0 software (Belém, PA, Brazil). Data are expressed as mean±standard deviation. The Wilcoxon test (signed-rank or rank-sum, where indicated) was used to compare results among the groups.

RESULTS

During the study period, 77 patients were diagnosed as having keratoconus, all of whom had presented for refractive surgery preoperative evaluation. Four patients (2 men and 2 women, corresponding to 5.2% of the total evaluated keratoconus patients) were diagnosed as having unilateral keratoconus, and 8 healthy patients (4 men and 4 women, 16 eyes) were used as controls. Mean age for the keratoconus and control groups was 32±12.8 years and 33.9±12.5 years, respectively. At slit-lamp examination, all eyes in the keratoconus group had corneal thinning and mild iron deposit (Fleischer ring) with no visible scar. Biomicroscopic examination of the remaining groups was within normal limits. Spherical equivalent refraction was −4.40±3.80 diopters (D) in the keratoconus group, −4.50±4.40 D in the fellow eye group, and −2.31±2.58 D in the control group.

Central corneal thickness was 508±16 µm in the keratoconus group, 531±12.7 µm in the fellow eye group, and 528.6±40.7 µm in the control group (P>.125, all comparisons). Average central keratometry was 43.70±2.70 D in the keratoconus group, 42.84±1.43 D in the fellow eye group, and 43.81±1.94 D in the control

TABLE 1

Demographic, Clinical, Tomographic, and Biomechanical Data in Patients With and Without Unilateral Keratoconus

	Keratoconus Group	Fellow Eye Group	Control Group
Gender (M/F)	2/2	2/2	4/4
Age (y)	32±12.8 (18 to 49)	32±12.8 (18 to 49)	33.9±12.5 (19 to 48)
SE (D)	−4.40±3.80 (−9.75 to −1.75)	−4.50±4.40 (−10.75 to −1.25)	−2.31±2.58 (−7.25 to +1.00)
Slit-lamp findings (all eyes)	Corneal thinning, Fleischer ring	None	None
K-Ave (D)	43.70±2.70 (40.40 to 46.20)	42.84±1.43 (40.85 to 44.00)	43.81±1.94 (39.90 to 46.20)
Corneal astigmatism (D)	3.34±2.20 (1.20 to 6.40)	1.38±1.49 (0.20 to 3.50)	1.34±1.13 (0.30 to 3.70)
ACD (mm)	3.3±0.2 (3.07 to 3.63)	3.26±0.28 (2.94 to 3.55)	3.12±0.39 (2.55 to 3.7)
CCT (μm)	508±16 (487 to 521)	531±12.7 (517 to 542)	528.6±40.7 (457 to 597)
CRF (mmHg)	7.96±2.43 (5.2 to 10.7)	8.92±1.39 (7.8 to 10.6)	9.90±2.24 (6.8 to 14.4)
CH (mmHg)	8.13±2.0 (6.6 to 11.1)	8.96±0.86 (8.1 to 10.1)	9.89±1.33 (7.8 to 12.3)

SE = spherical equivalent refraction, K-Ave = average central keratometry, ACD = anterior chamber depth, CCT = central corneal thickness, CRF = corneal resistance factor, CH = corneal hysteresis

TABLE 2

Comparative, Statistical Analysis of Patients With and Without Unilateral Keratoconus

	P Value					
Groups	**K-Ave**	**CA**	**ACD**	**CCT**	**CRF**	**CH**
Keratoconus vs fellow eye	.4576	.25	.25	.125	.375	.375
Keratoconus vs control	.8499	.0374*	.3947	.2902	.3352	.064
Fellow eye group vs control group	.2326	.3575	.0721	.2326	.2102	.1018

K-Ave = average central keratometry, CA = corneal astigmatism, ACD = anterior chamber depth, CCT = central corneal thickness, CRF = corneal resistance factor, CH = corneal hysteresis
**Statistical difference.*
Note. Results should be interpreted with caution because of the small sample size. An optimal sample would be composed of 20 individuals with unilateral keratoconus.

group (P>.45, all comparisons). Corneal astigmatism was 3.30±2.24 D in the keratoconus group, 1.38±1.49 D in the fellow eye group, and 1.34±1.13 D in the control group (P=.037 between the keratoconus and control groups; P=.25 between the keratoconus and fellow eye groups; P=.3575 between the fellow eye and control groups). Anterior chamber depth was 3.3±0.2 mm in the keratoconus group, 3.26±0.28 mm in the fellow eye group, and 3.12±0.39 mm in the control group (P>.072, all comparisons).

Corneal hysteresis was 8.13±2 mmHg in the keratoconus group, 8.96±0.86 mmHg in the fellow eye group, and 9.89±1.33 mmHg in the control group (P>.064, all comparisons). Corneal resistance factor was 7.96±2.43 mmHg in the keratoconus group, 8.92±1.39 mmHg in the fellow eye group, and 9.90±2.24 mmHg in the control group (P>.33, all comparisons). Demographic, clinical, tomographic, and biomechanical data are summarized in Table 1.

A statistically significant difference (P<.05) was only found in regards to corneal astigmatism between the keratoconus and control groups. Statistical analysis of all groups is presented in Table 2. Results should be interpreted with caution because of the small sample size. We used a power analysis statistical program to estimate the optimal sample to draw conclusive results regarding the present variables. To have a test power of 0.95 with alpha 0.01, an optimal sample would be composed of 20 individuals with unilateral keratoconus.

DISCUSSION

New biomechanical metrics (corneal hysteresis and corneal resistance factor) may be useful when determining corneal stiffness by indicating a "more fragile" tissue that is at greater risk for developing corneal ectasia. In addition, they could be used to differentiate mild (and forme fruste) keratoconus from healthy corneas before manifestation of typical topographic signs.

In the present study, we found a trend of lower biomechanical metric values in keratoconus and fellow eyes compared with controls. However, a great scatter in values was seen and a statistical difference was not shown. A possible explanation is the small sample size. An ideal sample of 20 patients with unilateral keratoconus would provide a better understanding and more conclusive results. As unilateral keratoconus is an unusual condition,[3-7] it is difficult to obtain a large population.

Unilateral chronic eye rubbing or ocular trauma and greater asymmetry in corneal curvature have been shown to be associated with unilateral keratoconus in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study.[4] It is a common belief among cornea specialists that patients at greater genetic risk for developing keratoconus may progress to corneal ectasia depending on certain risk factors (eg, corneal surgery, eye rubbing, or trauma) during their lifetime.[3] Li et al[3] and Holland et al[5] studied the incidence and fellow-eye disease progression in unilateral keratoconus and concluded that, if observed for a sufficient period of time, most cases developed the disease in the fellow eye. Currently, no method exists to identify these high-risk patients, as they often have normal ocular and topographic examinations.

Artificial intelligence "keratoconus detection indices" provided by both corneal topography and tomography were able to detect keratoconic eyes and discriminate from healthy corneas. New biomechanical metrics should not be relied on as a stand-alone method for keratoconus diagnosis, but may improve the sensitivity of its screening when combined with current corneal topographers and tomographers. Also, new data presented recently by Luce[25] regarding waveform parameters provided by the ORA signal may be more sensitive than corneal hysteresis and corneal resistance factor in discriminating abnormal corneas.

Biomechanical metrics were not statistically different among the study groups; however, a trend for lower values was found for keratoconus and fellow eyes compared to controls. Data should be interpreted with caution because of the small sample. Prospective studies with larger samples are warranted.

AUTHOR CONTRIBUTIONS

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

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3.6 Biomechanical evaluation of healthy thin corneas compared with matched keratoconus cases

ARTIGOS ORIGINAIS | ORIGINAL ARTICLES

Corneal biomechanical evaluation in healthy thin corneas compared with matched keratoconus cases

Análise da biomecânica corneana em córneas finas saudáveis comparadas com pacientes com ceratocone pareados por espessura corneana, sexo e idade

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ABSTRACT

Purpose: To evaluate and compare corneal hysteresis (CH) and corneal resistance factor (CRF) in healthy eyes with a central corneal thickness (CCT) ≤ 505 μm with CH and CRF in gender-, age-, and CCT-matched keratoconus cases, and to estimate the sensitivity and specificity of these parameters for discriminating between the two groups.

Methods: Prospective, comparative case series. In total 46 eyes from 30 healthy patients with CCT ≤ 505 μm, and 42 eyes from 30 CCT-, gender- and age-matched keratoconus cases were enrolled. Biomechanical metrics (CH and CRF) were measured using the Ocular Response Analyzer (ORA) and then compared. A receiver operating characteristic (ROC) curve was used to identify cut-off points to maximize the sensitivity and specificity for discriminating between the groups.

Results: The CCT was 485.96 ± 17.61 μm (range, 438 - 505) in healthy thin corneas and 483.64 ± 16.19 μm (range, 452 - 505) in keratoconus; p=0.5225. CH was 8.63 ± 1.23 mmHg (range, 5.95 - 12.2) and 8.07 ± 1.17 mmHg (range, 4.9 - 9.85), respectively; p=0.0312. CRF was 8.43 ± 1.29 mmHg (range, 5.45 - 11.10) and 7.22 ± 1.34 mmHg (range, 4.7 - 9.45), respectively; p<0.001. ROC curve analysis showed a poor overall predictive accuracy of CH (cut-off, 8.95 mmHg; sensitivity, 63%; specificity, 23.8%; test accuracy, 44.30%) and CRF (cut-off, 7.4 mmHg; sensitivity, 28.3%; specificity, 40.5%; test accuracy, 34.12%) for detecting keratoconus in the eyes studied.

Conclusion: CH and CRF were statistically lower in keratoconus than in healthy thin corneas. However, CH and CRF offered very low sensitivity and specificity for discriminating the groups.

Keywords: Cornea/physiology; Keratoconus; Corneal diseases; Biomechanics/physiology; Diagnostic techniques, ophthalmological

RESUMO

Objetivo: *Avaliar e comparar a histerese corneana (CH) e o fator de resistência corneano (CRF) em olhos saudáveis com espessura corneana central (CCT) ≤ 505 μm com os resultados de CH e CRF em pacientes com ceratocone pareados por sexo, idade e CCT, além de estimar a sensibilidade e especificidade destes parâmetros na diferenciação dos grupos.*

Métodos: *Estudo prospectivo, do tipo série de casos comparativa. No total, 46 olhos de 30 pacientes saudáveis com CCT ≤ 505 μm, e 42 olhos de 30 pacientes com ceratocone pareados por sexo, idade e CCT foram incluídos. Os parâmetros biomecânicos (CH e CRF) foram obtidos através do equipamento Ocular Response Analyzer (ORA) e depois comparados. Curvas ROC (Receiver operating characteristic) foram utilizadas para identificar o melhor valor de corte que apresentasse a maior sensibilidade e especificidade na discriminação entre ceratocone e córneas finas saudáveis para cada dado estudado.*

Resultados: *A CCT encontrada foi 485,96 ± 17,61 μm (de 438 a 505) no grupo de córneas finas saudáveis e 483,64 ± 16,19 μm (de 452 a 505) no grupo ceratocone; p=0,5225. CH 8,63 ± 1,23 mmHg (de 5,95 a 12,2) e 8,07 ± 1,17 mmHg (de 4,9 a 9,85), respectivamente; p=0,0312. CRF 8,43 ± 1,29 mmHg (de 5,45 a 11,10) e 7,22 ± 1,34 mmHg (de 4,7 a 9,45), respectivamente; p<0,001. Análise das curvas ROC mostrou baixa acurácia na diferenciação das córneas finas saudáveis daquelas com ceratocone tanto para CH (ponto de corte, 8,95 mmHg; sensibilidade, 63%; especificidade, 23,8%; acurácia, 44,30%) quanto para CRF (ponto de corte, 7,4 mmHg; sensibilidade, 28,3%; especificidade, 40,5%; acurácia, 34,12%).*

Conclusão: *Dados fornecidos pelo ORA (CH e CRF) mostraram-se estatisticamente mais baixos em pacientes com ceratocone quando comparados com córneas finas de indivíduos saudáveis. No entanto, os dois parâmetros biomecânicos estudados apresentaram sensibilidade e especificidade muito baixas na diferenciação dos grupos.*

Descritores: *Córnea/fisiologia; Ceratocone; Doenças da córnea; Biomecânica/fisiologia; Técnicas de diagnóstico oftalmológico*

INTRODUCTION

Corneal refractive surgery performed by either lamellar (LASIK) or surface (PRK, LASEK) techniques has shown safety, predictability and stability when performed in patients with healthy thin corneas[1-2]. However, proper patient selection is challenging in such cases, as preoperative thin corneas and thinner residual stromal bed after excimer laser ablation are widely described as risk factors for the development of postoperative ectasia[3-4].

Healthy patients can present with thin corneas (≤505 μm), and keratoconic eyes can have a "normal" (≤520 μm) central corneal thickness (CCT)[5-8]. For decision making in these cases, the surgeon should rely on analysis of corneal topography and tomography data (such as corneal volume, elevation maps and pachymetric distribution)[8-10]. The development of a test for reliable corneal stiffness assessment and response to excimer laser ablative surgery estimation is an essential step in the evolution of refractive surgery[11-13].

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No financial support was available for this project.
Renato Ambrósio, MD is Oculus and Reichert consultant.

Recebido para publicação em 25.05.2010
Aprovação em 14.01.2011

Central corneal thickness (CCT) is a biometric entity[14-15], and its biological variability in healthy eyes is believed to result from different amounts of collagen fibrils and interfibrillary substance in the corneal stroma[7,16]. It is a measure of tissue mass and perhaps an estimator of corneal rigidity[7]. However, CCT varies among ethnic groups and also demonstrates strong heritability in nuclear families[17-18].

The *in vivo* measurement of corneal resistance to deformation was enabled by the development of the ocular response analyzer (ORA) by Luce[19]. The ORA (Reichert Ophthalmic Instruments, New York, USA) determines corneal biomechanical metrics (CH and CRF) using an applied force - displacement relationship.

Our group has studied corneal biomechanical metrics in different scenarios. In a population of healthy subjects[5], we have found that corneal biomechanical metrics and CCT are strongly associated, while showing an inverse relationship with older age, and higher values in females. In a small sample of patients with unilateral / asymmetrical keratoconus[20], CH and CRF values were not statistically different between the studied groups, although a trend for lower values was found for keratoconus and fellow eyes versus the control group. When comparing 77 eyes from 43 patients with keratoconus and 86 eyes from 43 healthy controls (unpublished data), a statistical difference in CH and CRF was found between groups, but, when considered individually, the measures demonstrated low sensitivity, specificity, and test accuracy for keratoconus and healthy cornea differentiation. Similar findings were found by our group regarding CH and CRF in patients with mild keratoconus[21] and also in cases of keratoconus with CCT ≥ 520 µm[8]. In the present study, we investigated corneal biomechanical metrics in healthy eyes with CCT ≤ 505 µm and compared them with gender-, age-, and CCT-matched keratoconus cases.

METHODS

We used a prospective, comparative case series design. 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). Subjects were informed of the purpose of the study, and all gave informed consent before inclusion.

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

Diagnosis of keratoconus was made by clinical (corneal stromal thinning, Vogt's striae, Fleischer ring, scissoring of the red reflex or oil droplet sign identified by retinoscopy) and topographic evaluation (increased area of corneal power surrounded by concentric areas of decreasing power, inferior-superior power asymmetry, and skewing of the steepest radial axis above and below the horizontal meridian[22-24].

Healthy eyes with CCT ≤ 505 µm were matched with keratoconus cases according to CCT (± 15 µm), age (± 6 years) and gender. For analysis, we used CCT instead of the thinnest point (given by the Pentacam) because the air-jet delivered by the ORA is directed at the corneal center. Additionally, a CCT match of ± 15 µm was chosen based on the work by Khachikian et al.[15], 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. Our patients were divided in two groups for data comparison: the healthy thin cornea group and the keratoconus group.

Exclusion criteria were age less than 18 years, any previous corneal or ocular surgery, eye disease other than keratoconus (in particular, endothelial dysfunction or dystrophy), chronic or continuous use of topical medications, corneal scars or opacities, and refusal to provide 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 by a trained ophthalmic technician. 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 recorded), and the results were averaged. CCT was determined using the Pentacam rotating Scheimpflug camera.

Previously, we published a detailed description of the Pentacam system[5], as have other investigators[25-26]. 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. CCT 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[5,8,19,21]. Briefly, a precisely metered air pulse is delivered to the eye, causing the cornea to move inwards, 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 adsorbed 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 (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 (CRF) 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 (D. Luce. Methodology for Cornea Compensated IOP and Corneal Resistance Factor for the Reichert Ocular

Table 1. Summary data from the study groups

	Healthy thin corneas	Keratoconus	p value*
Gender	16 F / 14 M	16 F / 14 M	p=1
Age (years)	40.33 ± 17.38	40.30 ± 11.73	p=0.5103
range	(20 - 77)	(22 - 76)	
CCT (µm)	485.96 ± 17.61	483.64 ± 16.19	p=0.5225
range	(438 - 505)	(452 - 505)	
CH (mmHg)	8.63 ± 1.23	8.07 ± 1.17	p=0.0312
range	(5.95 - 12.2)	(4.9 - 9.85)	
CRF (mmHg)	8.43 ± 1.29	7.22 ± 1.34	p<0.0010
range	(5.45 - 11.10)	(4.7 - 9.45)	

*Welch modified two-sample *t*-test

M= male; F= female; CCT= central corneal thickness; CH= corneal hysteresis; CRF= corneal resistance factor

Response Analyzer. Invest Ophthalmol Vis Sci. 2006;47:E-Abstract 2266), 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.

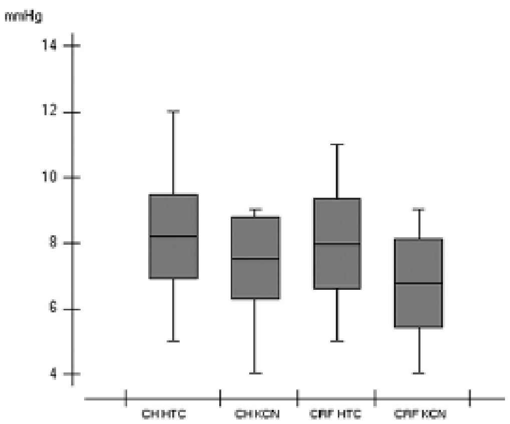

Figure 1. Box-plot distribution of corneal hysteresis (CH) and corneal resistance factor (CRF) in healthy thin corneas (HTC) and keratoconus (KCN).

Table 2. Data from the receiver operating characteristic (ROC) curves (plots of the sensitivity vs. 1 - specificity) for CH and CRF in the population studied. Due to the substantial overlap between the groups, the ROC curve analyses showed poor overall predictive accuracy of CH and CRF for differentiating healthy thin corneas from keratoconus in the eyes studied

	Cut-off point mmHg	Sensitivity (%)	Specificity (%)	Test accuracy (%)
CH	8.95	63.0	23.8	44.30
CRF	7.40	28.3	40.5	34.12

CH= corneal hysteresis; CRF= corneal resistance factor

Statistical analysis were performed using BioEstat 5.0 software (Federal University of Belém, PA, Brazil). The receiver operating characteristic (ROC) curve was used to identify the best CH and CRF cut-off 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% indicates that the test perfectly discriminates between groups. Logistic regression was used to support the cut-off point identified in the ROC curve analysis. Differences between data were evaluated using the Welch modified two-sample *t*-test. Data are expressed as the mean ± standard deviation.

RESULTS

In total, 46 eyes from 30 healthy patients with CCT ≤ 505 μm, and 42 eyes from 30 CCT-, gender- and age-matched keratoconus cases were enrolled.

The central corneal thickness (CCT) was 485.96 ± 17.61 μm (range, 438 - 505) in healthy thin corneas and 483.64 ± 16.19 μm (range, 452 - 505) μm in keratoconus Group; p=0.5225.

Corneal hysteresis (CH) was 8.63 ± 1.23 mmHg (range, 5.95 - 12.2) in healthy thin corneas and 8.07 ± 1.17 mmHg (range, 4.9 - 9.85) in keratoconus group; p=0.0312. Corneal resistance factor (CRF) was 8.43 ± 1.29 mmHg (range, 5.45 - 11.10) in healthy thin corneas and 7.22 ± 1.34 mmHg (range, 4.7 - 9.45) in keratoconus group; p<0.001.

The results are summarized in table 1. A box-plot of the distribution of CH and CRF in healthy thin corneas (HTC) and keratoconus (KCN) is shown in figure 1.

ROC curve analysis showed poor overall predictive accuracy of both corneal hysteresis and corneal resistance factor for discriminating healthy eyes with CCT ≤ 505 μm and those with keratoconus. For CH, the optimal cut-off point was 8.95 mmHg, with 63% sensitivity and 23.8% specificity (test accuracy, 44.30%). The best cut-off point for CRF was 7.4 mmHg, with 28.3% sensitivity and 40.5% specificity (test accuracy, 34.12%). Data from the ROC curves are presented in table 2.

DISCUSSION

Corneal biomechanical metrics are known to have a strong correlation with central corneal thickness and to be affected by aging[5,27]. Additionally, our first study in healthy patients found statistically significantly higher values in females[5]. Thus, we consider it important that these variables be matched when comparing CH and CRF

Table 3. Values of "normality" from some published studies (data expressed as mean ± standard deviation)

Paper	Eyes studied	CCT (μm)	CH (mmHg)	CRF (mmHg)
Fontes et al[13]	260	545.05 ± 35.41	10.17 ± 1.82	10.14 ± 1.80
		Range 454 - 640	Range 3.23 - 14.58	Range 5.45 - 15.10
Che et al[79]	43	549.87 ± 29.53	11.52 ± 1.28	11.68 ± 1.40
		Range 493 - 617	Range 9.25 - 14.30	Range 8.55 - 14.70
Medeiros et al[80]	153	538 ± 35	Not provided	9.47 ± 1.75
		Range 414 - 627		Range 4.68 - 14.15
Kamiya et al[56]	86	540 ± 31	10.20 ± 1.3	Not provided
		Range 476 - 598	Range 6.7 - 13.3	
Shah et al[81]	110	546.5 ± 33	11.4 ± 1.9	10.0 ± 1.6
		Range 467 - 640	Range 6.4 - 16.7	Range 6.6 - 14.9
Franco et al[64]	63	534 ± 33.1	10.8 ± 1.53	10.6 ± 1.71
		Range 448.3 - 610.7	Range 8.3 - 15.5	Range 6.9 - 14.9
Luce D, Taylor D (ORA brochure, 2005)	339	Not provided	12.36 ± 1.90	12.34 ± 2.08
			Range 7.73 - 18.01	Range 6.49 - 18.09

CCT= central corneal thickness; CH= corneal hysteresis; CRF= corneal resistance factor in different groups. When publishing about ORA corneal biomechanical metrics, authors should separate patients into groups in terms of factors known to influence them. A number of "normal" values for CH and CRF in healthy corneas found in previously published studies are shown in table 3.

Keratoconic eyes have a low tensile strength, thinning, and protrusion[12,21-22,24]. Our findings show that the lower resistance to deformation in keratoconus group is not due only to thinning, because the groups were matched by thickness. Additionally, higher corneal resistance after collagen cross-linking is often accompanied by thinning[28-29]. Therefore, corneal rigidity and resistance to deformation are likely affected by unknown factors in addition to corneal thickness[12]. Thus, reduced central corneal thickness is only part of the answer. The corneal stromal collagen fibrils of keratoconus patients are probably more fragile, more readily deformable by the air-jet, and perhaps thinner than those of normal subjects.

We found substantial overlap in the values of CH and CRF between the groups (Figure 1). Data recently published by Qazi et al.[30] indicate that waveform parameters provided by the ORA signal may contain additional important information that, could be more sensitive than CH or CRF in discriminating abnormal corneas. Additional studies are needed to determine whether signal analysis is useful in biomechanical studies of the cornea.

In conclusion, CH and CRF were statistically lower in keratoconus eyes than in matched thin healthy corneas. However, because of the large overlap between the groups, CH and CRF both had low sensitivity and specificity for discriminating between the two groups. Further research on new technologies for corneal stiffness measurement and biomechanical variability is warranted.

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4. CONSIDERAÇÕES

O ORA foi desenvolvido para ser um tonômetro de não contato capaz de fornecer parâmetros da resistência tecidual corneana perante a sua deformação frente a um jato de ar com força pré estabelecida. Desta forma, seria capaz de determinar a pressão intraocular levando em conta a resistência tecidual encontrada individualmente. É preciso enaltecer o brilhantismo e simplicidade da idéia original, que teve a originalidade de propor estas medidas de maneira rápida, indolor e relativamente simples.

Nosso primeiro estudo teve o objetivo de estabelecer os valores de CH e CRF em indivíduos saudáveis na população brasileira, assim como avaliar possíveis variáveis associadas a estes parâmetros.[61] Desta forma, definimos os valores de normalidade e formamos um banco de dados para comparação (grupo-controle) em nossos futuros trabalhos. Nosso estudo mostrou que os parâmetros biomecânicos (CH e CRF) são positivamente associados à espessura corneana central, negativamente associados à idade, e com valores estatisticamente mais baixos em homens do que em mulheres na população estudada.

Quando publicado, nosso trabalho continha o maior número de dados estudados (originados de 260 olhos de 150 pacientes) até então sobre o assunto na literatura mundial. Ainda, foi o primeiro a relacionar e estudar a associação de dados da tomografia de córnea (Pentacam) com parâmetros biomecânicos. A partir do mesmo, pesquisadores do mundo inteiro conduziram estudos em outras populações e etnias, aumentando consideravelmente o conhecimento sobre os parâmetros biomecânicos fornecidos pelo ORA.[27, 36, 37, 39, 40, 42, 48, 59] e suas possíveis aplicações práticas para benefício da ciência e sociedade.

A segunda publicação de nossa linha de pesquisa teve como objetivo investigar os parâmetros biomecânicos e tomográficos em grande grupo de pacientes com ceratocone (em todas as suas classificações) e compará-los com pacientes saudáveis.[74] Encontramos valores estatisticamente mais baixos e grande interseção de resultados, o que impossibilitou a determinação de pontos de corte entre os dados estudados para diferenciação dos grupos.

Nosso terceiro trabalho[73] estudou parâmetros biomecânicos e tomográficos (da córnea e segmento anterior) em pacientes com ceratocone leve, comparando os resultados com pacientes saudáveis (pareados aos fatores associados aos mesmos que foram descritos e discutidos em nosso primeiro estudo). Tínhamos grande expectativa na possibilidade de que os dados encontrados pudessem ser úteis na distinção dos grupos, aumentando o conhecimento sobre o ceratocone e fornecendo dados úteis para diagnóstico mais precoce e preciso desta patologia. No entanto, encontramos grande dispersão dos resultados de todos os fatores estudados. Desta forma, não foi possível estabelecer valores de corte nos quais a distinção entre pacientes com ceratocone leve pudessem ser distinguidos de indivíduos saudáveis. Outros autores se interessaram e aprofundaram o estudo neste grupo de pacientes.[37, 71, 75, 76]

O conhecimento sobre as propriedades biomecânicas da córnea avaliadas e definidas pelo ORA foi aumentando e diversos estudos publicados na literatura mundial.[27, 28, 35-60, 76-83] Estudamos os valores de CH e CRF em pacientes com ceratocone e espessura corneana central considerada normal em nossa quarta publicação.[72] Mais uma vez, encontramos valores estatisticamente mais baixos nos olhos acometidos quando comparados aos encontrados no grupo controle. Da mesma forma, encontramos grande dispersão dos resultados nos dois grupos, não sendo possível determinar um valor de ponto de corte capaz de diferenciar os grupos com sensibilidade e especificidade satisfatórias.

Em pacientes com ceratocone unilateral (muitos classificariam como assimétrico e não unilateral), não encontramos diferença estatística entre os olhos acometidos dos contralaterais e do grupo controle de indivíduos saudáveis. No entanto, nosso estudo contou com poucos casos (apenas quatro), devido à raridade do encontro de pacientes com esta condição. De qualquer forma, encontramos uma “tendência” de valores mais baixos nos olhos acometidos, seguidos pelos olhos contralaterais (dos mesmos indivíduos) e finalmente pelos olhos utilizados como controle. Este trabalho[41] trouxe mais conhecimento sobre esta condição particular e pouco freqüente, tendo o artigo discutido possíveis benefícios destes para a comunidade científica e sociedade.

O último estudo conduzido pelo nosso grupo está sendo avaliado para publicação (*peer review*) neste momento. Estudamos os valores encontrados em pacientes saudáveis com córneas finas e comparamos com grupo pareado de indivíduos com ceratocone leve. Mais uma vez encontramos grande dispersão de resultados e baixas sensibilidade e especificidade do valor de corte determinado pela análise estatística para diferenciação dos grupos.

Nosso grupo trabalhou no estudo dos parâmetros biomecânicos fornecidos pelo ORA. Determinamos os valores de normalidade em indivíduos saudáveis, assim como os valores em pacientes com ceratocone (sem distinção classificatória), ceratocone leve, ceratocone com espessura corneana central normal, ceratocone unilateral e em córneas finas saudáveis. Estimulamos a busca e acúmulo do conhecimento desta área por meio de pesquisa, publicações internacionais e apresentação dos resultados em congressos no Brasil e exterior. Planejamos continuar nossa pesquisa a fim de encontrar e divulgar possíveis novos métodos de avaliação da biomecânica corneana que tragam benefícios para pacientes com ceratocone e com outras patologias oculares.

5. CONCLUSÕES

Os parâmetros biomecânicos estudados mostraram associação com a espessura corneana central, gênero e idade em indivíduos saudáveis. Pacientes com diferentes apresentações e classificações de ceratocone exibiram valores estatisticamente inferiores aos do grupo controle (pacientes saudáveis). No entanto, a grande interseção dos valores obtidos não permitiu a determinação de valores de corte para diferenciação entre os grupos com sensibilidade e especificidade satisfatórias.

6. ANEXOS

Anexo1 – Parecer do Comitê de Ética em Pesquisa CEP/UNIFESP

UNIFESP
PAULISTA

Universidade Federal de São Paulo
Escola Paulista de Medicina

Comitê de Ética em Pesquisa
Hospital São Paulo

São Paulo, 17 de março de 2006.
CEP 0123/06

Ilmo(a). Sr(a).
Pesquisador(a) BRUNO MACHADO FONTES
Co-Investigadores: Renato Ambrósio Junior; Ruiz Simonato Alonso; Walton Nosé
Disciplina/Departamento: Oftalmologia da Universidade Federal de São Paulo/Hospital São Paulo
Patrocinador: Recursos Próprios.

PARECER DO COMITÊ DE ÉTICA INSTITUCIONAL

Ref: Projeto de pesquisa intitulado: **"Avaliação das propriedades biomecânicas corneanas em pacientes com ceratocone".**

CARACTERÍSTICA PRINCIPAL DO ESTUDO: Estudo clínico com intervenção diagnóstica não randomizado.
RISCOS ADICIONAIS PARA O PACIENTE: sem risco, desconforto mínimo, nenhum procedimento invasivo.
OBJETIVOS: Estudar as propriedades biomecânicas corneanas e suas alterações em pacientes com ceratocone, correlacionando os valores com suas diversas formas clínicas e classificações, comparando com os achados em um grupo de indivíduos normais.
RESUMO: Serão recrutados pacientes do ambulatório da Oftamologia da Unifesp e do Instituto de Olhos Renato Ambrósio da cidade do Rio de Janeiro. Inicialmente, todos os pacientes incluídos no protocolo de pesquisa serão submetidos a avaliação clínica oftalmológica geral. Após, serão classificados em dois grupos de acordo com os critérios de inclusão: grupo I, disponibilidade em participar do estudo e assinatura do termo de consentimento livre e esclarecido, idade maior ou igual a 18 anos e diagnóstico clínico e/ou topográfico de ceratocone, independente do grau evolutivo e/ou classifcação da doença; grupo II, disponibilidade em participar do estudo e assinatura do termo de consentimento livre e esclarecido, idade maior ou igual a 18 anos e exame oftalmológico sem alterações. Todas as informações relativas aos pacientes serão confidenciais, e seu uso restrito aos investigadores. Os dados serão armazenados em planilhas para posterior análise estatística..
FUNDAMENTOS E RACIONAL: Geração de novas informações e conhecimento sobre o ceratocone, além da possibilidade de diagnóstico precoce e reconhecimento de indivíduos com sua forma "frustra", possibilitando uma vigilância maior, aconselhamento pessoal e familiar, alem de contra-indicação de procedimentos cirúrgicos corneanos nos pacientes com maior risco.
MATERIAL E MÉTODO: descritas as avaliações oftalmológicas que serão realizadas por equipe especializada.
TCLE: adequado de acordo com a Res 196/96.
DETALHAMENTO FINANCEIRO: sem financiamento específico R$ 335,00.
CRONOGRAMA: 06 meses.
OBJETIVO ACADÊMICO: doutorado.
ENTREGA DE RELATÓRIOS PARCIAIS AO CEP PREVISTOS PARA: **12/03/2007** e **06/03/2008**.

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo **ANALISOU** e **APROVOU** o projeto de pesquisa referenciado.
1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas.
2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.
3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Atenciosamente,

Prof. Dr. José Osmar Medina Pestana
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Anexo 2 – Termo de Consentimento Livre e Esclarecido

Termo de Consentimento Livre e Esclarecido

AVALIAÇÃO DAS PROPRIEDADES BIOMECANICAS CORNEANAS

EM PACIENTES COM CERATOCONE

- Você está sendo convidado(a) a participar de um estudo que tem a finalidade de estudar propriedades estruturais corneanas em pacientes com doença ocular denominada ceratocone. Não há qualquer risco físico, apenas mínimo desconforto durante o exame.
- Você terá seu exame oftalmológico de rotina feito da mesma forma que a habitual, acrescido da realização de 3 (três) exames complementares. Será realizado da seguinte maneira:

Perguntaremos à você sobre como está sua visão, se há alguma queixa oftalmológica, no presente ou no passado, quais são os remédios que você está usando e se ha algum caso de doença ocular em sua família. Dura em média dez minutos e não existe nenhum tipo de desconforto.

Exame Oftalmológico de rotina : Você lerá algumas letras em uma tabela, terá seu exame das parte externa e interna dos olhos feita através de aparelhos especiais . Dura em média vinte minutos e há mínimo desconforto causado pela luz emitida pelos aparelhos.

Exames Complementares: você será posicionado, em seqüência, a três aparelhos:

I. Topografia Corneana

II. Pentacam

III. “*Ocular Response Analyzer*”

Cada exame dura em torno de 5 minutos e há somente mínimo desconforto, relacionado a exposição luminosa emitida pelos aparelhos.

- Você será informado sobre todos os procedimentos e exames realizados, e tem o direito de perguntar e se recusar a realizar os mesmos.
- Você terá seu exame Oftalmológico completo realizado, não resultando em nenhum prejuízo em favor da coleta dos dados.
- Não há nenhum risco de contaminação ou transmissão de doenças com a realização dos exames acima citados, nem necessidade de cuidados especiais ou uso de medicamentos após os mesmos, uma vez que não há indução de danos ou ferimentos.

- Garantia de acesso: em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é o Dr Bruno Machado Fontes, que pode ser encontrado no endereço: Rua Lucidio Lago 210, Méier. Telefone 2501-2893, ou 8134-6548. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) da Universidade Federal de São Paulo – Rua Botucatu, 572 – 1º andar – cj 14, 5571-1062, FAX: 5539-7162 – E-mail: cepunifesp@epm.br
- É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição.
- Direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente.
- Direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores.
- Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa.
- Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), o participante tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.
- Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo "Avaliação das propriedades biomecanicas corneanas em pacientes com ceratocone". Eu discuti com o Dr Bruno Machado Fontes, ou com um dos outros investigadores, sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente / representante legal Data ___/___/___

Assinatura da testemunha Data ___/___/___

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo Data ___/___/___

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