

Importance and use of corneal biomechanics and its diagnostic utility

Importancia y uso de la biomecánica corneal y su utilidad diagnóstica

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Abstract

The study of corneal biomechanics has become relevant in recent years due to its possible applications in the diagnosis, management, and treatment of various diseases such as glaucoma, keratorefractive surgery and different corneal diseases. The clinical biomechanical investigation has become of great importance in the setting of refractive surgery to identify patients at higher risk of developing iatrogenic ectasia. This review focuses on two of the technologies available for clinical use, the Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY, USA) and the Corvis ST (Oculus Optikergäte GmbH, Wetzlar, Germany). Both are non-contact tonometers that provided a clinical evaluation of corneal biomechanics. The fundamentals and main parameters of each device are described, as well as their use in eye surgery and the corneal biomechanical behavior in eye diseases. Finally, we will discuss the more recent Brillouin microscopy biomechanical analysis, and the integration Scheimpflug-based corneal tomography and biomechanical data with artificial intelligence to increase accuracy to detect risk of ectasia.

Keywords: Dynamic bidirectional applanation tonometry. Contactless Scheimpflug tonometry. Corneal biomechanics.

Resumen

El estudio de la biomecánica corneal ha cobrado relevancia en los últimos años debido a sus posibles aplicaciones en el diagnóstico, el manejo y el tratamiento de diversas enfermedades, como glaucoma, cirugía queratorefractiva y diferentes enfermedades corneales. La investigación de la biomecánica corneal es de mucha importancia en el contexto de cirugía refractiva, pues podría identificar pacientes en riesgo de desarrollar una ectasia corneal iatrogénica. Esta revisión se centra en dos de las tecnologías disponibles para uso clínico: el Ocular Response Analyzer (Reichert Ophthalmic Instruments, Buffalo, NY, EE. UU.) y el Corvis ST (Oculus Optikergäte GmbH, Wetzlar, Alemania). Ambos son tonómetros de no contacto que proporcionan una evaluación clínica de la biomecánica corneal. Se describen los fundamentos y los principales parámetros de cada dispositivo, así como su uso en cirugía ocular y el comportamiento biomecánico corneal en las enfermedades oculares. Finalmente, se mencionan los dispositivos más recientes de análisis biomecánico, como la microscopía de Brillouin, así como la integración de los datos biomecánicos y topográficos basados en Scheimpflug con la inteligencia artificial para aumentar la precisión en la detección del riesgo de ectasias.

Palabras clave: Tonometría de aplanación bidireccional. Tonometría Scheimpflug sin contacto. Biomecánica corneal.

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Introduction

Corneal overview

The cornea is a transparent, avascular connective tissue that acts as a structural barrier, protecting the eye from trauma and infection. Together with the tear film, it forms the first refractive surface of the eye. The cornea measures, on average, approximately 540 μm in central thickness and gradually increases in thickness towards the periphery¹. It also maintains a delicate and complex balance between stiffness, strength, extensibility, and overall hardness to withstand internal and external forces that stress its surfaces, distort its shape, or threaten its integrity.

The stiffness of the anterior stroma (40%) seems important in maintaining corneal curvature^{2,3}. The cornea is tensile, meaning it resists stretching because collagen is an extension-resistant material that has a great ability to absorb energy through viscous friction provided by its gelatinous proteoglycan matrix.

Corneal diseases, such as keratoconus, as well as refractive surgical procedures, can alter the mechanical and optical properties of the cornea. Therefore, it is essential to understand and determine the biomechanical consequences of these alterations in corneal shape, thus gaining a better understanding of its behavior and improving the safety and efficacy profile of various ocular procedures or refractive surgical techniques.

Biomechanics

Biomechanics is defined as “mechanics applied to biology”⁴. Given the variety and complexity of the behavior of biological structures, it is better defined as the development, extension, and application of mechanics to better understand physiology and pathophysiology, as well as to improve the diagnosis and treatment of diseases⁵.

The goal of biomechanical models is to describe the response of biological material to an applied load, correlating different input parameters with the output (mechanical behavior). This model depends on the internal constitution of the material studied. Its main goal in human tissues is to predict the outcomes or effects of various surgical treatments or therapies. Currently, there are different tests available that allow us to characterize corneal biomechanics both in vivo and ex vivo. Among the described in vivo methods, we have bidirectional applanation tonometry^{6,7}, non-contact Scheimpflug tonometry^{8,9},

Brillouin microscopy¹⁰, high-frequency ultrasonographic analysis¹¹, and ultrasound elastography. Ex vivo methods include speckle pattern electronic interferometry¹² and radial speckle pattern interferometry.

Biomechanically, the cornea can be compared to a composite material or fiber-reinforced tissue, consisting of 2 components. The first is mainly composed of collagen fibers, making it a rigid tissue that is the primary source of load resistance, while the second is the viscous extracellular matrix surrounding the collagen fibers and formed by glycosaminoglycans and proteoglycans^{13,14}. Although the primary function of the extracellular matrix is not necessarily mechanical, it significantly contributes to the mechanical properties of the tissue^{15,16}. Besides absorbing mechanical stress, the extracellular matrix also determines a tissue damping capacity and is considered a thixotropic substance that changes its viscosity through shear stress¹⁷. For these reasons, the cornea is considered a viscoelastic tissue, with viscoelasticity being a material property that implies that the way the material behaves depends on both the deformation rate (time) and the loading and unloading phases. Unlike purely elastic materials, viscoelastic materials do not return to their original state by the same stress-strain path during unloading as during loading. This leads to behavioral differences during the loading and unloading phases in corneal biomechanics, which is not a linearly elastic structure; instead, it is described as a complex, anisotropic composite with nonlinear elastic and viscoelastic properties, as its properties are not uniform in all directions but are determined by the interaction of various materials such as collagen and a hydrophilic base substance¹⁸.

For the purposes of this review, we will study the only 2 devices with potential for clinical use that provide corneal biomechanical data: the Ocular Response Analyzer (Reichert Technologies, Depew, NY, United States), a dynamic bidirectional applanation device, and Corvis ST (Oculus Optikerte GmbH, Germany), a dynamic Scheimpflug analyzer. Newer biomechanical analysis devices, such as Brillouin microscopy, as well as the integration of biomechanical data with artificial intelligence (AI) to enhance precision in detecting ectasia risk, will also be mentioned.

Bidirectional applanation tonometry

The Ocular Response Analyzer (ORA) uses a rapid air pulse to indent the cornea and an advanced electro-optical system to record 2 applanation pressure measurements: one while the cornea is indented and

another as the cornea returns to its normal position⁷. The difference between the 2 pressure values is called corneal hysteresis (CH: $P_1 - P_2$), which reflects the cornea viscous properties. It is important to note that the maximum applied air pressure is not constant and depends on P_1 , which is determined by the actual intraocular pressure (IOP) value and the structural resistance inherent to each individual⁷. Moreover, the corneal resistance factor (CRF) is an empirical measure representing the cornea elastic properties, derived from the formula $P_1 - Pk^2$, with k being a constant determined by the relationship between applanation pressures and central corneal thickness, strongly associated with a positive correlation with CH and CRF¹⁹ (Fig. 1).

The measurements of both corneal hysteresis and CRF appear to have adequate accuracy, according to various studies^{20,21}.

The primary measurements reported by the ORA have been used to measure and even predict the progression of various corneal diseases. In patients with varying degrees of keratoconus severity, CH and CRF values are lower than in healthy subjects⁶. However, other studies have found that these differences are not statistically significant²². Within the spectrum of glaucoma diseases, numerous studies have found that CH values are reduced in this group of patients²³. The 2 main measurements performed by the ORA (CH and CRF) can change after refractive surgery. A systematic review and meta-analysis demonstrated that the type of refractive surgery performed alters CH and CRF to a greater or lesser extent, with less corneal strength changes in patients treated with SMILE vs those who underwent FS-LASIK or LASIK²⁴.

Non-contact Scheimpflug tonometry

Although Corneal Visualization Scheimpflug Technology (Corvis ST), like the ORA, is also a dynamic applanation device, it uses an ultra-high-speed Scheimpflug camera to record the corneal deformation process across an 8.5 mm horizontal span at 4330 frames per second (Fig. 2).

The Corvis ST is similar to the ORA in that both are non-contact instruments that use an air puff with similar dimensions and profiles. However, there are several differences, the first one being that the maximum air puff pressure is constant in the Corvis ST, while in the ORA it is variable (depending on P_1); the second is that the amount of information collected on corneal deformation is greater in the Corvis ST, and finally, while the ORA main parameters are based on applanation

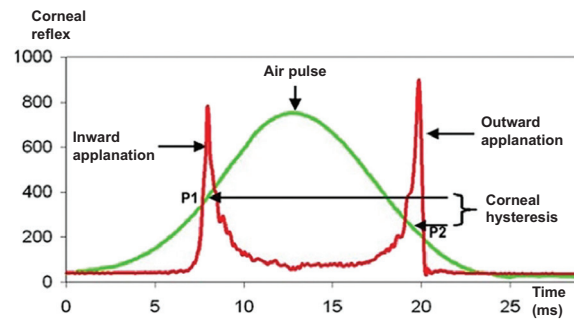


Figure 1. Measurements of the Ocular Response Analyzer. The effect of the air pulse on the deformation of the cornea (first applanation) is recorded as the corneal signal along the Y-axis over time in milliseconds on the X-axis, where P_1 represents the first moment of applanation. When the air pulse signal ceases, the cornea adopts a concave shape as the magnitude of the air pulse continues to increase. In the release phase (when the air pressure decreases), the cornea experiences a second applanation, at which point the air pulse pressure is recorded again (P_2). The parameters derived from the pressure are corneal hysteresis and the corneal resistance factor.

pressures P_1 and P_2 , the Corvis ST relies on the change in dynamic corneal response parameters (Fig. 3). The parameters that the device allows for evaluation are described in Table 1. The Corvis ST calculates corneal deformation parameters based on the dynamic inspection of the corneal response. Once the cornea starts to move backward due to the air pressure, the entire eye instantly begins a slow linear movement in the same direction, which increases once the cornea has reached its maximum displacement.

Therefore, dynamic corneal response parameters must compensate for this eye movement. The parameters described as "deformation" do not include this compensation, while those of "deflection" do account for and compensate for eye displacement.

Corneal deformation amplitude (DA) refers to the displacement of the corneal apex in the anterior-posterior direction at the moment of highest corneal concavity. The DA ratio at 1 mm or 2 mm is the central deformation divided by an average deformation at 1 mm or 2 mm on either side of the center just before the first applanation. Applanation lengths (AL) and corneal velocities (CVel) are also recorded during the indentation and return phases. Additionally, the radius of curvature at highest corneal concavity is documented, and the integrated inverse radius is the reciprocal of the radius obtained during the corneal concave state. Of note that a larger concave radius is associated with greater resistance to deformation or a stiffer cornea. Therefore, the greater the integrated inverse radius and maximum inverse radius, the lower the resistance to

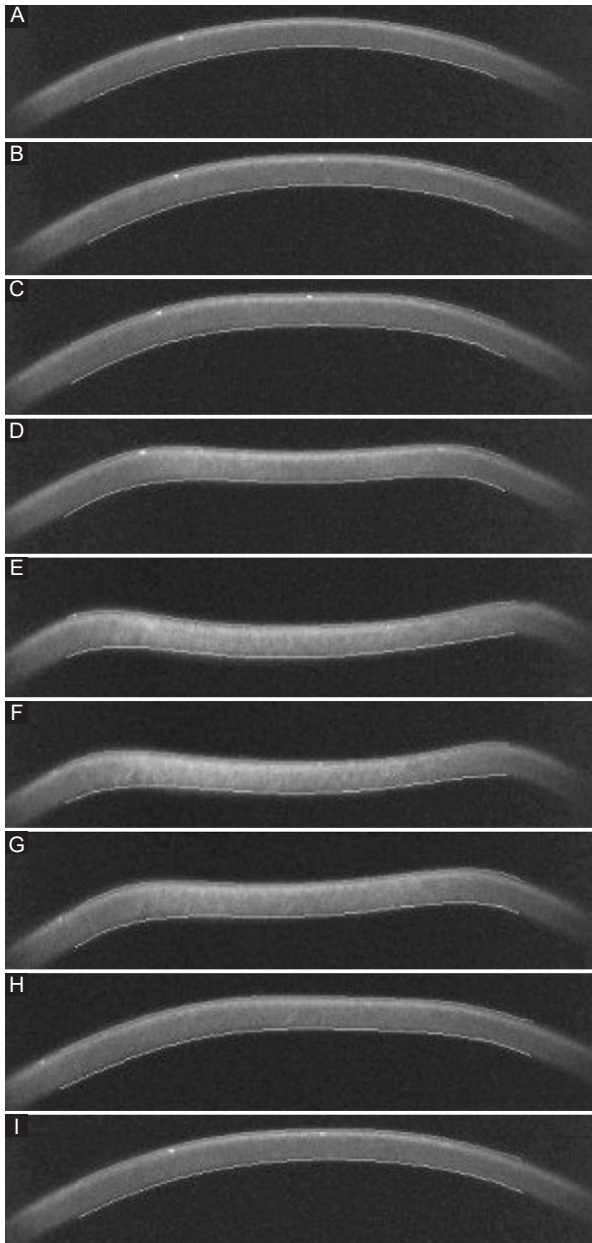


Figure 2. Scheimpflug image from the Corvis ST during the moments of applanation: baseline (A), deformation begins (B), first moment of applanation (C), onset of concavity phase (D), moment of highest concavity (E), oscillation period (F), exit from concavity (G), second moment of applanation (H), and after the second applanation (I).

deformation and the less rigid the cornea²⁵. Corneal thickness, standard Goldman-correlated IOP, and biomechanically compensated IOP (bIOP) are also recorded. Similarly, the corrected IOP is determined using compensatory formulas based on central corneal thickness (ccIOP).

Vinciguerra's report (Fig. 4) provides correlations of normal values, and the bIOP accounts for central corneal

thickness and age along with deformation response parameters to reduce the effect of corneal stiffness when estimating IOP²⁶.

In addition to the above-mentioned parameters, the Corvis ST can measure central corneal thickness (CCT) thanks to the horizontal Scheimpflug imaging. The horizontal Scheimpflug image of the basal cornea allows for the calculation of the Ambrosio Relational Thickness over the horizontal meridian (ARTh), which consists of dividing the corneal thickness at the thinnest point by the pachymetric progression index²⁷. Researchers used linear regression analysis and combined ARTh with corneal deformation parameters to generate the Corvis Biomechanical Index (CBI), which, with a cutoff value of 0.5, allows for the identification of 98.2% of keratoconus cases in normal eyes with 100% specificity²⁸. Moreover, the Tomographic Biomechanical Index (TBI) combines tomographic and biomechanical information to improve the detection of ectasia.

The Corvis AT also presents parameters that function as biomarkers of corneal stiffness, such as SP-A1, which has been reported to be lower in thinner corneas²⁸. The most recent development has been the introduction of the Stress Strain Index (SSI) algorithm, which allows for the detection of patients at higher risk of developing ectasia or progression after refractive surgery and provides clinical documentation of post-CXL corneal biomechanical changes²⁹. Parameters that differentiate healthy corneas from keratoconus and CXL-treated ectatic corneas from non-treated ones include applanation velocity 2 (A2V), second applanation length (A2L), and the difference between first applanation length (A1L) and A2L, demonstrating their utility in monitoring post-CXL corneal changes³⁰.

Precision and reproducibility with the Corvis ST

Several publications in this field have reached different conclusions. Hon and Lam⁸ concluded that highest concavity deformation amplitude (HCDA) and first applanation time (AT1) were the only 2 corneal distortion parameters with good reproducibility and no session differences, along with CCT. Hong et al.³¹ vs the IOP of the Corvis ST with that of other devices, concluding that the Corvis ST had the best reproducibility and repeatability. Bak-Nielsen et al.³² concluded that the following parameters had a coefficient of variation < 10%: IOP, CCT, AT1, AL1, highest concavity time (HCT), highest concavity radius (HCR), HCDA,

Table 1. Parameters obtained with the Corvis ST

Parameter	Description
Length A1 (mm)	Length of the flattened cornea during the first applanation
Speed A1 (mm/ms)	Speed of corneal deformation during the first applanation
Time A1 (ms)	Time from the start of measurement until the first applanation
IOP	Intraocular pressure measurement in mmHg
Radius DA (2 mm)	Deformation amplitude radius at 2 mm
SP-A1	Stiffness parameter at A1
SP-HC	Stiffness parameter at the highest concavity
Maximum deformation amplitude (mm)	Maximum deformation amplitude measured at the point of maximum corneal concavity. It is the sum of corneal deflection amplitude and total eye movement
Time HC (ms)	Time from the start of measurement until highest corneal concavity is reached
HCDeflAmp (mm)	Corneal deflection amplitude at the point of highest corneal concavity
Peak distance (mm)	Distance between corneal peaks at the point of highest corneal concavity
Radius HC (mm)	Corneal curvature radius during highest corneal concavity
InvRadMax (1/mm)	Maximum inverse radius
ARTh	Ambrosio Relational Thickness across the horizontal meridian, based on the thickness profile from the temporal-nasal direction
Length A2 (mm)	Length of the flattened cornea during the second applanation
Speed A2 (mm/ms)	Speed of corneal deformation during the second applanation
Time A2 (ms)	Time from the start of measurement until the second applanation
bIOP	Biomechanically corrected IOP. A measurement of IOP that is less dependent on corneal biomechanics and thickness
Maximum total eye movement (mm)	Length of the total anteroposterior linear movement of the entire eye following maximum corneal displacement
Maximum total eye movement (ms)	Time taken for the total anteroposterior linear movement of the entire eye following maximum corneal displacement
SSI	Stress-Strain Index
CBI	Corvis Biomechanical Index: general biomechanical index for detecting keratoconus
TBI	Tomographic Biomechanical Index: combines tomographic and biomechanical data to improve ectasia detection
Integrated radius	Area under the inverse concave radius vs time curve
Inverse concave radius	Inverse curvature radius during the concave deformation phase
Corneal thickness	Measurement of corneal thickness in mm
Normal curvature radius	Corneal curvature radius in its natural state (in mm)
HC curvature radius	Corneal curvature radius at the point of highest concavity during the air pulse (in mm)

highest concavity deflection length, highest concavity deflection amplitude (in millimeters and milliseconds), and AT2. Chen et al.³³ compared 40 healthy eyes with 42 post-PRK eyes, finding similar results, with healthy

eyes showing an intraclass correlation coefficient (ICC) $\geq 92\%$ for IOP, CCT, and AT1, followed by HCDA (ICC, 0.88), curvature radius (ICC, 0.70), A2V (ICC, 0.65), and maximum concavity time (ICC, 0.64). The rest

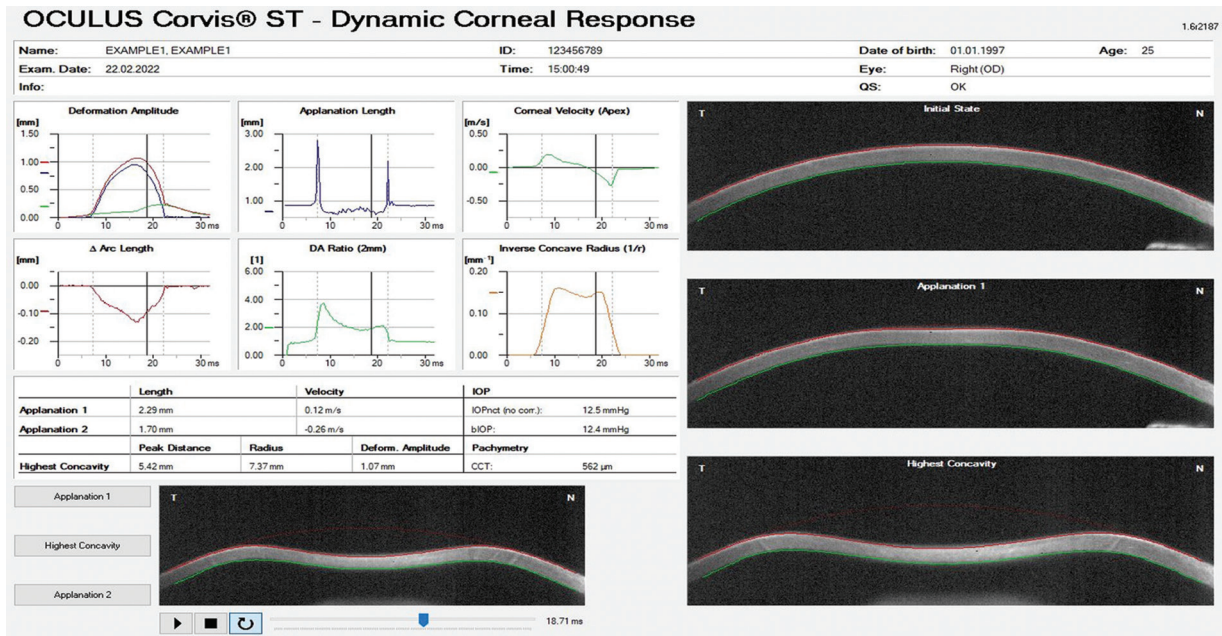


Figure 3. Standard parameters of the Corvis ST. The image shows deformation amplitude, applanation lengths, corneal velocities, radius of curvature at highest corneal concavity, corneal thickness, and intraocular pressure during the phases of indentation and recovery.

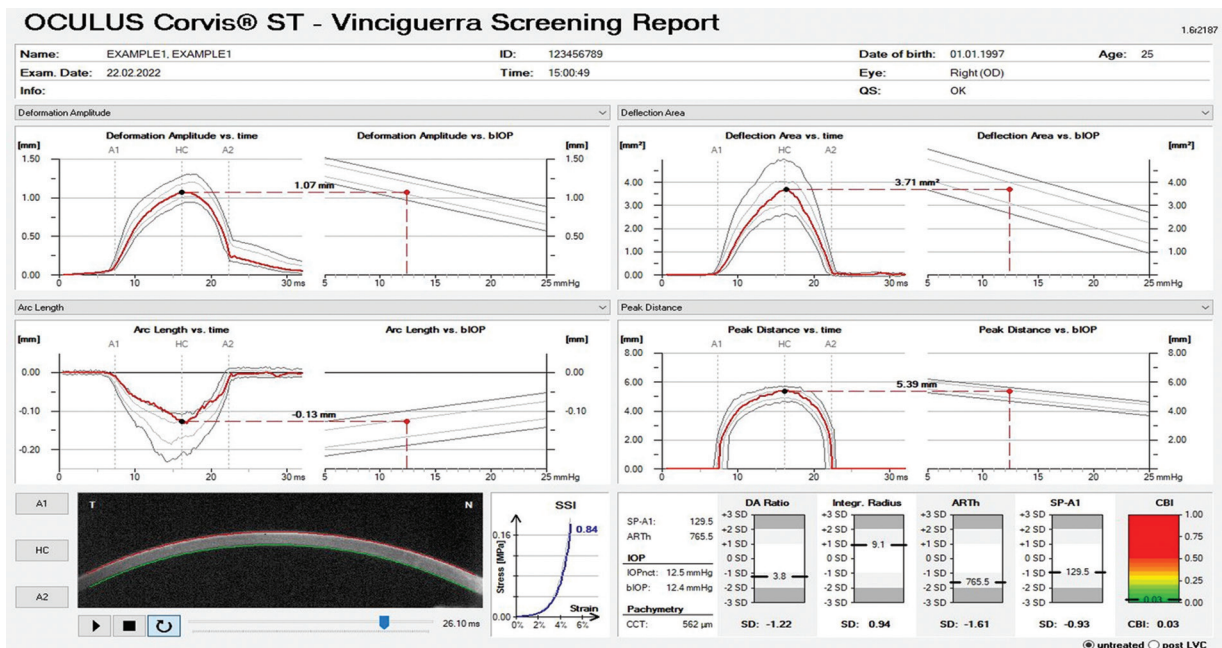


Figure 4. Vinciguerra report. This screen shows the correlation between normal values and biomechanically adjusted intraocular pressure (IOP). A calibration factor is used to calculate the IOP based on the pressure at the first applanation. It allows for the calculation of the Ambrosio Relational Thickness over the horizontal meridian (ARTh) and the Corvis Biomechanical Index (CBI).

of the parameters showed wide variation coefficients and low ICCs. In post-PRK patients, the highest repeatability was observed in IOP, CCT, AT1, and HCDA (ICC $\geq$.90), followed by AT2 (ICC, 0.89), A2V

(ICC, 0.79), HCT (ICC, 0.66), and curvature radius (ICC, 0.63). Similarly, Yang et al.³⁴ concluded that the repeatability of parameters is acceptable in both normal and keratoconus eyes.

Corvis ST in corneal diseases

Yang et al.³⁴ studied 77 eyes with keratoconus from 47 patients and 77 right eyes of 77 normal individuals. They concluded that the new parameters of the Corvis ST (inverse maximum radius, DA ratio max [2 mm], Pachy slope, DA ratio max [1 mm], ARTh, Integrated radius, SP-A1, and CBI) can diagnose keratoconus. Similar findings were made by Ren et al.³⁵, who stated that the results of the new parameters obtained in subclinical keratoconus were significantly different from those of normal controls and keratoconus eyes; thus, they could be used to distinguish keratoconus and subclinical keratoconus from normal eyes. Additionally, Liu et al.³⁶ and Vinciguerra et al.³⁷ claimed that combining this technology with corneal tomography improves the accuracy for detecting subclinical keratoconus, with TBI and CBI being the most valuable indices due to their high sensitivity and specificity. Conversely, Tian et al.³⁸ and Ali et al.³⁹ found that HCDA may be useful in combination with other parameters for the diagnosis and management of keratoconus patients.

A meta-analysis published by Wang et al.⁴⁰ determined that corneal biomechanics are altered in patients with diabetes mellitus, associated with increased values of CH, CRF, cclOP, and Goldman-correlated IOP.

When studying the effects of glaucoma on corneal biomechanics, diverse results have been found. In a study published by Jung et al.⁴¹, patients with glaucoma showed significantly less deformable corneas than controls, with differences depending on the severity of glaucoma. This contrasts with information published by Pradhan et al.⁴², who stated that the biomechanical parameters obtained by the Corvis ST do not differ between individuals with pseudoexfoliation glaucoma, primary open-angle glaucoma, and controls after IOP adjustment.

Corvis ST in ocular surgery

Zarei-Ghanavati et al.⁴³ studied 74 patients, 37 undergoing SMILE and 37 PRK, and concluded that both procedures significantly alter the biomechanical properties of the cornea; however, the changes were more prominent after SMILE.

Bak-Nielsen et al.⁴⁴ stated that there are no significant differences in deformation resistance between keratoconic eyes and keratoconic eyes that underwent CXL. Lanza et al.⁴⁵ reported that deformation resistance was still lower in post-CXL keratoconic corneas

compared to those that had not undergone CXL, and it also took longer to return to the flattened position and recover their original shape. Similar results were presented by Tomita et al.⁴⁶, who compared corneal deformation before and 1 year after conventional and accelerated CXL treatment, finding no significant differences between the 2 groups before and after treatment.

Lanza et al.⁴⁵ found that PRK-treated corneas exhibited similar resistance to deformation as the normal eyes studied, suggesting that PRK-induced corneal thinning does not change the corneal biomechanical properties. In contrast, Pedersen et al.⁴⁷ reported that flap-based keratorefractive procedures, such as LASIK and ReLEx FLEX, and flap-free procedures, such as ReLEx SMILE, change the CH and CRF vs the control group, resulting in a similar reduction in corneal biomechanics, except for CH time, which was shorter in LASIK-treated patients.

Brillouin optical microscopy

Brillouin optical microscopy is a recent technique used to measure corneal biomechanics in vivo through light scattering analysis and mapping corneal biomechanical properties in 3 dimensions. This method allows for the determination of intrinsic viscoelastic properties independently of structural information and applied pressure.

The cornea exhibits non-linear stress-strain behavior, indicating that its modulus is not constant. The tangent modulus, which represents the change in stiffness with tension or applied pressure, gradually increases.⁴⁸ Seiler et al.⁴⁹ conducted a study using Brillouin spectroscopy to investigate the impact of age on corneal stiffness, finding statistically significant differences between normal corneas and keratoconus. However, the accuracy of initial findings reported using this technique is relatively limited and requires additional validation and refinement, as advanced keratoconus corneas are clearly visible on Brillouin maps as regions with significantly reduced Brillouin shift. However, the correspondence between Brillouin maps and pachymetry and topography is less clear in early-stage keratoconus corneas, and Brillouin shifts correlate weakly with morphological parameters such as thickness and curvature. The large variations may originate from physiological factors and possibly additional factors associated with keratoconus pathogenesis⁵⁰.

Conclusions

Corneal biomechanics is a topic of great interest in modern ophthalmology research. Novel tools, such as Brillouin optical microscopy, provide information on the biomechanical properties of the cornea. However, most clinical data are related to the biomechanical response to non-contact tonometry. Despite substantial advances over the past 2 decades, *in vivo* characterization of corneal biomechanical response is influenced by intraocular pressure and central corneal thickness, which, as measured by Corvis ST, was also validated as not significantly different compared to ultrasonic pachymetry, the reference method. However, as with ORA, it was shown that central corneal pressure and thickness were correlated with the measured parameters and could, therefore, be potentially confounding. Even in light-scattering measurements, such as Brillouin optical microscopy, corneal hydration could be a confounding factor⁵¹.

However, new developments, such as the strain-deformation index provided by the Corvis ST, have managed to estimate stiffening after CXL treatment.

Understanding corneal biomechanics would be useful in various clinical applications, including glaucoma management, assessing the risk of ectasia, and determining the degree and depth of CXL. The integration of tomographic and biomechanical data has shown potential for improving accuracy in detecting ectatic diseases and identifying susceptibility to developing this complication after corneal laser vision correction. Additionally, integration with other data, such as ocular wavefront, axial length, and segmented layer tomography (epithelial) and microlaminar (Bowman), is also promising. We foresee continued and accelerated research and development in this field, which will further integrate corneal multimodal imaging, biomechanics, molecular biology, and genetics. In this environment, with an overwhelming amount of clinical data, AI will play a fundamental role in improving patient care efficiency. Since its introduction in 1956, AI has become increasingly relevant in ophthalmology, offering numerous potential applications. AI algorithms leverage computer processing power to simulate and enhance human interpretation, streamlining data analysis and clinical decision-making. A pioneering study used a neural network based on 11 indices from Placido disc topography to perform an automated interpretation of corneal maps. Although this model achieved correct classification for all maps in the training set, AI has had an even greater impact

on detecting and treating keratoconus and other corneal ectatic diseases. This advancement has led to a paradigm shift in the management of these diseases, especially with the introduction of techniques like cross-linking and intracorneal ring segments. Early or subclinical detection of corneal ectatic diseases is of paramount importance, particularly for identifying patients at risk of developing ectasia after undergoing laser corneal refractive surgery. TBI has been developed using AI, demonstrating high sensitivity and specificity for detecting these diseases in external validation studies.

Despite these advances, some research has found relatively low sensitivity in detecting abnormalities in subclinical keratoconus cases. This indicates the need to improve sensitivity to more effectively identify mild or subclinical cases. AI is playing an increasingly important role in ophthalmology, particularly in the early detection and treatment of corneal ectatic diseases, and there is a focus on improving detection accuracy through the optimization of AI algorithms in biomechanics⁵².

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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