



Corneal hysteresis and its relevance to glaucoma

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Purpose of review

Glaucoma is a leading cause of irreversible blindness worldwide. It is estimated that roughly 60.5 million people had glaucoma in 2010 and that this number is increasing. Many patients continue to lose vision despite apparent disease control according to traditional risk factors. The purpose of this review is to discuss the recent findings with regard to corneal hysteresis, a variable that is thought to be associated with the risk and progression of glaucoma.

Recent findings

Low corneal hysteresis is associated with optic nerve and visual field damage in glaucoma and the risk of structural and functional glaucoma progression. In addition, hysteresis may enhance intraocular pressure (IOP) interpretation: low corneal hysteresis is associated with a larger magnitude of IOP reduction following various glaucoma therapies. Corneal hysteresis is dynamic and may increase in eyes after IOP-lowering interventions are implemented.

Summary

It is widely accepted that central corneal thickness is a predictive factor for the risk of glaucoma progression. Recent evidence shows that corneal hysteresis also provides valuable information for several aspects of glaucoma management. In fact, corneal hysteresis may be more strongly associated with glaucoma presence, risk of progression, and effectiveness of glaucoma treatments than central corneal thickness.

Keywords

biomechanics, corneal hysteresis, glaucoma

INTRODUCTION

The cornea can be defined by its physical dimensions, such as its thickness, or physical behavior, for example, biomechanics. Initially, the biomechanical properties of the cornea were of interest primarily to refractive surgeons trying to understand keratoconus or risk factors for post-laser-assisted in-situ keratomileusis ectasia. Early work on this topic sought to identify Young's modulus of the cornea in a variety of models. The development and commercialization of the corneal hysteresis measurement, however, made possible by the Reichert ocular response analyzer (ORA), accelerated research and clinical experience in this arena for the field of glaucoma [1,2].

The ORA is based on noncontact tonometer technology, which uses an air jet to apply force to the cornea and an electrooptical system to determine applanation [3]. This machine was initially developed to provide a Goldmann applanation tonometry (GAT)-like intraocular pressure (IOP) measurement without anesthesia or ocular contact; however, after David Luce, PhD, discovered that additional corneal information was also present in

the measurement signal, a more advanced ORA was launched in 2005 (D. Luce, personal communication).

The Corvis ST, produced by Oculus (Wetzlar, Germany), has also been developed for biomechanical assessment of the eye. It uses an air jet tonometer to measure pressure and a high-speed Scheimpflug camera to simultaneously monitor corneal movement. It can calculate various parameters; however, there is limited published literature and the device is not yet approved by the Food and Drug Administration for measuring biomechanical properties.

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Curr Opin Ophthalmol 2015, 26:000–000

DOI:10.1097/ICU.000000000000130

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KEY POINTS

- Corneal hysteresis is a biomechanical corneal behavior and not a static physical property like corneal thickness. Corneal hysteresis is lower in eyes with higher IOP and normalizes after IOP reduction.
- Corneal hysteresis has been shown to be lower in various types of glaucomatous eyes in comparison to normal eyes; these include POAG, PACG, NTG, and pseudoexfoliative glaucoma.
- Low corneal hysteresis is associated with glaucomatous visual field and optic nerve progression.
- Low-baseline corneal hysteresis is associated with a greater magnitude of IOP reduction following various glaucoma therapies including topical prostaglandin therapy and SLT.
- African-Americans have lower corneal hysteresis than Hispanics and Whites, but it is unclear whether this is explained by the association between corneal hysteresis and CCT or intergroup differences in corneal hysteresis that are independent of CCT.

THE CORNEA IS VISCOELASTIC

The cornea, like most biological materials, is 'viscoelastic', meaning that it contains characteristics of both elastic and viscous materials. A viscoelastic system can be illustrated by an automotive suspension strut. When a load is applied to the strut, the response is dependent on both the elastic properties of the component of the coil spring and the viscosity of the oil in the shock absorber.

Viscoelastic materials and systems are often characterized by hysteresis. Hysteresis is not actually an intrinsic or constant property, but a measurement characterizing how a material or system responds to the loading and unloading of an applied force [4,5].

Corneal hysteresis reflects the ability of corneal tissue to absorb and dissipate energy during a bidirectional applanation process (where energy is lost as heat during the rapid loading/unloading of the cornea).

OPERATION OF THE OCULAR RESPONSE ANALYZER

As the cornea moves inward and outward in response to the increasing and decreasing velocity of the air jet, its deformation is tracked by an electro-optical system. The inward and outward applanation events are identified by the peak amplitude of the reflected light hitting the photodetector.

Pressure values are recorded at the inward (P1) and outward (P2) applanation states. P1 and P2 are a

function of the actual IOP, the static resistance of the cornea, and the dynamic (viscous) resistance of the cornea. The average of P1 and P2 provides a Goldmann-correlated IOP value referred to as IOPg. The difference between P1 and P2 is termed corneal hysteresis, given in mmHg (Fig. 1).

CORNEAL HYSTERESIS: A NEW OCULAR PARAMETER

The corneal hysteresis measurement is repeatable in individual eyes [6[¶]] and strongly correlated in right and left eyes of the same patient [7]. Corneal hysteresis, however, differs from person to person. It is not strongly correlated with other common metrics such as corneal radius, astigmatism, spherical equivalence (SE), axial length, and IOP measured by GAT. Corneal hysteresis and central corneal thickness (CCT) are moderately correlated in normal corneas ($r=0.43$ [8], $r=0.42$ [9], $r=0.74$ [10]) and weakly to moderately correlated in corneas with disorder ($r=0.20$ [11], $r=0.43$ [10], $r=0.44$ [12], $r=0.45$ [9], $r=0.51$ [13[¶]]). Corneal hysteresis is lower than normal in patients with corneal disorders, such as Fuchs' keratoconus, and glaucoma [14].

CORNEAL BIOMECHANICS AND THE MEASUREMENT OF INTRAOCULAR PRESSURE

The IOPg measurement provided by the ORA is intended to estimate GAT. In studies involving more than 200 patients with glaucoma, both Broman *et al.* [11] and Ehrlich *et al.* [15] demonstrated that GAT and ORA IOPg show good agreement, with Ehrlich

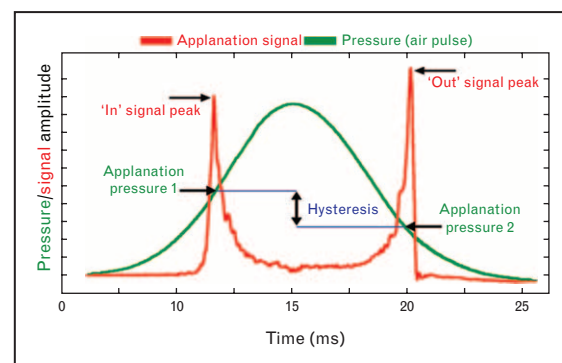


FIGURE 1. Ocular response analyzer (ORA) reading. Applanation signal as a function of air jet pressure during the bidirectional applanation process of the ORA. The time point P1 indicates the air-jet pressure when the cornea undergoes inward applanation, and P2 is the pressure at which the cornea bends back outward. Corneal hysteresis is defined as P1–P2. Reproduced by courtesy of Reichert Inc., Depew, NY, USA.

et al. finding a mean GAT–IOPg difference of 0.1 mmHg (± 0.3). Lam *et al.* [16] showed that IOPg had a mean difference of 0.33 compared with GAT in a study of 125 normal Chinese eyes.

CORNEAL HYSTERESIS IN NORMAL EYES

Shah *et al.* [9] reported an average corneal hysteresis of 10.7 in 207 normal eyes (average age = 62.1 years) and Carbonaro *et al.* [17] reported a mean corneal hysteresis of 10.24 in a large twin study. Other studies have reported similar measurements. Several investigations have also shown that, in normal eyes, corneal hysteresis does not vary significantly throughout the day [7,18–20].

CORNEAL HYSTERESIS AND STRUCTURAL MARKERS OF GLAUCOMA

Various investigators have found associations between corneal hysteresis and optic nerve head (ONH) morphology. In a prospective study of untreated patients with primary open-angle glaucoma (POAG), Prata *et al.* [21] showed that low corneal hysteresis was associated with greater mean cup depth ($r = -0.34$, $P = 0.03$) and a larger cup-to-disc ratio ($r = 0.41$, $P = 0.01$), independent of IOP and disc size. Low CCT was only associated with mean cup depth ($r = 0.35$, $P = 0.02$). Khawaja *et al.* [22^{*}] analyzed data from 5134 participants in the European Prospective Investigation of Cancer–Norfolk Eye Study and found that corneal hysteresis was positively associated with Heidelberg retina tomograph (HRT) rim area ($P < 0.001$) and negatively associated with HRT linear cup-to-disc ratio ($P < 0.001$), after adjustment for IOPg and other possible confounders. Corneal hysteresis was also positively associated with GDx variable cornea compensation retinal nerve fiber layer (RNFL) average thickness ($P = 0.006$). Finally, Bochmann *et al.* [23] showed that patients with acquired pit of the optic nerve had significantly lower corneal hysteresis than patients without such structural changes of the optic disc. These findings may be due to the pressure-independent mechanisms involved in the pathogenesis of optic nerve changes in glaucoma or they may indicate that corneal hysteresis is somehow associated with the accumulation of IOP-related optic nerve damage.

Corneal hysteresis is also associated with ONH deformation after acute IOP reduction in patients with POAG. Prata *et al.* [24] found that low corneal hysteresis was associated with a greater change in cup area ($r^2 = 0.17$, $P < 0.01$), after controlling for baseline IOP and magnitude of IOP change. This did not hold in a multivariable model incorporating all

significant factors. Wells *et al.* [25] showed that low corneal hysteresis was correlated with greater mean cup depth increase ($P = 0.032$). Eyes with higher corneal hysteresis experienced more ONH deformation with IOP elevation, a process that may allow the eye to dissipate mechanical forces and better protect the retinal nerve fibers than an eye with lower corneal hysteresis. Baseline CCT was not associated with ONH parameters in either study.

In general, there has been very limited evidence for a relationship between structural optic nerve damage and corneal hysteresis. Mansouri *et al.* [26] conducted a cross-sectional study of 299 glaucomatous eyes. After adjusting for CCT, age, and axial length, corneal hysteresis was not associated with RNFL thickness measured by either polarimetry or spectral-domain optical coherence tomography. Vu *et al.* [27^{*}] conducted a retrospective study of 131 patients with glaucoma. In a univariable model, corneal hysteresis varied as a function of mean deviation and spectral-domain optical coherence tomography RNFL thickness ($\beta = 0.2$, $P = 0.001$); after multivariable analysis, however, the relationship between corneal hysteresis and RNFL did not hold. Finally, Carbonaro *et al.* [28^{*}] conducted a study in 1754 population-based (normal) study participants from the TwinsUK cohort and did not find an association between either corneal hysteresis or CCT and quantitative measures of optic disc cupping (optic disc area, cup area, and vertical cup-to-disc ratio).

LOW CORNEAL HYSTERESIS IS ASSOCIATED WITH VARIOUS TYPES OF GLAUCOMA

Several studies have compared the biochemical characteristics of eyes with and without glaucoma. It has been repeatedly shown that patients with glaucoma have significantly lower corneal hysteresis and CCT than individuals with normal eyes [23,29].

Primary open-angle glaucoma

Corneal hysteresis is significantly lower in POAG eyes than normal eyes [10,30]. With analysis of variance, Sullivan-Mee *et al.* [31] demonstrated that corneal hysteresis was significantly lower in POAG patients than ocular hypertension, glaucoma suspect, and normal patients. In a multivariable model, corneal hysteresis continued to discriminate between the POAG and the normal group, whereas CCT did not do so.

Castro *et al.* [32] examined corneal hysteresis in POAG patients with and without diabetes mellitus. Patients with diabetes presented significantly higher

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corneal hysteresis values than patients without diabetes ($P=0.04$); CCT did not differ between the groups ($P=0.21$).

Asymmetric primary open-angle glaucoma

Anand *et al.* [33] found that corneal hysteresis was significantly lower in the worse eye of POAG patients with visual field asymmetry ($P<0.001$), independent of its effect on IOP measurement. No difference was seen in CCT or GAT values. On the contrary, Hirneiss *et al.* [34] did not find a significant difference in corneal hysteresis between eyes of patients with unilateral POAG, after correcting for IOP.

Primary angle-closure glaucoma

Narayanaswamy *et al.* [35] compared corneal hysteresis and IOPg in 443 Chinese patients with primary angle-closure glaucoma (PACG), POAG, or normal eyes in a prospective observational study. After adjusting for age, sex, and GAT–IOP, corneal hysteresis was significantly lower only in eyes with PACG in comparison with normal eyes (9.4 vs. 10.1 mmHg; $P=0.006$). Corneal hysteresis did not differ between eyes with PACG and POAG.

Normal tension glaucoma and ocular hypertension

Multiple investigators have shown that corneal hysteresis was significantly lower in patients with normal tension glaucoma (NTG) compared with normal patients [30,36,37]. Of these, both Grise-Dulac *et al.* [36] and Morita *et al.* [37] did not find a significant difference in CCT between the two groups. Ang *et al.* [38] showed that mean corneal hysteresis was higher in eyes with NTG than eyes with POAG, albeit it was a small but significant difference.

Pseudoexfoliative glaucoma

In a prospective case series of 73 eyes, Ozkok *et al.* [39] showed that corneal hysteresis was significantly lower in patients with pseudoexfoliative glaucoma (PEXG) (8.8 ± 1.4 mmHg) than in patients with POAG (9.9 ± 1.2 mmHg; $P=0.0007$); CCT did not differ between groups ($P=0.66$). Ayala [40] retrospectively determined that corneal hysteresis was lower in patients with PEXG in comparison with POAG ($P=0.042$) and normal patients ($P=0.0001$).

Congenital glaucoma

Both Kirwan *et al.* [41] and Gatzoufas *et al.* [13] found that patients with congenital glaucoma had

significantly lower corneal hysteresis than normal eyes.

CORNEAL HYSTERESIS AND GLAUCOMA PROGRESSION

In the first publication to investigate the potential utility of the corneal hysteresis measurement in glaucoma, Congdon *et al.* [42] determined that low corneal hysteresis, but not CCT, was associated with progressive visual field loss in 230 patients with 5 years of visual field follow-up history.

Medeiros *et al.* [43] conducted a prospective cohort study to determine if baseline corneal hysteresis was predictive of rate of visual field index (VFI) decline in glaucomatous patients. The study included 68 patients (114 eyes) with glaucoma, followed for an average of 4.0 years. Linear mixed models showed that corneal hysteresis and baseline IOP, but not CCT, influenced the rate of visual field progression. In a univariable model, each 1 mmHg decrease in baseline corneal hysteresis was associated with a 0.25%/year faster rate of VFI decline over time ($P<0.001$). A multivariable model examined the interaction between and combined effect of baseline corneal hysteresis and baseline IOP on rate of progression. In individuals with low-baseline corneal hysteresis, baseline IOP had a significantly larger influence on rate of visual field loss. The fastest rate of decline was expected in individuals with low corneal hysteresis and high IOP. The multivariable model also showed that CCT was associated with rate of visual field loss; corneal hysteresis, however, explained three times as much of the variation in slopes of VFI change than CCT (17.4 vs. 5.2%, respectively).

De Moraes *et al.* [44] also demonstrated in a retrospective cohort study that low corneal hysteresis is associated with faster rates of glaucoma progression. In 153 patients, followed for an average of 5.3 years, the mean rate of VFI change was -0.34 dB/year. Individuals who met a preestablished definition of progression had lower corneal hysteresis (7.5 ± 1.4 vs. 9.0 ± 1.8 mmHg, $P<0.01$) and lower CCT (525.0 vs. 542.3 μm , $P=0.04$) compared with individuals who did not. After multivariate analysis, corneal hysteresis (OR = 1.55 per mmHg lower, $P<0.01$) remained a statistically significant predictor of VFI change. The authors concluded that although both corneal biomechanical (corneal hysteresis) and physical (CCT) properties are correlated with glaucoma progression, corneal hysteresis may be more strongly associated.

Finally, Chee *et al.* [45] demonstrated that corneal hysteresis (but not CCT or IOP) was associated with overall structural glaucomatous progression

seen on a retrospective study of serial fundus photographs analyzed using flicker chronoscopy. This finding indicated that corneal hysteresis is directly associated with progressive glaucomatous optic neuropathy.

CORNEAL HYSTERESIS AND INTRAOCULAR PRESSURE REDUCTION THERAPY: INTRAOCULAR PRESSURE REDUCTION LEADS TO AN INCREASE IN CORNEAL HYSTERESIS

Studies have shown an inverse relationship between corneal hysteresis and IOP [38,46]. As IOP decreases, corneal hysteresis increases, and vice versa. Tsikripis *et al.* [47[¶]] showed in a 3-year study of 108 eyes with POAG that IOP values significantly decreased and corneal hysteresis constantly and significantly increased after local prostaglandin analogue (PGA) treatment.

Sun *et al.* [46] showed the same result at 2 weeks in 40 unilateral patients with PACG who underwent IOP reduction medically, followed by trabeculectomy. Corneal hysteresis in the treated eye still remained lower than that of the fellow, healthy eye.

In a prospective comparative case series by Pakravan *et al.* [48[¶]], corneal hysteresis was assessed before and 3 months after surgery in 23 eyes undergoing trabeculectomy, 23 eyes undergoing phacotrabeculectomy, 17 eyes undergoing Ahmed glaucoma valve implantation, and 26 nonglaucomatous eyes undergoing phacoemulsification. Corneal hysteresis significantly increased after 3 months following the glaucoma surgeries ($P < 0.001$). Postoperative corneal hysteresis increase in glaucomatous eyes was more significant when IOP was reduced by >10 mmHg.

BASELINE CORNEAL HYSTERESIS IS ASSOCIATED WITH MAGNITUDE OF INTRAOCULAR PRESSURE REDUCTION FOLLOWING THERAPY

Agarwal *et al.* [49] conducted a retrospective study with 109 eyes of 57 patients with POAG to examine factors associated with the magnitude of IOP reduction following PGA therapy. Low-baseline corneal hysteresis (but not baseline CCT) was associated with greater IOP reduction. Patients in the lowest quartile of corneal hysteresis (mean 7.0 mmHg) experienced 29.0% IOP reduction whereas those in the highest corneal hysteresis quartile (mean 11.9 mmHg) experienced 7.6% IOP reduction ($P = 0.006$). A multivariate analysis controlling for baseline IOP demonstrated that baseline corneal hysteresis independently predicted the magnitude of IOP reduction from PGA therapy ($\beta = 3.5$, $P = 0.01$).

In addition, Hirneiss *et al.* [50[¶]] showed that low corneal hysteresis was associated with greater IOP reduction following selective laser trabeculectomy (SLT). Sixty-eight patients with open angle glaucoma uncontrolled with topical medication were enrolled. In linear regression analysis, both corneal hysteresis and corneal resistance factor together with the baseline IOP improved the modeling power for the IOP lowering effect of SLT ($R^2 = 0.64$, respectively). CCT did not improve the predictive power of baseline IOP ($P = 0.67$). This finding suggests that greater IOP lowering in eyes with low corneal hysteresis cannot be explained by medication absorption, but instead must be related to either measurement artifact or truly greater pressure lowering in eyes with lower corneal hysteresis. The data thus far are consistent with the possibility that in eyes with high corneal hysteresis, IOP reduction may appear modest following therapy, perhaps because of high corneal hysteresis levels bias toward elevated IOP readings from GAT.

CORNEAL HYSTERESIS AND DEMOGRAPHICS

Haseltine *et al.* [51] retrospectively evaluated 270 patients with glaucoma and found that African-Americans have lower CCT (529.3 μm) and corneal hysteresis (8.7 mmHg) compared with Hispanics (544.7 μm , $P = 0.008$; 9.4 mmHg, $P = 0.007$) and Whites (549.9 μm , $P < 0.001$; 9.8 mmHg, $P < 0.001$).

Detry-Morel *et al.* [52] also found that corneal hysteresis was lower in African normal and POAG patients in comparison to their White counterparts ($P < 0.001$). African patients with POAG were younger than White patients with POAG, and low corneal hysteresis may be a contributing factor.

On the contrary, Leite *et al.* [53] did not find a difference in corneal hysteresis between African-American and White patients after adjusting for CCT, age, axial length, and corneal curvature. A significant relationship was found between corneal hysteresis and CCT, and investigators concluded that the increased susceptibility to disease among Blacks may be explained in part by differences in CCT. David *et al.* [54[¶]] showed that corneal hysteresis did not significantly differ by sex in normal eyes.

CONCLUSION

Corneal biomechanics can influence the accuracy of GAT and other tonometers. Although valuable in estimating glaucoma risk, CCT is a suboptimal surrogate for the mechanical bending characteristics of the cornea. Correction of IOP based on a CCT

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formula is mathematically imperfect [55]; using biomechanical properties, such as corneal hysteresis, to adjust IOP may be less biased by corneal thickness and better associated with glaucoma status.

Biomechanical properties provide valuable information about the risk of glaucoma development and progression and may predict the effectiveness of various glaucoma therapies for individual patients. Although CCT continues to be a valuable tool, clinicians should also consider incorporating hysteresis measurements into practice. In several studies comparing the two variables, corneal hysteresis was more strongly related to progression than CCT. Corneal hysteresis has been the subject of considerable research recently, and with further investigation, its clinical implications for the diagnosis and management of glaucoma will become clearer.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the Seth Sprague Educational and Charitable Foundation (Providence, NY), the Research to Prevent Blindness (New York), and the American Glaucoma Society through the Mentoring for Advancement of Physician-Scientists Award Program (San Francisco, CA).

Conflicts of interest

M.D. has no conflicts of interest. D.A.T. is an employee with Reichert Inc. N.M.R. is associated as a Consultant with Reichert and Glaukos, a Consultant and Speaker with Allergan, Inc., Alcon Laboratories, Iridex, Merge Healthcare, and Carl Zeiss Meditec, and a Speaker with Merck Pharmaceuticals.

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