

# Corneal biomechanics and glaucoma beyond the bidirectional impact of intraocular pressure and corneal deformation response

Biomecânica corneana e glaucoma além do impacto bidirecional da pressão intraocular e da resposta da deformação corneana.

Rodrigo Brazuna<sup>1</sup>, Marcella Salomão<sup>2</sup>, Bruno Esporcatte<sup>3</sup>, Marcelo Macedo<sup>4</sup>, Louise Esporcatte<sup>2</sup>, Giovanni Nicola Umberto Italiano Colombini<sup>1</sup>, Renato Ambrósio Júnior<sup>1</sup>

<sup>1</sup> Department of Ophthalmology, Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

<sup>2</sup> Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, RJ, Brazil.

<sup>3</sup> Department of Ophthalmology, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

<sup>4</sup> Department of Ophthalmology, Universidade de São Paulo, São Paulo, SP, Brazil.

## How to cite:

Brazuna R, Salomão M, Esporcatte B, Macedo M, Esporcatte L, Colombini GN, Ambrósio Júnior R. Corneal biomechanics and glaucoma beyond the bidirectional impact of intraocular pressure and corneal deformation response. Rev Bras Oftalmol. 2022;81:e0036.

## doi:

<https://doi.org/10.37039/1982.8551.20220036>

## Keywords:

ORA; Hysteresis; Cornea; Biomechanics; Corvis® ST; Glaucoma; Dynamic corneal response; Tonometry; Intraocular pressure

## Descritores:

ORA; Histerese, Córnea; Biomecânica; Corvis® ST; Glaucoma; Resposta corneana dinâmica; Tonometria; Pressão intraocular

**Received on:**  
Aug. 12, 2021

**Accepted on:**  
Dec 28, 2021

## Corresponding author:

Renato Ambrósio Júnior  
Rua Conde de Bonfim 211/712  
Zip code: 20520-050 – Rio de Janeiro,  
RJ, Brazil  
E-mail: dr.renatoambrosio@gmail.com

## Institution:

Universidade Federal do Estado do Rio de Janeiro.

## Conflict of interest:

the authors declare no conflict of interest.

## Financial support:

the authors received no financial support for this work.



Copyright ©2022

## ABSTRACT

The purpose of this study was to highlight the impact of biomechanical corneal response in available *in vivo* tonometry methods for glaucoma management. Systematic review of non-contact air-puff tonometers that analyzes the corneal deformation response, with special focus on the investigation of the correlation of derived parameters with intraocular pressure measurements. The two actual and commercially available *in vivo* corneal tonometers provide promising information about biomechanical characteristics of the cornea and its relation to glaucoma, allowing the development of new protocols to evaluate, diagnose, and manage this disease.

## RESUMO

O objetivo deste estudo é destacar o impacto da resposta biomecânica corneana em métodos de tonometria *in vivo* disponíveis para o manejo do glaucoma. Trata-se de revisão sistemática de tonômetros de ar que analisa a resposta à deformação corneana, com foco especial na investigação da correlação dos parâmetros derivados com as medições da pressão intraocular. Os dois tonômetros mais recentes e comercialmente disponíveis fornecem informações promissoras sobre as características biomecânicas da córnea e sua relação com o glaucoma, permitindo o desenvolvimento de novos protocolos para avaliar, diagnosticar e controlar a doença.

## INTRODUCTION

According to the World Health Organization (WHO), glaucoma is the first cause of irreversible blindness and the second cause of total blindness around the world. There is a consensus that high intraocular pressure (IOP) is the main risk factor for glaucoma development and progression. Therefore, properly measuring the IOP is essential for glaucoma diagnosis and follow-up. Goldmann applanation tonometry (GAT) is the gold standard method for IOP measurement. Several devices, including the Perkins, Tono-Pen, Icare, and Non-contact tonometers (NCTs), can provide reliable IOP measurements in adults.<sup>(1)</sup>

Since the 1970s, the concept was that central corneal thickness (CCT) below 525µm was related to an underestimation of IOP, and the opposite occurred as well, as pachymetric measurements higher than 555µm were correlated to overestimated IOP measurements.<sup>(2)</sup> This relation was already recognized in the past by the Swiss ophthalmologist Goldmann, who pointed out to the need of performing pachymetric measurements and correlating these with IOP when investigating glaucoma.<sup>(3)</sup> Interestingly, the Ocular Hypertension Treatment Study (OHTS), a multicentric randomized study developed by Brandt et al. in 2001,<sup>(3)</sup> showed a direct correlation between CCT and glaucoma, and CCT was considered a major risk factor for glaucoma development. These findings were posteriorly validated by the European Glaucoma Prevention Study (EGPS), which showed a higher risk of glaucoma progression in patients with thinner corneas. According to this study, for each lowering of 40µm on CCT, the risk of glaucoma progression was doubled.<sup>(4)</sup> However, these results were not compatible with the ones found on the Early Manifest Glaucoma Trial (EMGT). According to this study, after five years of follow-up, CCT did not represent a predictor for glaucoma progression. Interestingly, at the time point of 11 years of follow-up, the authors found that CCT influenced patients with high IOP but not patients with lower IOP.<sup>(5)</sup> Additionally, Leske et al. did not find a direct correlation between CCT and glaucoma on Barbados Eye study as well.

Further studies have shown that parameters such as corneal curvature and axial length have an important influence on GAT measurements.<sup>(6)</sup> Some studies found that thicker and steeper corneas tend to overestimate IOP.<sup>(7)</sup> Congdon has demonstrated that the risk of glaucoma progression may be associated with high axial length, particularly on black people.<sup>(8)</sup> One of the principles behind that may be related to myopia, lower CCT, and greater optic discs. Black people have a

higher incidence of glaucoma. One theory is that they have more fragility of collagen structures on the cornea, sclera, and lamina cribrosa, and a consequent risk of damage by the mechanical mechanism.

Significant sources of GAT errors and cofounders are astigmatism, gaze direction, corneal hydration, tear thickness, examiner's experience, corneal surgeries, corneal scars, elasticity, and other biomechanical characteristics beyond CCT. As a consequence, there is a risk of IOP misinterpretation, which, in turn, may compromise the evaluation of glaucoma patients and suspects.<sup>(3,4)</sup> Many formulas have been postulated to measure the real IOP based on CCT, but none has been well accepted.<sup>(5)</sup>

One of the major challenges of ophthalmology is to measure corneal biomechanical properties accurately. Biomechanics is defined as mechanics applied to Biology. Due to the complexity and variety of biological structure behavior, corneal biomechanical properties must be fully investigated and understood.<sup>(9)</sup> When submitted to tension, the corneal and scleral behaviors are similar to elastometric materials. The structure, geometry, and thickness of the cornea influence IOP measurements, and also, in turn, IOP influences the corneal deformation response as well. Therefore, it is very difficult to simulate the corneal behavior in vivo. Mathematical and predictive prototypes and ex vivo laboratory studies tried to simulate in vivo corneal structure behavior.<sup>(10)</sup> In ex vivo human corneas, X-ray scattering and scanning electron microscopy measurements reveal that collagen fibers have a disorganized orientation structure in the anterior part of the stroma, with the presence of a higher interweaving and branching in the anterior cornea compared to the posterior. These characteristics show that the cornea is an anisotropic, non-linear and inhomogeneous material and, therefore, shows different mechanical properties.<sup>(11,12)</sup>

Liu et al. created a mathematical model, the corneal Young's modulus, to simulate corneal behavior. This model shows that biomechanical properties have a superior and more independent influence on IOP measurements than thickness and curvature.<sup>(13)</sup> Knowledge of corneal biomechanics can help optimize several treatments and manage procedures that mechanically interact or interfere with the eye. This includes measurement of IOP for effective glaucoma management, keratoconus risk profiling, refractive surgery planning, and even optimization of different collagen crosslinking treatment protocols.<sup>(14,15)</sup>

The main challenge of estimating in vivo corneal biomechanical behavior is the difficulty separating these behavior effects from those of the IOP on ocular response to

mechanical stimuli. Thus, it is a challenge to produce accurate IOP measurements free from the effects of corneal biomechanics. The same challenge exists in determining the tissue's biomechanics free from the impact of IOP.<sup>(9)</sup>

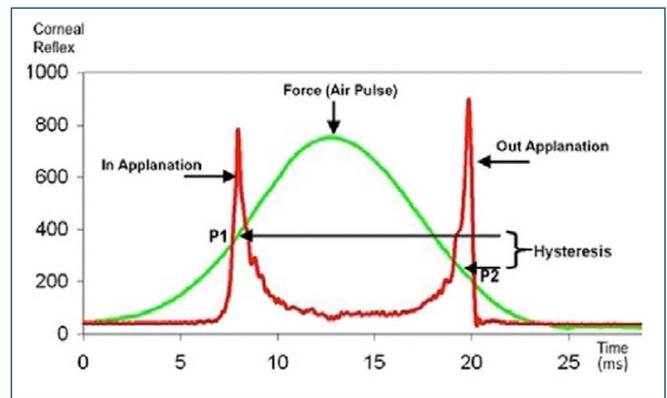
For this reason, new devices have been developed involving measurements of structure, geometry, and biomechanical features of the cornea, in an attempt to provide a more precise measurement of the IOP. This article reviews the two commercially available NCTs that provide corneal biomechanical measurements and discusses their interactions with IOP.

## THE OCULAR RESPONSE ANALYZER

Ocular Response Analyzer® (ORA, Reichert Ophthalmics Instruments, Depew, New York, United States), introduced in 2005 by David Luce, was the first device to assess in vivo biological, biomechanical properties.<sup>(16)</sup> The ORA is a modified non-contact tonometer (NCT) designed to provide a possibly more accurate measurement of IOP than GAT by compensating for corneal biomechanics. It produces a fast air jet that deforms the corneal curvature and records each moment of deformation. As the air pulse starts, the cornea begins an applanation process and moves inwardly, up to the first stage of applanation. At this point, the first IOP measurement is taken (P1). After a brief state of concavity, the air pulse ends, and the cornea moves back to its initial position while passing through the second stage of applanation, where the system provides a second IOP measurement (P2) (Figure 1). The difference between P1-P2 is considered corneal hysteresis (CH).<sup>(6,7)</sup>

Corneal hysteresis is conditioned to different ways to dissipate the energy during the loading and unloading applanation pressure. It is a viscoelastic capacity of the cornea to dissipate energy and is determined and influenced by the viscosity of glycosaminoglycans (GAGs) and proteoglycans (PGs), as well as by a collagen matrix interaction B1. Studies have demonstrated that CH has an inverse correlation with IOP.<sup>(16)</sup> Clinical situations with higher stiffness, like aging or higher IOP, can be associated with low CH values. A stiffer cornea with a high IOP has a low deformation and poor capacity to dissipate energy.<sup>(16)</sup> Interestingly, CH does not represent corneal stiffness, the elastic modulus, and the elastic resistance to deformation.

Corneal resistance factor (CRF) is another parameter calculated by the formula  $(P1 - KP2)$ , a linear equation, where K is a constant given by an empirical analysis between CCT and P1, and P2. Corneal resistance factor is



**Figure 1.** Ocular Response Analyzer® measurements showing the air pulse deforming the cornea (ingoing phase) and registering P1 (first applanation moment), the Gaussian configuration is formed when the air pulse gradually shuts off; then, with the continuity of the air pulse, the cornea assumes a concavity configuration. In the outgoing phase (air pressure decreases), the cornea passes through a second applanation, when the pressure of the air pulse (P2) is again registered. The pressure-derived parameters generated are corneal hysteresis and corneal resistance factor. This is a composite made by the authors of classic pictures available in the public domain.

theoretically a measure of the elastic properties of the cornea.<sup>(16)</sup> But, in fact, this is not true. This index is related to the loading and unloading phase and is a measure of viscoelastic properties weighted by elasticity.<sup>(16,17)</sup>

An additional parameter provided by the software is the compensated intraocular pressure (IOPcc). The IOPcc is an empirically determined linear combination of P1 and P2. Different studies have shown that IOPcc is less influenced by corneal structure properties, particularly CCT, than IOP given by GAT.<sup>(18)</sup> Another parameter provided is the Goldmann correlated IOP (IOPg). This parameter is analogous to Goldmann tonometry and is calculated by the average of P1 and P2.<sup>(19)</sup>

Investigators have found that the waveform derived from the response to corneal deformation during the different applanation moments provides important biomechanics information as well.<sup>(14)</sup> Studies have shown some particular situations, such as crosslinking, that viscous modifications masked the elastic modifications after the procedure, keeping the exact difference between the P1 and P2, even after stiffening the cornea, with higher peaks of P1 and P2.<sup>(15)</sup>

Another contribution of the analysis of the infrared signal from the waveform and the 38 parameters developed by David Luce is a new comprehension of the hysteresis and its linkage with glaucoma damage. Some authors suggest that corneal response deformation is directly influenced by the response of the entire eye and mainly by

the response of the sclera to deformation. Some studies have shown that a stiffer sclera has a lower deformation and hysteresis. Patients submitted to scleral buckle have different waveform parameters, with lower IOP measurements from GAT than corneal-compensated IOP when compared to controls. These parameters were mainly related to the second peak of unloading applanation, suggesting that a stiffer sclera promotes a faster corneal recovery to its natural convex shape.<sup>(20)</sup>

Several researchers have investigated the associations between ORA parameters and glaucoma. Congdon et al. showed that CH is associated with visual perimeter damage and glaucoma progression risk.<sup>(21)</sup> Mansouri found a weak relation between corneal biomechanical parameters and measurements of structural and functional damage in glaucoma in a cross-sectional study.<sup>(22)</sup> Some investigators have suggested that CH and CRF, when associated with CCT, could be considered a risk factor for different glaucoma types. They have concluded that CH may describe corneal properties more completely than thickness alone and may be a better parameter associated with progression.<sup>(23)</sup>

Vinciguerra et al. investigated how the optic disc biomechanics properties and the scleral channel connective tissue could determine different responses to variations of IOP.<sup>(24)</sup> They found abnormal corneal biomechanical properties in normal-tension glaucoma (NTG) and a significant correlation with visual field (VF) index, which might suggest a new risk factor for the diagnostic and progression of NTG. Biomechanical abnormalities of the optic disc head connective tissue, lamina cribrosa, and peripapillary sclera, are associated with axon damage, even before any changes in IOP. This could explain why some patients have glaucoma or disc optic damage, even in normal pressure conditions.<sup>(25)</sup> In a systematic review, Zhang et al. compared ORA and GAT in post-refractive surgery eyes. The authors found that IOPcc may be closer to the true IOP after corneal procedures when compared with GAT and IOPg.<sup>(26)</sup>

## THE CORVIS® ST DYNAMIC SCHEIMPFLUG ANALYZER

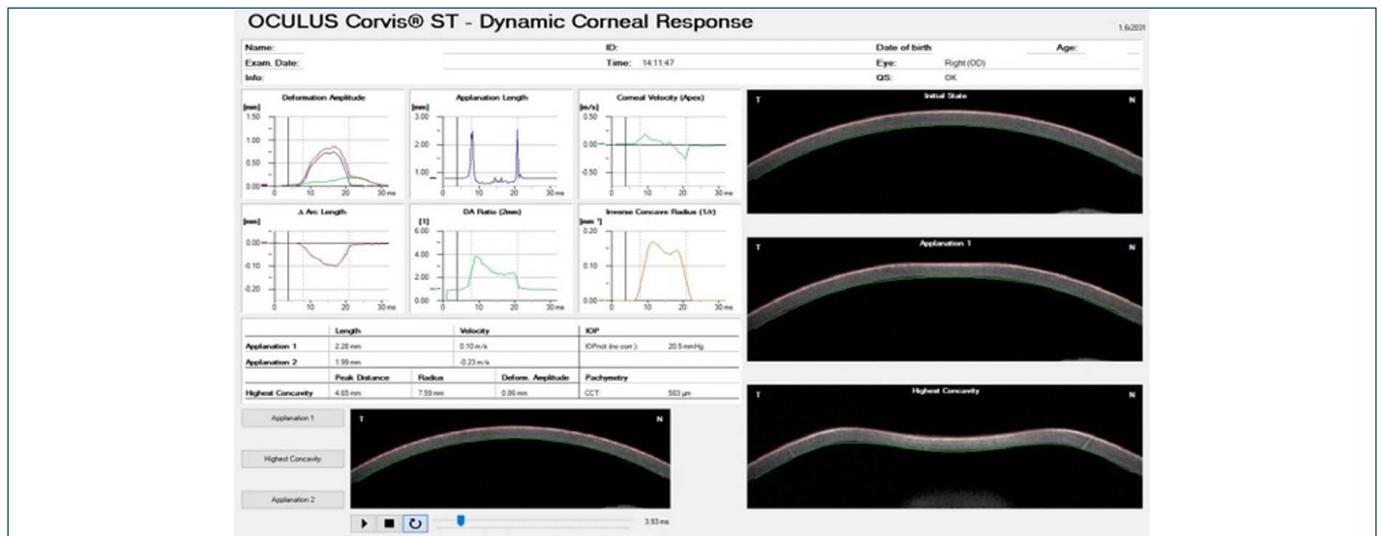
The Corvis® ST (CST, Oculus, Wetzlar, Germany) is also a NCT system, with a constant collimated air pulse and a consistent pressure profile. The maximum air pressure is 25 kPa. The device acquires 4,300 frames per second using an ultra-high-speed (UHS) Scheimpflug camera with UV-free 455nm blue light, covering 8.5mm horizontally of a single slit, which allows for dynamical evaluation

of corneal deformation, resulting in 140 images over the 30-millisecond air blow.<sup>(27)</sup> The bidirectional corneal movement induced by the air jet is monitored during the whole process.

Similar to the ORA, an air jet deforms the cornea inwards to the first applanation and then into a concave shape, to the point that the highest concavity (HC) is achieved (Figure 2). In sequence, the cornea recovers in the outward direction and undergoes a second applanation before returning to its natural position. Timing and corresponding pressures are monitored throughout the measurement. Once the measurement is performed, the device provides a set of corneal deformation parameters based on the dynamic inspection of the corneal response, including analysis of those parameters that are extracted at the HC point (Table 1).<sup>(19,27)</sup> Advanced algorithms identify the cornea's anterior and posterior limits, and the IOP is measured on the first corneal applanation moment.

The CST calculates the IOP value based on the first applanation time pressure.<sup>(24)</sup> The biomechanical-compensated IOP (bIOP), a new and validated estimation of the corrected IOP, is intended to be not influenced by corneal thickness and stiffness parameters.<sup>(28,29)</sup> The Vinciguerra Screening Report (Figure 3) shows an IOP parameter corrected through a finite element method, using deformation data beyond CCT and age, including the deformation response.<sup>(30)</sup> It is important to mention that the CST provides parameters associated with shape and that does not depend on IOP, but also provides parameters that depend on IOP and are associated with depth, like deformation amplitude, (DA) timing, and velocity.<sup>(31)</sup> The most sensitive parameters to changes in stiffness that do not depend on IOP are integrated inverse radius, the DA ratio, and SP-A1. The development of Stiffness parameters is dependent on load/displacement, and since the IOP is calculated at a determined location, the applanation is the reference. The DA can be measured from the initial position of the cornea to maximum depth. The DA is the most sensitive parameter influenced by IOP.<sup>(32)</sup>

A recently proposed parameter is the stiffness parameter. The stiffness parameter at A1 (SP-A1) is measured by the displacement from apex to applanation, and the stiffness parameter at HC (SP-HC) is measured by the displacement from applanation from HC.<sup>(33,34)</sup> Higher values of SP-HC and SP-A1 indicate a stiffer response and can be interpreted as less displacement for the same load with greater resistance to deformation. Glaucoma suspect eyes with higher corneal SPs and lower CCT, suggestive of thin and stiff corneas, are at greater



**Figure 2.** Standard Corvis® ST parameters. The figure shows the deformation amplitude, applanation lengths, corneal velocities recorded during ingoing and outgoing phases and the radius of curvature at the highest concavity (curvature radius highest concavity), thereby corneal thickness and intraocular pressure are calculated and registered.

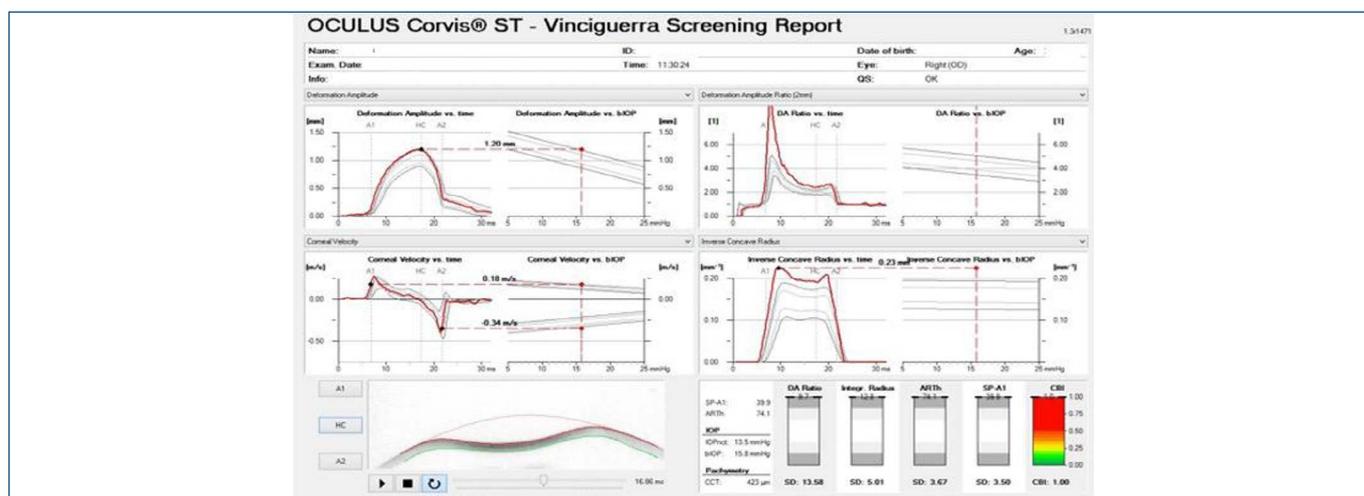
**Table 1.** Corneal deformation parameters provided by the Corvis® ST

Corvis® ST – parameters	
First applanation	The first applanation of the cornea during the air puff (in milliseconds). The length of the applanation at this moment appears in parenthesis (in millimeters)
Highest concavity	The instant that the cornea assumes its maximum concavity during the air puff (in milliseconds). The length of the distance between the two peaks of the cornea at this moment appears in parenthesis (in millimeters)
Second applanation	The second applanation of the cornea during the air puff (in milliseconds). The length of the applanation at this moment appears in parenthesis (in millimeters)
Maximum deformation	The amount (in millimeters) of the maximum cornea deformation during the air puff
Wing distance	The length of the distance between the two peaks of the cornea at this instant (in millimeters)
Maximum velocity (in)	Maximum velocity during the ingoing phase (in meters per second)
Maximum velocity	The maximum velocity during the outgoing phase (in meters per second)
Curvature radius normal	The cornea in its natural state radius of curvature (in millimeters)
Curvature radius highest concavity	The cornea radius of curvature at the time of maximum concavity during the air puff (in millimeters)
Cornea thickness	Measurement of the corneal thickness (in millimeters)
IOP	Measurement of the intraocular pressure (in mmHg)
bIOP	Biomechanically-corrected IOP
Deformation amplitude ratio maximum 2mm	Ratio between the deformation amplitude at the apex and the average deformation amplitude measured at 2mm from the center
Ambrósio's relational thickness to the horizontal profile	Describes thickness profile in the temporal-nasal direction and is defined as the thinnest corneal thickness to pachymetric progression
Stiffness parameter at A1	Describes corneal stiffness as defined by the resultant pressure divided by deflection amplitude at A1
Stiffness parameter- highest concavity	Corneal stiffness at the highest concavity point
Tomographic biomechanical index	Index that combined tomographic and biomechanical data to keratoconus detection
Biomechanical glaucoma factor	Independent risk indicator for normal tension glaucoma
Stress-strain index	Index that indicates the position of the stress-strain curves. Less dependent on corneal thickness and IOP
Corvis® biomechanical index	Overall biomechanical index for keratoconus detection

risk of progression.<sup>(35)</sup> Other parameters related to a stiffer response are lower values of DA ratio and integrated inverse radius. These parameters can indicate a greater resistance for a shape change and deformation.

Studies have shown that greater IOP produces stiffer corneal behavior under an applied air puff and a stiffer globe produces a stiffer corneal behavior.<sup>(36)</sup> Another further study concluded that when deformation is maximum, the sclera is mainly involved in biomechanics response, showing DA ratios and SP-A1 response with no significant changes, but with great and significant changes in SP-HC.<sup>(37)</sup>

An important complication factor is that biological tissue stress-strain behavior, including cornea and sclera, is non-linear.<sup>(38)</sup> Therefore, the tangent modulus ( $E_t$ ), a measure of the material stiffness, is not constant and increases with stress and strain. This effectively means that, as IOP increases, the stress and strain to which the eye is subjected increases, causing a rise in the tangent modulus. Therefore, it is almost impossible to separate IOP and corneal biomechanics effects on eye behavior; and IOP also affects the immediate corneal stiffness. In an attempt to solve this, Elsheikh et al. introduced the concept of bIOP, the biomechanically-corrected IOP.<sup>(39)</sup>

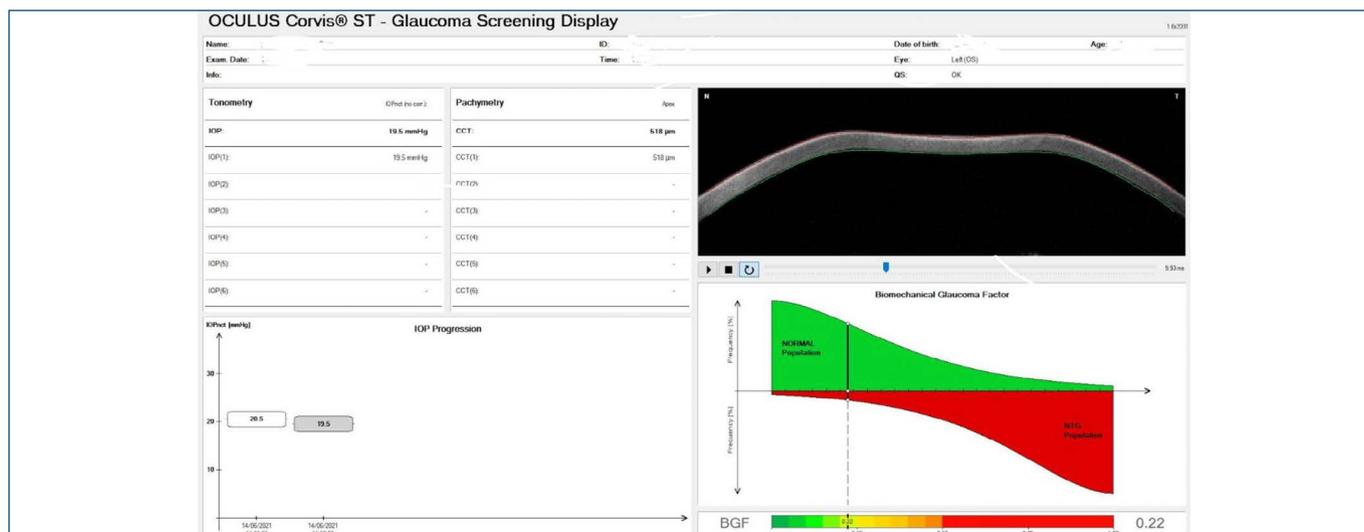


**Figure 3.** The Vinciguerra Screening Report. This display provides correlations of normality values and a biomechanically adjusted intraocular pressure. It uses a calibration factor to calculate the intraocular pressure value based on the pressure at the time of the first appplanation. It empowers the calculation of the Ambrósio Relational Thickness over the horizontal meridian and the Corvis® Biomechanical Index.

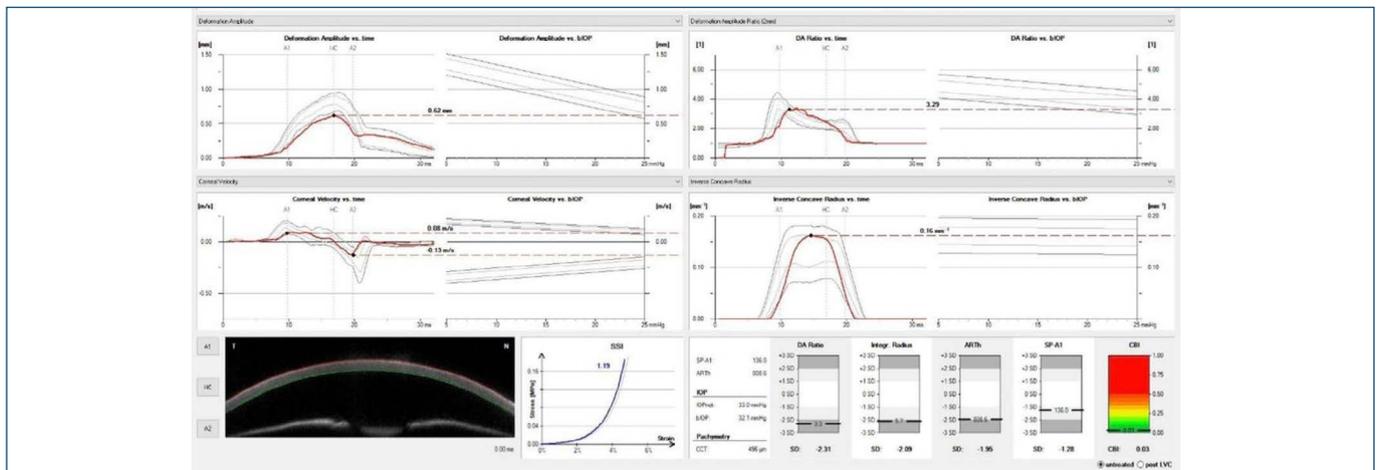
The bIOP algorithm was developed using a combination of numerical modeling, experimental and clinical validation, and corneal deformation parameters to reduce the effect of stiffness on IOP calculated.<sup>(2,30,40)</sup> Ye found that bIOP was less affected by CCT and higher than GAT-IOP measurements in patients with open-angle glaucoma and ocular hypertension.<sup>(41)</sup> Chen et al. showed that bIOP is less correlated with the cornea stiffness parameters than GAT and the uncorrected CST-IOP measurements.<sup>(2,42)</sup> Matsuura et al. have supported that bIOP is less dependent on biomechanical properties and suggested high repeatability of bIOP values, based on previous studies. His group compared the relationship between (IOP) measured with CST and CCT and CH, in comparison with IOP measured with GAT and the ORA. The authors concluded that the bIOP

measurement from CST was independent of CCT but dependent on CH and CRF.<sup>(29,43)</sup>

Vinciguerra verified a significant correlation between VF parameters and abnormal corneal biomechanics in NTG, suggesting a new risk factor for the progression or development of this condition.<sup>(24)</sup> The biomechanical glaucoma factor (BGF) was introduced as an independent risk factor for NTG. The cornea of NTG patients is more deformable than healthy controls, and this index was developed for the screening of these patients<sup>(24,44)</sup> (Figure 4). Some researchers tested the GAT's effectiveness, the Dynamic Contour Tonometer, the ORA, and the CST in measuring IOP following Femtosecond-LASIK. Their results showed that bIOP measurements were in closest agreement with those obtained before surgery.<sup>(26)</sup> Hong et al. compared Topcon NCT,



**Figure 4.** The biomechanical glaucoma factor. This index shows the likelihood for specific patient being more comparable to biomechanical behavior of healthy patients or normal-tension glaucoma.



**Figure 5.** The Stress-Strain Index. This index indicates the cornea's stiffness and describes the cornea's intrinsic elastic properties less dependent on corneal thickness or intraocular pressure. It is calculated by element finite and describes the position of the stress-strain curve, and the cornea is considered softer when curves are shifted to the right or the index value is smaller than one. Furthermore, it is considered stiffer when the curves are shifted to the left and the index is bigger than one.

GAT, and the CST (CST) and found good agreement of the IOP measurements of the devices. Nevertheless, the authors pointed out that IOP measurements taken with these devices may not be interchangeable.<sup>(28)</sup>

Eliasy et al. introduced a new algorithm that can determine the human cornea's biomechanical properties in vivo, the stress-strain index, the SSI, which is a new intelligent algorithm of material stiffness parameter (Figure 5). While SSI showed no significant correlation with CCT ( $p > 0.05$ ) and IOP ( $p > 0.05$ ), this index was significantly correlated with age ( $p < 0.01$ ). The stiffness estimates and age variation were also significantly correlated ( $p < 0.01$ ), with stiffness estimates obtained earlier in studies on ex-vivo human tissue.<sup>(45)</sup>

The SSI provides an estimation of the whole stress-strain behavior of the cornea regardless of CCT under any IOP, maintaining a positive correlation with age. It could help to isolate the impact of biomechanics properties in glaucoma patients regardless of IOP and thickness.<sup>(19)</sup>

Fujihiro et al. investigated a possible association between CST measurements and CH. Measurements of CST, ORA, axial length, average corneal curvature (CCT), and IOP with GAT were performed in 104 eyes of 104 patients with primary open-angle glaucoma and 35 eyes from normal subjects. The association between CST and ORA parameters was investigated using linear regression analysis. Parameters including DA ratio (corneal softness;  $R = -0.51$ ), a stiffer parameter of first applanation (SP A1; corneal stiffness;  $R = 0.41$ ), and Inverse Radius (integrated area under the curve of the inverse concave radius;  $R = -0.44$ ) were significantly correlated with CH ( $p < 0.05$ ), but CST parameters were significant, but weakly or moderately, related to ORA measured CH.<sup>(46)</sup>

Li et al. investigated the association between corneal biomechanical parameters and VF progression in NTG using the CST device and identified the ability of corneal biomechanical parameters to predict the VF progression. Progressive eyes evidenced a quicker response to reach first-degree applanation and a larger degree of corneal deformability. This could explain the glaucomatous optic nerve damage. Time A1 was considered the best biomechanical parameter to predict the progression of the VF.<sup>(47)</sup> Aoki et al. studied the associations between CST-measured corneal biomechanical parameters and glaucomatous optic nerve head (ONH) morphology. They concluded that eyes with a superior-dominant rim volume reduction of ONH were associated with small deformations and the cornea's slow recovery.<sup>(48)</sup> Jung et al. found a correlation between Corneal deflection amplitude and glaucoma progression. Eyes with greater corneal deflection amplitude showed a faster VF progression rate in patients with POAG. This same group investigated a relationship between corneal DA and ONH structure in primary open-angle glaucoma and concluded that patients with lower corneal DA showed greater lamina cribrosa depth cup area, deeper cup, and smaller peripapillary atrophy area (PPA) than those with higher corneal DA.<sup>(49)</sup> Qassim has found in a recent longitudinal study in glaucoma suspects that the combination of higher SP-A1 with thinner CCT could accelerate RNFL thinning, and a higher SP-A1 could be associated with a greater risk of VF progression.<sup>(35)</sup>

Another recent publication that reinforces that stiffness of sclera could contribute to biomechanics deformation and could be the gap between the progression of glaucoma and the IOP is the analysis of treated patients with analogs

of prostaglandins. These drugs decrease the extracellular matrix in the sclera and ciliary body and affect the ocular rigidity, affecting both sclera and corneal stiffness.<sup>(50)</sup> An interesting finding to consider is that some patients decrease the pressure and the ocular rigidity, as expected, but increase the volume and the anterior chamber volume unexpectedly. One possible explanation for this finding is because these patients present a decrease in CCT and CH, and therefore the cornea becomes more compliant.<sup>(50)</sup>

## CONCLUSION

Clinical investigation of in vivo corneal biomechanics is a challenging but a promising area of contemporary ophthalmology. Understanding the biomechanical corneal deformation behavior might be useful in several clinical situations, including glaucoma and ectasia corneal diseases. The inspection of the corneal slit during the deformation allows for objective and subjective analysis. The dynamic corneal response provides a more precise intraocular pressure measure, which is also important and influential for deformation response. The ability of the Corvis® to provide both biomechanical corneal properties and intraocular pressure by advanced intelligent algorithms might improve the accuracy of diagnosing diseases as keratoconus and glaucoma or even improve the efficacy and safety of corneal surgeries.

In conclusion, Ora and Corvis® ST provide biomechanical measurements in different pathways, and their index provides important information about corneal deformation response. Nevertheless, these measurements are not interchangeable and seem to have a poor correlation but combining both technologies may be a promising area to explore in the future, in order to help the creation of new protocols for diagnosis and management glaucoma.

Despite significant improvements over the last years, additional research is still needed. Nevertheless, we expect accelerated growth in knowledge in this field in the next years to come.

## REFERENCES

- Cook JA, Botello AP, Elders A, Ali AF, Azuara-Blanco A, Fraser C, et al. Systematic review of the agreement of tonometers with Goldmann applanation tonometry. *Ophthalmology*. 2012;119(8):1552-7.
- Eliasy A, Chen KJ, Vinciguerra R, Maklad O, Vinciguerra P, Ambrósio R Jr., et al. Ex-vivo experimental validation of biomechanically-corrected intraocular pressure measurements on human eyes using the CorVis ST. *Exp Eye Res*. 2018;175:98-102.
- Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology*. 2001;108(10):1779-88.
- European Glaucoma Prevention Study Group, Pfeiffer N, Torri V, Miglior S, Zeyen T, Adamsons I, Cunha-Vaz J. Central corneal thickness in the European Glaucoma Prevention Study. *Ophthalmology*. 2007;114(3):454-9.
- Iester M, Mete M, Figus M, Frezzotti P. Incorporating corneal pachymetry into the management of glaucoma. *J Cataract Refract Surg*. 2009;35(9):1623-8.
- Zakrzewska A, Wiącek MP, Machalińska A. Impact of corneal parameters on intraocular pressure measurements in different tonometry methods. *Int J Ophthalmol*. 2019;12(12):1853-8.
- Nuyen B, Mansouri K. Fundamentals and Advances in Tonometry. *Asia Pac J Ophthalmol (Phila)*. 2015;4(2):66-75.
- Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, et al. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol*. 2004;122(4):532-8.
- Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. *J Cataract Refract Surg*. 2005;31(1):146-55.
- Dupps WJ. Biomechanical modeling of corneal ectasia. *J Refract Surg*. 2005;21(2):186-90.
- Meek KM, Boote C. The organization of collagen in the corneal stroma. *Exp Eye Res*. 2004;78(3):503-12.
- Bueno JM, Gualda EJ, Giakoumaki A, Pérez-Merino P, Marcos S, Artal P. Multiphoton microscopy of ex vivo corneas after collagen cross-linking. *Invest Ophthalmol Vis Sci*. 2011;52(8):5325-31.
- Liu J, He X, Pan X, Roberts CJ. Ultrasonic model and system for measurement of corneal biomechanical properties and validation on phantoms. *J Biomech*. 2007;40(5):1177-82.
- Elsheikh A, Geraghty B, Rama P, Campanelli M, Meek KM. Characterization of age-related variation in corneal biomechanical properties. *J R Soc Interface*. 2010;7(51):1475-85.
- Ambrósio R Jr, Lopes BT, Faria-Correia F, Salomão MQ, Bühren J, Roberts CJ, et al. Integration of Scheimpflug-Based Corneal Tomography and Biomechanical Assessments for Enhancing Ectasia Detection. *J Refract Surg*. 2017;33(7):434-43.
- Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg*. 2005;31(1):156-62.
- Roberts CJ. Corneal hysteresis and beyond: Does it involve the sclera? *J Cataract Refract Surg*. 2021;47(4):427-9.
- Hager A, Loge K, Schroeder B, Füllhas MO, Wiegand W. Effect of central corneal thickness and corneal hysteresis on tonometry as measured by dynamic contour tonometry, ocular response analyzer, and Goldmann tonometry in glaucomatous eyes. *J Glaucoma*. 2008;17(5):361-5.
- Roberts CJ. Concepts and misconceptions in corneal biomechanics. *J Cataract Refract Surg*. 2014;40(6):862-9.
- Roberts CJ. Corneal hysteresis and beyond: Does it involve the sclera? *J Cataract Refract Surg*. 2021;47(4):427-9.
- Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol*. 2006;141(5):868-75.
- Mansouri K, Leite MT, Weinreb RN, Tafreshi A, Zangwill LM, Medeiros FA. Association between corneal biomechanical properties and glaucoma severity. *Am J Ophthalmol*. 2012;153(3):419-27.e1.
- Susanna CN, Diniz-Filho A, Daga FB, Susanna BN, Zhu F, Ogata NG, et al. A Prospective Longitudinal Study to Investigate Corneal Hysteresis as a Risk Factor for Predicting Development of Glaucoma. *Am J Ophthalmol*. 2018;187:148-52.
- Vinciguerra R, Rehman S, Vallabh NA, Batterbury M, Czanner G, Choudhary A, et al. Corneal biomechanics and biomechanically corrected intraocular pressure in primary open-angle glaucoma, ocular hypertension and controls. *Br J Ophthalmol*. 2020;104(1):121-6.
- Grise-Dulac A, Saad A, Abitbol O, Febraro JL, Azan E, Moulin-Tyrode C, et al. Assessment of corneal biomechanical properties in normal tension glaucoma and comparison with open-angle glaucoma, ocular hypertension, and normal eyes. *J Glaucoma*. 2012;21(7):486-9.
- Zhang H, Sun Z, Li L, Sun R, Zhang H. Comparison of intraocular pressure measured by ocular response analyzer and Goldmann applanation tonometer after corneal refractive surgery: a systematic review and meta-analysis. *BMC Ophthalmol*. 2020;20(1):23.
- Ambrósio R Jr, Ramos I, Luz A, Faria FC, Steinmueller A, Krug M, et al. Dynamic ultra high speed Scheimpflug imaging for assessing corneal biomechanical properties. *Rev Bras Oftalmol*. 2013;72:99-102.

28. Hong J, Xu J, Wei A, Deng SX, Cui X, Yu X, et al. A new tonometer—the Corvis ST tonometer: clinical comparison with noncontact and Goldmann applanation tonometers. *Invest Ophthalmol Vis Sci.* 2013;54(1):659-65.
29. Matsuura M, Murata H, Fujino Y, Yanagisawa M, Nakao Y, Tokumo K, et al. Relationship between novel intraocular pressure measurement from Corvis ST and central corneal thickness and corneal hysteresis. *Br J Ophthalmol.* 2020;104(4):563-8.
30. Joda AA, Shervin MM, Kook D, Elsheikh A. Development and validation of a correction equation for Corvis tonometry. *Comput Methods Biomech Biomed Engin.* 2016;19(9):943-53.
31. Vinciguerra R, Elsheikh A, Roberts CJ, Ambrósio R Jr., Kang DS, Lopes BT, et al. Influence of Pachymetry and Intraocular Pressure on Dynamic Corneal Response Parameters in Healthy Patients. *J Refract Surg.* 2016;32(8):550-61.
32. Ruberti JW, Roy AS, Roberts CJ. Corneal Biomechanics and Biomaterials. *Ann Revf Biomed Eng.* 2011;13(1):269-95.
33. Salomão MQ, Hofling-Lima AL, Gomes Esporcatte LP, Lopes B, Vinciguerra R, Vinciguerra P, et al. The Role of Corneal Biomechanics for the Evaluation of Ectasia Patients. *Int J Environ Res Public Health.* 2020;17(6):2113.
34. Esporcatte LP, Salomão MQ, Lopes BT, Vinciguerra P, Vinciguerra R, Roberts C, et al. Biomechanical diagnostics of the cornea. *Eye Vis (Lond).* 2020;7:9.
35. Qassim A, Mullany S, Abedi F, Marshall H, Hassall MM, Kolovos A, et al. Corneal Stiffness Parameters Are Predictive of Structural and Functional Progression in Glaucoma Suspect Eyes. *Ophthalmology.* 2021;128(7):993-1004.
36. Metzler KM, Mahmoud AM, Liu J, Roberts CJ. Deformation response of paired donor corneas to an air puff: intact whole globe versus mounted corneoscleral rim. *J Cataract Refract Surg.* 2014;40(6):888-96.
37. Nguyen BA, Roberts CJ, Reilly MA. Biomechanical Impact of the Sclera on Corneal Deformation Response to an Air-Puff: A Finite-Element Study. *Front Bioeng Biotechnol.* 2018;6:210.
38. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. *Curr Eye Res.* 2007;32(1):11-9.
39. Elsheikh A, Joda A, Vinciguerra R, Vinciguerra P, Kook D, Sefat S, et al. Clinical evaluation of correction algorithm for corvis ST tonometry. *Invest Ophthalmol Vis Sci.* 2015;56(7):101.
40. Elsheikh A, Geraghty B, Alhasso D, Knappett J, Campanelli M, Rama P. Regional variation in the biomechanical properties of the human sclera. *Exp Eye Res.* 2010;90(5):624-33.
41. Ye Y, Yang Y, Fan Y, Lan M, Yu K, Yu M. Comparison of biomechanically corrected intraocular pressure obtained by corvis st and goldmann applanation tonometry in patients with open-angle glaucoma and ocular hypertension. *J Glaucoma.* 2019;28(10):922-8.
42. Chen KJ, Joda A, Vinciguerra R, Eliasy A, Sefat SM, Kook D, et al. Clinical evaluation of a new correction algorithm for dynamic Scheimpflug analyzer tonometry before and after laser in situ keratomileusis and small-incision lenticule extraction. *J Cataract Refract Surg.* 2018;44(5):581-8.
43. Fujishiro T, Matsuura M, Fujino Y, Murata H, Tokumo K, Nakakura S, et al. The Relationship Between Corvis ST Tonometry Parameters and Ocular Response Analyzer Corneal Hysteresis. *J Glaucoma.* 2020;29(6):479-84.
44. Pillunat KR, Herber R, Spoerl E, Erb C, Pillunat LE. A new biomechanical glaucoma factor to discriminate normal eyes from normal pressure glaucoma eyes. *Acta Ophthalmol.* 2019;97(7):e962-e7.
45. Eliasy A, Chen KJ, Vinciguerra R, Lopes BT, Abass A, Vinciguerra P, et al. Determination of Corneal Biomechanical Behavior in-vivo for Healthy Eyes Using CorVis ST Tonometry: Stress-Strain Index. *Front Bioeng Biotechnol.* 2019;7:105.
46. Fujishiro T, Matsuura M, Fujino Y, Murata H, Tokumo K, Nakakura S, et al. The Relationship Between Corvis ST Tonometry Parameters and Ocular Response Analyzer Corneal Hysteresis. *J Glaucoma.* 2020;29(6):479-84.
47. Li BB, Cai Y, Pan YZ, Li M, Fang Y, Tian T, et al. [The association between corneal biomechanical parameters and visual field progression in patients with normal tension glaucoma]. *Zhonghua Yan Ke Za Zhi.* 2018;54(3):171-6. Chinese.
48. Aoki S, Kiuchi Y, Tokumo K, Fujino Y, Matsuura M, Murata H, et al. Association between optic nerve head morphology in open-angle glaucoma and corneal biomechanical parameters measured with Corvis ST. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(3):629-37.
49. Jung Y, Park HL, Park CK. Relationship between corneal deformation amplitude and optic nerve head structure in primary open-angle glaucoma. *Medicine (Baltimore).* 2019;98(38):e17223.
50. Scott JA, Roberts CJ, Mahmoud AM, Jain SG. Evaluating the relationship of intraocular pressure and anterior chamber volume with use of prostaglandin analogues. *J Glaucoma.* 2021;30(5):421-7.