REVIEW ARTICLE

Corneal Hysteresis and its relevance to the Eye: past, present and future

Author

Francis Carbonaro MD PhD FRCOphth.

Email: franciscarbonaro@gmail.com

Abstract

Corneal hysteresis is a measure of viscoelasticity of the cornea. It was first measured using the Ocular Response Analyser (ORA); Reichert Ophthalmic Instruments, Buffalo, NY) in 2005. Since the introduction of the ORA there has been an exponential growth in interest in CH, which is proving to be a very useful parameter for prediction of glaucoma risk and progression. This review sets out to describe the importance of this parameter not only as a predictor of glaucoma development and progression, but also its relevance to corneal structure with regards to structural diseases of the cornea and outcome predictions in corrective eye laser.

Introduction

Together with the tear film, the cornea is the first optical interface of the visual system and is responsible for about 80% of the refractive convergence power of the eye, determining whether a person is emmetropic, myopic or hyperopic. It also acts a barrier against trauma and microbes. The cornea is often described as the “window to the eye”.

Hysteresis is derived from the Greek, meaning ‘‘lagging behind’. Hysteresis is the physical term that describes the ability of an elastic material to return to its natural shape after being deformed by an external force.

The cornea is an extremely efficient and unified structure, which provides the eye with a clear refractive interface, tensile strength and protection. It is made up of five layers, the thickest being the stroma, which constitutes 90% of the volume of the cornea. Corneal avascularity is essential to transmit light, but this demands oxygenation mainly from the tears externally and from the aqueous humour internally.

Corneal Hysteresis

The cornea has viscoelastic properties which result in the dissipation of energy when a stress is applied to it. Hysteresis is the energy lost during the stress-strain cycle[1]. It is not an actual intrinsic property, but a measure of how a material responds to the loading and unloading of a force.

In vivo measurements of corneal biomechanical response first became available with the introduction of the ORA (Ocular Response Analyzer; Reichert Ophthalmic Instruments, Buffalo, NY) in 2005[2] (Luce DA, 2005). Prior to this, a literature search on “corneal hysteresis” would have produced only one result[3,4]. Since the introduction of the ORA there has been an exponential growth in interest in CH, which is proving to be a very useful parameter for prediction of glaucoma risk and progression. An air jet generates force lasting milliseconds on the cornea, which indents it into a slight concavity. The cornea passes through a second applanated state; as the pressure decreases, while returning to its normal convex curvature.

Energy adsorption during rapid corneal deformation delays the occurrence of the inward and outward applanation signal peaks, resulting in a difference between the applanation pressures. The difference between these inward and outward motion applanation pressures is called corneal hysteresis (CH). To distinguish between corneal biomechanical properties and intraocular pressure (IOP), the ORA uses a method that eliminates the potential interference between the 2 factors in a single measurement. Pairs of measurements are used because a measurement of a single parameter cannot determine the independent corneal properties and IOP. The 2 measurements take place within approximately 20 milliseconds, a time sufficiently short to ensure that ocular pulse effects and other variables such as eye position do not change during the measurement process (Figure 1). The author of this review compared the reliability of the ORA and Goldmann tonometer; together with that of the Dynamic Contour Tonometer (DCT, Pascal; Swiss Microtechnology AG, Port, Switzerland F software version 2.2) and found similar reliability in all three tonometers[5]. CH is measured in mmHg and the mean was found to be 10.24mmHg in a separate study by this author[6].

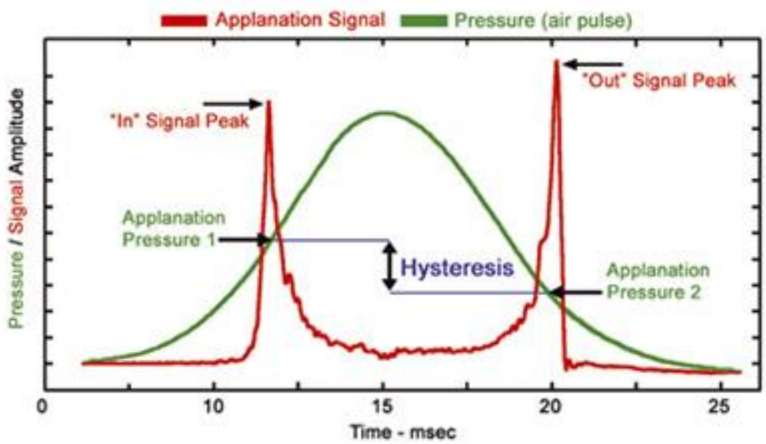

Fig 1: Diagrammatic representation of the air pulse and 2 applanation pressures recorded by the ORA. Adapted from JCRS 2005; 31:156–162.

A second instrument, the Corvis ST (Oculus, Wetzlar, Germany) was introduced in 2013[7,8],to measure "in vivo" biomechanical properties of the cornea. It also uses a non-contact tonometer system, but in addition has an ultra-fast Scheimpflug camera which gives detailed evaluation of the corneal deformation. The Corvis ST calculates corneal deformation parameters based on the dynamic inspection of the corneal response.

There are novel tools, such as the Brillouin optical microscopy, which provide information about corneal biomechanical properties. However, most of the clinical data is related to the biomechanical response to non-contact tonometry, namely the ORA and more recently the aforementioned Corvis ST.

Corneal Hysteresis and corneal disorders

Being able to better understand the cornea's biomechanical behaviour with relevance to the pre-clinical detection of disorders such as keratoconus, or for the detection of ectasia progression would be of great use to the clinician. With regards to ectatic corneal diseases, such as keratoconus and pellucid marginal degeneration, having a better knowledge of corneal biomechanics would offer a significant contribution to the diagnosis, staging, and prognosis of the disease[9]. CH has already been shown to be higher in normal than in keratoconic eyes[10].

The biomechanical investigation of corneal properties and behaviour has become significant in the setting of refractive surgery. It helps with the prediction of which patients are at higher risk of developing post-op ectasia after laser vision correction, along with enhancing the predictability and efficacy of these elective procedures; resulting in a better outcome[9,11,12].

Although corneal ectasia is relatively rare it is a very serious complication of laser corrective surgery potentially requiring a corneal graft. The elasticity and strength of the cornea are of obvious importance when considering the mechanics of laser corrective surgery. In a recent meta-analysis comparing SMILE with all the other corneal refractive surgeries in corneal biomechanical properties, it was shown that CH was higher after SMILE than LASIK, proving that the corneal biomechanical strength was preserved significantly better[13]. This is to be expected as the amount of tissue removed from the cornea is less in SMILE and in fact it has been shown that CH was significantly reduced following LASIK surgery[14,15]. One can infer from these results that it is probably due to a loss in viscoelasticity of the cornea following the thinning of the corneal stroma from the different types of laser.

Clear corneal cataract surgery has been shown to cause an increase in CCT, but diminished CH[16]. The authors believe this to be due to the postoperative corneal oedema, which leads to a change in visco-elasticity of the cornea. These findings further prove that CH is most likely an actual measure of the elasticity of the cornea, which is an important physical property of the eye.

Corneal Hysteresis and glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide[17,18]. It is a chronic progressive optic neuropathy which results in characteristic loss of visual field potentially resulting in traffic accidents, restricted mobility and falls, thus affecting quality of life[19]. Intraocular pressure – IOP remains the single modifiable risk factor for glaucoma. Glaucoma can broadly be divided into open and closed angle, depending on whether the angle from where aqueous humour drains is narrow or wide. The commonest type of glaucoma is primary open angle glaucoma, but there are many different types of glaucoma, both primary and secondary to other causes. Other known ocular risk factors reported to predict the onset or progression of glaucoma include worse visual field at baseline, increased cup-to-disc ratio and thinner central cornea[20,21]. Central corneal thickness measurement has been an integral part of the examination of patients with glaucoma or suspected glaucoma, but more recent research has suggested that CH may be a stronger indicator of glaucoma progression[22,23]. In a recent study CH was shown to account for three times as much glaucoma progression as CCT[23].

Several studies have shown that CH is significantly lower in glaucoma patients than individuals with normal eyes[24,25]. One group compared the two eyes of patients with glaucoma and found that CH was significantly lower in the worse eye of patients with visual field asymmetry, independent of its effect on IOP measurement[22]. In another group, CH continued to discriminate between the primary open angle glaucoma and the normal group, whereas central corneal thickness did not do so[26]. CH has also been shown to be lower in normal tension glaucoma patients compared with normal patients[27,28]. In this type of glaucoma, the lower viscoelasticity of the corneo-scleral structure may offer another pathophysiological explanation as to why the optic nerve and lamina cribrosa suffer damage at relatively normal pressures. Other studies showed that CH was also lower in patients with pseudoexfoliative glaucoma, whereas central corneal thickness did not differ between groups[29].

Some researchers have suggested that CH may be related to certain characteristics of the lamina cribrosa and sclera, resulting in increased susceptibility of the optic nerve head to glaucomatous damage[30,31]. Others have suggested that CH could be associated with the biomechanical properties of the optic nerve head[32]. Prata et al. found that low CH was associated with a greater change in cup area, after controlling for baseline IOP and magnitude of IOP change[33], however this did not hold true in a multivariable model. Eyes with higher CH experienced more optic nerve head deformation with IOP elevation, a process that may allow the eye to dissipate mechanical forces and better protect the retinal nerve fibres than an eye with lower CH. A metanalysis by Gapsar et al, found a significant inverse correlation between CH and glaucoma[34].

The evidence for a relationship between structural optic nerve damage and CH is weak at best. When using multivariable models, two recent studies did not show that CH was associated with retinal nerve fibre layer thickness[35,36]. The author of this review conducted a study on 1754 population-based (normal) study participants from the TwinsUK cohort and did not find an association between either CH or central corneal thickness and quantitative measures of optic disc cupping (optic disc area, cup area, and vertical cup-to-disc ratio)[37]. The same group did however show that CH is a highly heritable parameter with a heritability of 0.77[6].

Congdon et al, was one of the first to show an inverse correlation between CH and visual field loss[38], however when axial length was included in the model, the correlation was no longer of significance. Medeiros et al. conducted a prospective cohort study to determine if baseline CH was predictive of rate of visual field index decline in glaucomatous patients. The study followed a cohort of glaucoma patients over a period of four years. Linear mixed models showed that CH and baseline intraocular pressure influenced the rate of visual field progression. Interestingly, in a univariable model, each 1 mmHg decrease in baseline CH was associated with a 0.25%/year faster rate of visual field index decline over time. The fastest rate of decline was expected in individuals with low CH and high intraocular pressure. CH explained three times as much of the variation in visual field index change than central corneal thickness (17.4 vs. 5.2%, respectively)[39].

A retrospective study analysing serial fundus photographs using flicker chronoscopy, demonstrated that CH, but not central corneal thickness or intraocular pressure, was associated with overall structural glaucomatous progression[40]. This led the authors to surmise that CH is directly associated with progressive glaucomatous optic neuropathy. De Moraes et al. concluded that although both CH and central corneal thickness properties are correlated with glaucoma progression, CH may be more strongly associated[41]. This retrospective cohort study also demonstrated that low CH is associated with faster rates of glaucoma progression. After multivariate analysis, CH remained a statistically significant predictor of visual field index change.

Conclusion

Several researchers have suggested that CH may be related to the biomechanical characteristics of the sclera and lamina cribrosa[13,30] The cornea, sclera, and lamina cribrosa share the same continuous collagen and thus it is possible that similar biomechanical characteristics and CH represents the response of the entire eye wall[32], rather than of the cornea alone, thus lower CH may be related to increased susceptibility of the optic disc to glaucomatous damage, induced by IOP elevation.

It has been shown using non-human primates, that intraocular pressure elevation results in displacement of the lamina cribrosa and expansion of the scleral canal[4445]. Hysteresis is a physical property related to the ability of connective tissues to dampen pressure changes. As the deformability of the cornea and sclera are likely to be closely related, it is believed these changes may contribute to glaucomatous retinal ganglion cell loss as a result of mechanical pressure on retinal ganglion cell axons passing through the lamina pores, in eyes with lower viscoelasticity. Therefore, more rigid eyes, with lower CH, could be indicative of susceptibility of the optic nerve head to intraocular pressure-induced biomechanical changes.

It is possible that eyes with a higher CH are more able to compensate for raised intraocular pressure and therefore do not develop glaucomatous damage, whereas the lamina and peripapillary sclera of eyes with lower CH would be less able to dampen intraocular pressure changes, potentially exposing retinal ganglion cells to greater mechanical strain with elevated intraocular pressure[41].

To summarise, CH is a biomechanical behaviour and not a static physical property. It has been shown in several well powered studies to be lower in eyes with higher IOP and normalizes after IOP reduction. Low CH is associated with glaucomatous visual field and optic nerve progression.

References

1. Kotecha A. What biomechanical properties of the cornea are relevant for the clinician? *Surv Ophthalmol*. 2007;52 Suppl 2(6 SUPPL.):S109-14. doi:10.1016/j.survophthal.2007.08.004
2. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg*. 2005;31(1):156-162. doi:10.1016/j.jcrs.2004.10.044
3. Dupps WJ. Hysteresis: New mechanospeak for the ophthalmologist. *J Cataract Refract Surg*. 2007;33(9):1499-1501. doi:10.1016/j.jcrs.2007.07.008
4. Hoeltzel DA, Altman P, Buzard K, Choe K Il. Strip extensiometry for comparison of the mechanical response of bovine, rabbit, and human corneas. *J Biomech Eng*. 1992;114(2):202-215. doi:10.1115/1.2891373
5. Carbonaro F, Andrew T, MacKey DA, Spector TD, Hammond CJ. Comparison of three methods of intraocular pressure measurement and their relation to central corneal thickness. *Eye*. 2010;24(7). doi:10.1038/eye.2010.11
6. Carbonaro F, Andrew T, Mackey DA, Spector TD, Hammond CJ. The Heritability of Corneal Hysteresis and Ocular Pulse Amplitude. A Twin Study. *Ophthalmology*. 2008;115(9). doi:10.1016/j.ophtha.2008.02.011
7. Hong J, Xu J, Wei A, et al. A new tonometer-the corvis ST tonometer: Clinical comparison with noncontact and goldmann applanation tonometers. *Investig Ophthalmol Vis Sci*. 2013;54(1):659-665. doi:10.1167/iovs.12-10984
8. Reznicek L, Muth D, Kampik A, Neubauer AS, Hirneiss C. Evaluation of a novel Scheimpflug-based non-contact tonometer in healthy subjects and patients with ocular hypertension and glaucoma. *Br J Ophthalmol*. 2013;97(11):1410-1414. doi:10.1136/bjophthalmol-2013-303400
9. Esporcatte LPG, Salomão MQ, Lopes BT, et al. Biomechanical diagnostics of the cornea. *Eye Vis*. 2020;7(1). doi:10.1186/s40662-020-0174-x
10. Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. *Investig Ophthalmol Vis Sci*. 2007;48(7):3026-3031. doi:10.1167/iovs.04-0694
11. Bao F, Geraghty B, Wang Q, Elsheikh A. Consideration of corneal biomechanics in the diagnosis and management of keratoconus: is it important? *Eye Vis*. 2016;3(1). doi:10.1186/s40662-016-0048-4
12. Ambrósio, Jr R, Correia FF, Lopes B, et al. Corneal Biomechanics in Ectatic Diseases: Refractive Surgery Implications. *Open Ophthalmol J*. 2017;11(1):176-193. doi:10.2174/1874364101711010176

13. Guo H, Hosseini-Moghaddam SM, Hodge W. Corneal biomechanical properties after SMILE versus FLEX, LASIK, LASEK, or PRK: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):167. doi:10.1186/s12886-019-1165-3
14. Ortiz D, Piñero D, Shabayek MH, Arnalich-Montiel F, Alió JL. Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. *J Cataract Refract Surg*. 2007;33(8):1371-1375. doi:10.1016/j.jcrs.2007.04.021
15. Pepose JS, Feigenbaum SK, Qazi MA, Sanderson JP, Roberts CJ. Changes in Corneal Biomechanics and Intraocular Pressure Following LASIK Using Static, Dynamic, and Noncontact Tonometry. *Am J Ophthalmol*. 2007;143(1). doi:10.1016/j.ajo.2006.09.036
16. Hager A, Loge K, Füllhas MO, Schroeder B, Großherr M, Wiegand W. Changes in Corneal Hysteresis After Clear Corneal Cataract Surgery. *Am J Ophthalmol*. 2007;144(3):341-346. doi:10.1016/j.ajo.2007.05.023
17. Klein BEK, Klein R, Sponsel WE, et al. Prevalence of Glaucoma: The Beaver Dam Eye Study. *Ophthalmology*. 1992;99(10):1499-1504. doi:10.1016/S0161-6420(92)31774-9
18. Bengtsson B. The prevalence of glaucoma. *Br J Ophthalmol*. 1981;65(1):46-49. doi:10.1136/bjo.65.1.46
19. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): A randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385(9975):1295-1304. doi:10.1016/S0140-6736(14)62111-5
20. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(11):1965-1972. doi:10.1016/j.ophtha.2007.03.016
21. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: Baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):714-720. doi:10.1001/archopht.120.6.714
22. Anand A, de Moraes CG V., Teng CC, Tello C, Liebmann JM, Ritch R. Corneal hysteresis and visual field asymmetry in open angle glaucoma. *Investig Ophthalmol Vis Sci*. 2010;51(12):6514-6518. doi:10.1167/iovs.10-5580
23. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: A prospective longitudinal study. *Ophthalmology*. 2013;120(8):1533-1540. doi:10.1016/j.ophtha.2013.01.032
24. Bochmann F, Ang GS, Azuara-Blanco A. Lower corneal hysteresis in glaucoma patients with acquired pit of the optic nerve (APON). *Graefes Arch Clin Exp Ophthalmol*. 2008;246(5):735-

738. doi:10.1007/s00417-007-0756-5

25. Abitbol O, Bouden J, Doan S, Hoang-Xuan T, Gatinel D. Corneal hysteresis measured with the ocular response analyzer ® in normal and glaucomatous eyes. *Acta Ophthalmol*. 2010;88(1):116-119. doi:10.1111/j.1755-3768.2009.01554.x

26. Sullivan-Mee M, Katiyar S, Pensyl D, Halverson KD, Qualls C. Relative importance of factors affecting corneal hysteresis measurement. *Optom Vis Sci*. 2012. doi:10.1097/OPX.0b013e3182504214

27. Grise-Dulac A, Saad A, Abitbol O, 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):486-489. doi:10.1097/IJG.0b013e318220daf0

28. Morita T, Shoji N, Kamiya K, Fujimura F, Shimizu K. Corneal biomechanical properties in normal-tension glaucoma. *Acta Ophthalmol*. 2012;90(1). doi:10.1111/j.1755-3768.2011.02242.x

29. Ayala M. Corneal hysteresis in normal subjects and in patients with primary open-angle glaucoma and pseudoexfoliation glaucoma. *Ophthalmic Res*. 2011;46(4):187-191. doi:10.1159/000326896

30. Zhang C, Tatham AJ, Abe RY, et al. Corneal Hysteresis and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma. *Am J Ophthalmol*. 2016;166:29-36. doi:10.1016/j.ajo.2016.02.034

31. Zhang B, Shweikh Y, Khawaja AP, et al. Associations with Corneal Hysteresis in a Population Cohort: Results from 96 010 UK Biobank Participants. *Ophthalmology*. 2019;126(11):1500-1510. doi:10.1016/j.ophtha.2019.06.029

32. Park K, Shin J, Lee J. Relationship between corneal biomechanical properties and structural biomarkers in patients with normal-tension glaucoma: A retrospective study. *BMC Ophthalmol*. 2018;18(1). doi:10.1186/s12886-018-0673-x

33. Prata TS, Lima VC, De Moraes CGV, et al. Factors associated with topographic changes of the optic nerve head induced by acute intraocular pressure reduction in glaucoma patients. *Eye*. 2011;25(2):201-207. doi:10.1038/eye.2010.179

34. Gaspar R, Pinto LA, Sousa DC. Corneal properties and glaucoma: a review of the literature and meta-analysis. *Arq Bras Oftalmol*. 2017;80(3):202-206. doi:10.5935/0004-2749.20170050

35. 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):419-427.e1. doi:10.1016/j.ajo.2011.08.022

36. Vu DM, Silva FQ, Haseltine SJ, Ehrlich JR, Radcliffe NM. Relationship

between corneal hysteresis and optic nerve parameters measured with spectral domain optical coherence tomography. *Graefe's Arch Clin Exp Ophthalmol*. 2013;251(7):1777-1783. doi:10.1007/s00417-013-2311-x

37. Carbonaro F, Hysi PG, Fahy SJ, Nag A, Hammond CJ. Optic disc planimetry, corneal hysteresis, central corneal thickness, and intraocular pressure as risk factors for glaucoma. *Am J Ophthalmol*. 2014;157(2). doi:10.1016/j.ajo.2013.10.017

38. 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):868-875. doi:10.1016/j.ajo.2005.12.007

39. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: A prospective longitudinal study. *Ophthalmology*. 2013;120(8):1533-1540. doi:10.1016/j.ophtha.2013.01.032

40. Chee RI, Silva FQ, Ehrlich JR, Radcliffe NM. Agreement of flicker chronoscopy for structural glaucomatous progression detection and factors associated with progression. *Am J Ophthalmol*. 2013;155(6). doi:10.1016/j.ajo.2013.01.005

41. De Moraes CVG, Hill V, Tello C, Liebmann JM, Ritch R. Lower corneal hysteresis is associated with more rapid glaucomatous visual field progression. *J Glaucoma*. 2012;21(4):209-213. doi:10.1097/IJG.0b013e3182071b92

42. Wells AP, Garway-Heath DF, Poostchi A, Wong T, Chan KCY, Sachdev N. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. *Invest Ophthalmol Vis Sci*. 2008;49(8):3262-3268. doi:10.1167/iovs.07-1556

43. Liang L, Zhang R, He L-Y. Corneal hysteresis and glaucoma. *Int Ophthalmol*. 2019;39(8):1909-1916. doi:10.1007/s10792-018-1011-2

44. Sigal IA, Yang H, Roberts MD, Burgoyne CF, Crawford Downs J. IOP-induced lamina cribrosa displacement and scleral canal expansion: An analysis of factor interactions using parameterized eye-specific models. *Investig Ophthalmol Vis Sci*. 2011;52(3):1896-1907. doi:10.1167/iovs.10-5500

45. Burgoyne CF, Downs JC. Premise and prediction-how optic nerve head biomechanics underlies the susceptibility and clinical behavior of the aged optic nerve head. *J Glaucoma*. 2008;17(4):318-328. doi:10.1097/IJG.0b013e31815a343b

