Review

Corneal Biomechanics and Glaucoma

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Review

Corneal Biomechanics and Glaucoma

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Abstract: Biomechanics is a branch of biophysics that deals with mechanics applied to biology. The biomechanics of the cornea plays a significant role in managing patients with glaucoma. While evidence suggests a higher risk of glaucoma in patients with thin and stiffer corneas, it also affects the measurement of intraocular pressure (IOP). We reviewed the pertinent literature to help the understanding of corneal biomechanics and how it can help optimize clinical and surgical treatments and a better approach to diagnosing and managing patients with glaucoma.

Keywords: glaucoma; hysteresis; biomechanics; ORA; Corvis

1. Introduction

Biomechanics is a branch of biophysics that deals with mechanics applied to biology for the human or animal bodies. While biomechanics is especially concerned with the muscles and the skeleton, it is also used for referring to the functioning of any other part of a body, such as a cornea [1]. The analysis of the corneal biomechanics has helped clinicians detect early or mild corneal ectasias [2–4], which can be further enhanced by integrating tomographic data obtained with the Pentacam (Oculus GmbH; Wetzlar, Germany) [3].

Corneal biomechanics also plays a significant role in managing patients with glaucoma [5]. First, evidence suggests a higher risk of glaucoma in patients with thin and stiffer corneas [6–8]. Second, corneal biomechanics affects and is affected by intraocular pressure (IOP) [9–11]. Therefore, one of the significant challenges of contemporary ophthalmology is understanding the independent role of corneal biomechanical properties and IOP on the ocular response to mechanical stimuli to ensure accurate measurements and proper monitoring of glaucoma patients [1].

2. The Ocular Response Analyzer

The first device that allowed the assessment of in vivo biomechanical properties was the ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA), introduced in 2005 by David Luce (Figure 1) [12]. The ORA is a modified non-contact tonometer (NCT) designed to provide a more accurate measurement of the IOP than the Goldmann applanation tonometer (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 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. 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). The difference between P1-P2 is considered corneal hysteresis (CH) (Figure 2) [13]. The CH corresponds to a dissipation of energy during the loading and unloading phases representing the viscoelastic characteristics of the cornea and sclera. It has no direct correspondence to corneal stiffness [14]. Studies have shown that CH is a dynamic parameter affected directly by the IOP with an inverse correlation. An increase in IOP decreases CH and vice versa. The CH is a parameter of the entire globe, not exclusively of the cornea. The whole eye globe responds when a loading force is applied to the cornea. As a consequence, it dissipates energy [15]. Studies have shown that CH will decrease the stiffening sclera, confirming that CH is not a local corneal parameter [16].

Other parameters generated by the ORA software are the corneal resistance factor (CRF), the compensated intraocular pressure (IOPcc), and the Goldmann correlated IOP (IOPg). The CRF is a theoretical measure of the elastic properties of the cornea, calculated with the formula a [P1–0.7P2] + d where a and d are calibration and regression constants to maximize correlation with the central corneal thickness (CCT) [17]. The IOPcc is less influenced by corneal structure properties, particularly CCT, than IOP measured by conventional GAT [18]. In a systematic review, Zhang and collaborators compared ORA and GAT in post-refractive surgery eyes. They showed that the IOPcc is closer to the true IOP in eyes that underwent corneal procedures [19]. Lastly, the IOPg is the mean of the applanation pressures and is given by the formula IOPg= (P1-P2)/2.

Figure 1. Ocular Response Analyzer tonometer (Image from Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA).

IOP is a constant force (loading) per unit area under the globe, playing an essential role in the biomechanical response [9–11]. The IOP is the most impactor predictor of deformation amplitude (DA) under an air jet load, followed by stiffness and thickness [20]. A greater IOP on a weaker cornea can produce a stiffer response than a lower IOP on a stronger cornea. The cornea and sclera have a non-linear stiffening response under the increase of IOP. Stress is a force per unit of cross-sectional area in a loaded stretched tissue. Strain is a non-dimensional deformation or percent stretch when the tissue is pulled [21]. The tangent elastic moduli are related to stiffness and are given by the stress-strain slope at a determined strain value. The slope has a non-linear behavior: as the load increases, the slope increases too [21]. The stress distribution in the cornea can be quantified using the Hoop stress formula, $\sigma = P \bullet R/2t$, where σ is the stress, P is the IOP, R is the radius of curvature, and t is the corneal thickness. We can conclude with this equation that a thinner and cornea flatter cornea is associated with higher stress [21].

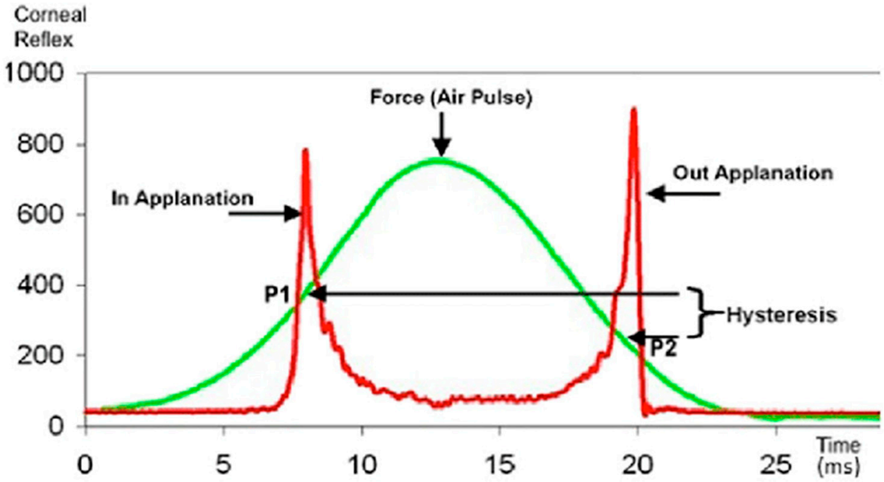


Figure 2. ORA measurements show the air pulse deforming the cornea. The parameters generated are corneal Hysteresis (CH) and corneal resistance factor (CRF). Image from Kaushik S, et al. Pandav SS. Ocular Response Analyzer. J Curr Glaucoma Pract. 2012 Jan-Apr;6(1):17-19.

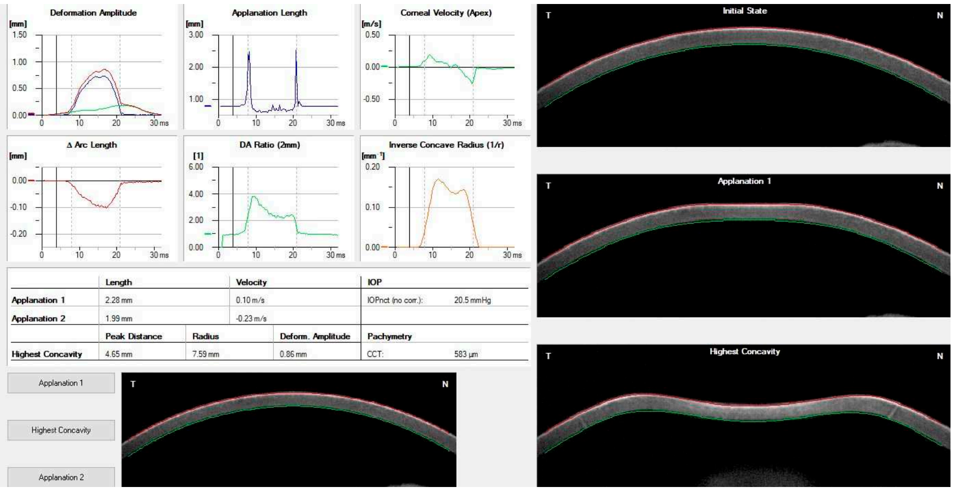
The scleral material biochemical properties also contribute to the observed corneal response in air-puff-induced deformation [20,22]. The biomechanical resistance of the sclera occurs after the aqueous displacement during the corneal recovery on the second applanation in jet air commercial tonometry. Studies have shown that the stiffer the sclera, the greater the resistance to aqueous motion, which could be wrongly interpreted as a stiffer corneal deformation [23].

3. The Corvis ST Dynamic Scheimpflug Analyzer

The Corvis ST (Oculus, Wetzlar, Germany) is also a non-contact tonometer system with a collimated air pulse and a consistent pressure profile (Figure 3). The device uses an ultra-high-speed (UHS) Scheimpflug camera to acquire 4,300 frames per second, covering 8.5 mm horizontally of a single slit, which allows a dynamical evaluation of the corneal deformation [24].

Figure 3. Oculus Corvis ST (Wetzlar,Germany).

Although similar to the ORA, in which an air jet deforms the cornea, the Corvis ST uses a fixed pressure from the air jet. The cornea bends inwards to the first applanation, and then to the point that the highest concavity (HC) is achieved (Figure 4). Afterward, the cornea recovers in the outward direction and undergoes a second applanation before returning to its natural position. Advanced algorithms identify the cornea's anterior and posterior limits, and the IOP is measured on the first corneal applanation moment. 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 highest concavity point [14,24].



	Length		Velocity	IOP	
Applanation 1	2.28 mm		0.10 m/s	IOPnct (no corr.):	20.5 mmHg
Applanation 2	1.99 mm		-0.23 m/s		
	Peak Distance	Radius	Deform. Amplitude	Pachymetry	
Highest Concavity	4.65 mm	7.59 mm	0.86 mm	CCT:	583 µm

Figure 4. Dynamic ultra-high-speed Scheimpflug imaging for assessing corneal biomechanical response and properties. The highest point concavity (HC) is shown in the image's lower right corner. Personal archive.

Whole-eye movement (WEM) is the resistance of other tissues after the cornea reaches its deformation limits and the air pressure increases. The orbital soft tissue and structure limit the WEM. The dynamic corneal response (DCR) parameters associated with the loading phase are elastic in nature [21]. One of these parameters is the point of highest concavity, the time point of the most significant resistance to aqueous movement. The stiffness parameter at the highest concavity (SP-HC), which is the moment of capture of the scleral response, is the load at first applanation (Air pressure-IOP) divided by displacement from first applanation (A1) to highest concavity [25]. Deformation ratio 2 mm (DA ratio) and integrated inverse radius (IIR) are DCR parameters related to the shape of the cornea during deformation, independent of IOP and associated with CCT. Other elastic DCR parameters associated with corneal stiffness are stress-strain index (SSI) and stiffness at the first applanation point (SP-A1) [21]. All the elastic parameters like SSI, SP-A1, and SP-HC are calculated with different algorithms, and their interpretation must be considered as different forms of stiffness. Decreasing the DA ratio, peak distance, and IIR are related to greater resistance to change in the shape of the cornea and stiffness increase. A list of all deformation parameters provided by the Corvis ST is presented in Table 1.

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

Corvis ST parameter	Definition
1st Applanation	The first applanation of the cornea during the air puff (in ms). The length of the applanation at this moment appears in parenthesis (in mm).
Highest Concavity	The instant that the cornea assumes its maximum concavity during the air puff (in ms). The length of the distance between the two peaks of the cornea at this moment appears in parenthesis (in mm).

2nd 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 mm).
Maximum Deformation	The amount (in mm) 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 mm)
Maximum Velocity (in)	The maximum velocity during the ingoing phase (in m/s)
Maximum Velocity	The maximum velocity during the outgoing phase (in m/s)
Curvature Radius Normal	The cornea in its natural state radius of curvature (in mm)
Curvature Radius HC	The cornea radius of curvature at the time of maximum concavity during the air puff (in mm)
Cornea Thickness	Measurement of the corneal thickness (in mm)
IOP	Measurement of the intraocular pressure (in mmHg)
bIOP	Biomechanically-corrected IOP
DA ratio Max (Deformation amplitude ratiomax 2mm)	Ratio between the deformation amplitude at the apex and the average deformation amplitude measured at 2 mm from the center
ARth (Ambrósio's relational thickness to the horizontal profile)	Describes thickness profile in the temporal-nasal direction and defined as corneal thickness thinnest to pachymetric progression
SP-A1(Stiffness parameter at A1)	Describes corneal stiffness as defined by resultant pressure (Pr) divided by deflection amplitude at A1
SP-HC	Corneal stiffness at the highest concavity point
TBI (Tomographic biomechanical index)	Index that combined tomographic and biomechanical data for keratoconus detection
BGF (Biomechanical Glaucoma factor)	Independent risk indicator for normal tension glaucoma
SSI (Stress-strain index)	Index that indicates the position of the stress-strain curves. Less dependent on corneal thickness and IOP.
CBI (Corvis biomechanical index	Overall biomechanical index for keratoconus detection
Whole eye movement (WEM)	The entire globe's movement after the cornea passes its limits during the jet air pulse resisted by the orbital structures.
Deformation Amplitude (DA)	The movement of the corneal deformation from apex to highest concavity
Deflection amplitude DeflA	The difference between The DA and the WEM

The Corvis ST calculates the IOP value based on the first applanation time pressure [24]. The biomechanical-compensated IOP (bIOP), available in the Vinciguerra Screening Report (Figure 5), is an IOP parameter corrected through a finite element method, using deformation data beyond CCT and age, including the deformation response [26]. For the development of the bIOP algorithm, the analysis considered eyes with different variations of IOP (10- 30mmHg), CCT (445-645 microns), and age (30- 90 years old). In each case, the corneal deformation response was predicted and used to estimate the Corvis IOP. The final analysis led to an algorithm relating the real IOP as a function of the Corvis IOP, CCT, and age. Subsequently, this algorithm of predictions of the corrected IOP was applied to a clinical data set involving a large number of normal eyes to investigate the association with corneal stiffness parameters, age, and CCT. Results demonstrated that the uncorrected IOP has a strong correlation with CCT and a waek correlation with age, whereas applying the algorithm to IOP measurements resulted in an IOP less correlated with both CCT and age. The Vinciguerra screen enabled the calculation of indexes, including Ambrósio Relational Thickness over the horizontal meridian (ARTh) and Corvis Biomechanical Index (CBI), which helps to discriminate between keratoconic and normal healthy cases [27].

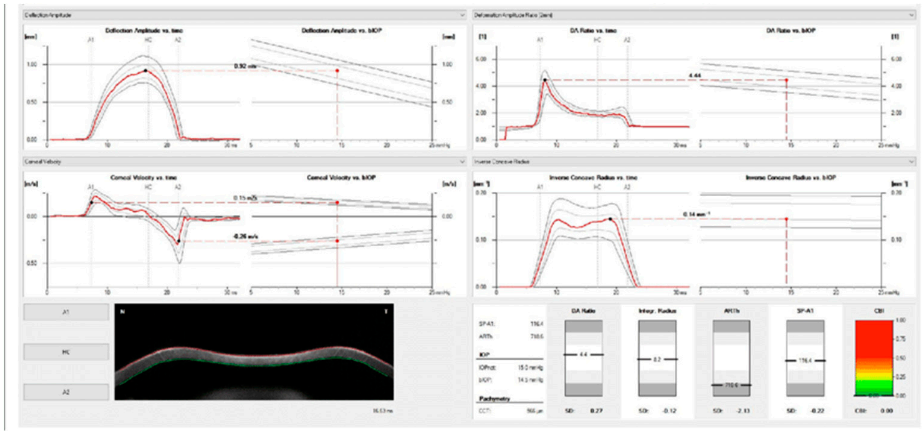


Figure 5. The Vinciguerra screening report shows the adjusted biomechanically intraocular pressure (bIOP), the Ambrósio Relational Thickness over the horizontal meridian(ARTh), and The Corvis Biomechanical Index(CBI). Personal archive.

More recently, Ambrósio and coworkers applied artificial intelligence to combine biomechanical and tomographic data and developed the Tomographic Biomechanical Index (TBI). This index demonstrated high sensitivity to diagnose mild or subclinical ectasia in very asymmetric ectasia with normal tomographic maps (VAE-NT) cases (Figure 6) [28,29].

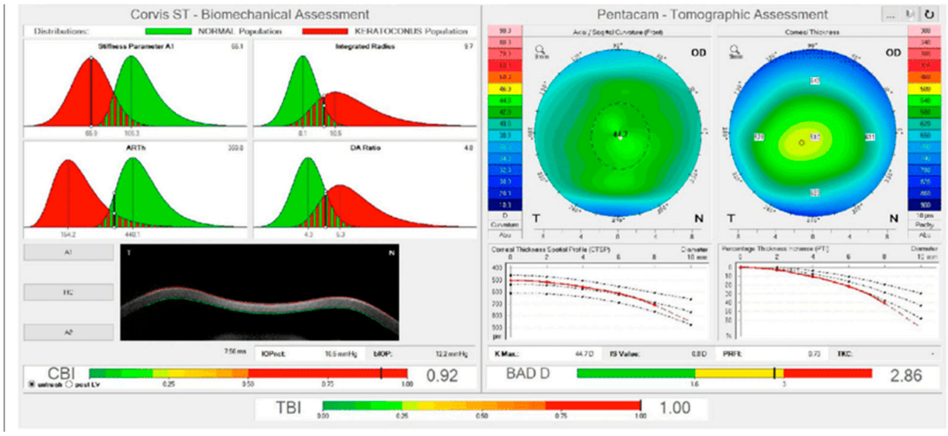


Figure 6. The ARV (Ambrosio, Roberts, and Vinciguerra) biomechanical and tomographic assessment shows the Tomographic Biomechanical Index (TBI) and the Corvis Biomechanical Index (CBI). Personal archive.

Ahmed et al. introduced a new intelligent algorithm of material stiffness to assess the biomechanical properties of the human cornea in vivo, the Stress-Strain Index (SSI). While the SSI showed no significant correlation with CCT and IOP, this index was significantly correlated with age [30]. Another study showed a possible association between Corvis ST (CSV) measurements and CH. Measurements of CST, ORA, axial length, average corneal curvature, CCT, and IOP with GAT were performed in patients with primary OAG and eyes from normal subjects. Parameters including DA (corneal softness), SP A1 (corneal stiffness), and Inverse Radius (integrated area under the curve of the inverse concave radius) were significantly correlated with CH. However, CST parameters were significant but weakly or moderately related to ORA-measured CH [31].

4. Hysteresis and Glaucoma

Although it is still debatable whether a stiffer globe contributes to glaucoma or rather it is a consequence of the disease [21], there is growing evidence supporting an association between stiffer corneas and OAG and a higher risk of glaucoma in patients with thin and stiffer corneas [6–8,32].

Congdon et al. investigated the association of CH with visual perimeter damage and glaucoma progression risk [33]. Another study suggested that CH and CRF, associated with CCT, could be considered risk factors for glaucoma [34]. Suzanna et al. have found that lower hysteresis was associated with the risk of developing OAG, even when controlling for IOP, CCT, field status, age, and medical glaucoma therapy. Each one mmHg reduction in CH was associated with a risk of 21 % converting to glaucoma in patients with ocular hypertension [35]. The CH increases with surgeries, medical treatment, and lasers [36–38]. Patients with low CH respond better to IOP reduction treatments [36].

Unlike CCT, the CH is a dynamic parameter that changes with age, surgeries, prostaglandin treatment, and IOP [21]. There is a positive relationship between CCT and CH but a negative relationship between IOP and CH [39]. Thick corneas dissipate better energy than thin corneas, and eyes with higher pressure tend to dissipate less energy. The age-related thinning of the cornea happens slowly over time, which explains why it causes a lower impact on the CH than the acute variations of IOP [34,40,41]. Also important to note that an increase in CCT caused by corneal edema is associated with a lower CH, stressing the importance of considering all parameters and not only CCT [42].

The sclera also plays a central role in the biomechanical effects of the eye, being an anatomic link between the cornea and lamina cribrosa [43]. Many studies are trying to investigate the central role of the sclera in glaucoma and its relationship with lamina cribrosa [9,44]. It is unclear if scleral stiffness protects against the IOP peaks, maintaining the integrity of the optic head disc and the LC, or could be the cause of glaucoma [11,45].

Two randomized clinical trials, the Collaborative Initial Glaucoma Treatment Study and the Advanced Glaucoma Intervention Study have suggested that progressive visual field loss in OAG is associated with high IOP variations [46,47]. These studies indicate that transient high variations on IOP may expand the scleral channel, increasing strain in lamina cribrosa and causing axon damage. The biomechanical capacity of biomechanics properties of the entire eye, including the optic disc and the connective tissue within the scleral channel to dissipate energy and preserve RGC axons, may play an essential role in explaining different responses to IOP variations [44,48]. Age and CH are related to LC displacement of the lamina cribosa, and the ability to dampen IOP fluctuations could protect eyes with glaucoma from further damage [9]. Considering that CH is the ability of the cornea and the entire eye to dampen energy, a lower CH has been associated with visual field loss in OAG and normal tension glaucoma [49,50]. The CH is indeed the most important predictor compared to CRF, CCT, Goldmann-correlated IOP, corneal-compensated IOP, and refractive error [49].

Interestingly, other studies did not show any differences in corneal mechanics between glaucoma or healthy controls and some even suggest that glaucoma patients in fact have more deformable corneas [51–53]. A plausible explication is using incorrect Corvis ST parameters to evaluate corneal stiffness. Another reason for these differences may be a selection bias of patients in prostaglandin treatment, which leads to the consequent lowering of the stiffness of the entire globe. The bind of analogs of prostaglandins to F-receptors located at the ciliary body, trabecular meshwork, episclera, sclera, and cornea likely explains the increase of the CH [54–56]. This mechanism activates the F-receptors increasing the extracellular matrix expansion and reducing the collagen [57]. The remodeling of these structures decreases the resistance of aqueous flow at the uveoscleral outflow pathway and possibly increases the capacity of the entire globe to dissipate energy [58,59]. The fact that change in corneal compensated IOP from PGA therapy persist for 6 weeks after the cessation of therapy raises the question whether the PGA-induced structural alterations are reversible [56].

The stiffness parameter at highest concavity (SP-HC) is a new parameter that evaluates scleral stiffness, although its relationship with the risk of glaucoma is still unclear. Vinciguerra et al. showed that a low SP-HC is associated with advanced visual field defects in OAG. However, a limitation of the study is that a substantial number of glaucoma patients included in the analysis were treated with analogs of prostaglandins, which are known to decrease corneal stiffness [48,60]. Other researchers also studied patients under therapy for glaucoma and did not find an association between SP-HC and the risk of glaucoma [7]. For that reason, further studies are needed to clarify the role of SP-HC in OAG, glaucoma suspects, and healthy patients, and its relationship with CH and other conditions that change ocular rigidity, like aging and race. Studies have suggested that ORA waveform parameters related to the shape of the second peak are associated with scleral stiffness. This new approach may help us evaluate and understand in vivo the association between scleral stiffness and the risk of glaucoma [61].

5. Conclusions

Understanding corneal biomechanics can help diagnose and evaluate the prognosis of glaucoma. It will also allow the optimization of clinical and surgical treatments and better manage the procedures that mechanically interact or interfere with the eye. This includes a better approach to diagnosing and managing patients with glaucoma, keratoconus risk profiling, refractive surgery planning, and optimization of different collagen crosslinking treatment protocols [62,63].

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