

Corneal hysteresis and glaucoma

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Abstract

Purpose To review and summarize the characteristics of corneal hysteresis (CH) and its relationship with glaucoma.

Methods A PubMed search was carried out using the terms “corneal hysteresis”, “glaucoma”, and “biomechanics”. Up to March 2018, all studies published in English are included in this review.

Results The value of CH reflects the ability of corneal tissue to absorb and release energy during bidirectional flattening. It is an important biomechanical parameter of the cornea. The CH value of healthy adults is about 11 mmHg. The measurement of CH is reproducible and different. People have different CH values, which are determined by the shape of the individual’s cornea. The study found that all types of glaucoma, including primary open angle glaucoma, angle-closure glaucoma, normal tension glaucoma, congenital glaucoma, binocular asymmetrical glaucoma, CH values are lower than normal people, therefore, CH is therefore a good indicator of glaucoma diagnosis and screening. Lower CH values are associated with thinner retinal nerve fiber layer (RNFL), larger linear cup/disk ratio (LCDR) and

degree of optic disc defect. A lower CH value can also result in a lower visual field index. CH and the basic intraocular pressure play a synergistic role in the progression of glaucoma. The study found that CH can change with changes in basic intraocular pressure, means CH increases when intraocular pressure decreases, while the CH decreases conversely when intraocular pressure increases. Most clinical case studies have shown a decrease in CH after LASER refractive surgery. CH has its limitations, such as corneal damage or corneal surgery, but in general, CH is a risk factor for glaucoma progression.

Conclusion CH is used as a predictor of glaucoma risk and may help to assess the effect of corneal thickness on intraocular pressure. The clinical significance of CH in the diagnosis and efficacy of glaucoma will become more explicit. In the future, CH can also play an important role in the diagnosis and treatment of glaucoma.

Keywords Corneal hysteresis · Glaucoma · Biomechanics

Introduction

As one of the important indexes of glaucoma screening and diagnosis, intraocular pressure is limited by many factors. There is a deviation between the measurement of intraocular pressure and the actual

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intraocular pressure which affects diagnosis of the disease by the clinician. We often use physical indicators of the cornea, namely the central corneal thickness (central corneal thickness, CCT) to calibrate the measured intraocular pressure value. The corneal and scleral collagen fibres continue to connect with each other and both have similar extracellular matrix components. The biomechanical characteristics of the optic nerve lamina may be related to the biomechanical properties of the cornea. So the study of corneal biomechanical characteristics will help clinicians to define the diagnosis of glaucoma. With the development of science and technology, corneal hysteresis (CH) in the corneal biomechanical characteristics gradually attracted the attention of glaucoma researchers. Ocular response analyzer (ORA) can accurately measure corneal hysteresis and make the hysteresis of the cornea become a parameter of repeatable measurement, thus accelerating the application of corneal biomechanical indicators in the study of glaucoma [1, 2].

CH measurement

The cornea is as viscoelastic as most biological materials, which means that it has the properties of viscoelastic material. Viscoelastic materials have a certain degree of hysteresis when they are in contraction or diastole. Such hysteresis is not an inherent or constant property, but rather an ability of the viscoelastic material to remove its force when stimulated by external forces [3]. CH reflects the ability of corneal tissue to absorb and release energy during bidirectional flattening, and it is an important biomechanical parameter of the cornea.

The principle of ocular response analyzer measuring CH is similar to the non-contact tonometer, and the recorded data is more accurate, comprehensive. Moreover, it is tracked by the optoelectronic system throughout the entire process. Curve is plotted and the calculated data is analysed. When the instrument ejects high-speed air to flow cornea, the cornea will form inward with depression deformation, which the inward pressure of the cornea is marked as P1. Cornea in the process of continuing to release the pressure of depression; when the pressure is completely released cornea will return to its original shape, and the process of corneal second flattening is recorded as P2; CH is

the difference between P1 and P2 in mmHg (1 mmHg = 0.133 kPa), indicating the adhesive resistance of corneal tissue.

Researches are constantly exploring the corneal hysteresis in healthy human eyes. Al-Arfaj and Yassin [4] measured CH of 215 healthy adults, and the data were 11.16 ± 2.11 mmHg. Dana et al. [5] surveyed a large group of people and found that CH was 11.0 ± 1.51 mmHg. Many studies have received similar results.

The measurement of CH is repeatable, and different people have different CH. CH is determined by the individual's corneal shape [6]. It has no significant correlation with other common corneal index such as corneal curvature, corneal astigmatism, equivalent spherical power and axial length. CH of both eyes should be similar, and if the difference is too large, we need to consider the possibility of related diseases. The study found that CH in patients with keratoconus and glaucoma will change, often lower than healthy people [7].

CH and various types of glaucoma

At present, we often need to consult CCT to correct the measured intraocular pressure value in the diagnosis of glaucoma. Some scholars hold the view that CCT is related to glaucoma [8]. When we illustrate the relationship between CH and various types of glaucoma, the differences between CH and CCT in glaucoma should be compared.

1. Primary open-angle glaucoma (POAG): The CH of patients with POAG is significantly lower than healthy eyes. Hussnain et al. [9] found that patients with POAG had a significantly greater rate of CH decline compared to normal person. Castro et al. [10] found that patients with diabetes mellitus had a significantly higher CH than patients with open-angle glaucoma ($P = 0.04$), whereas CCT did not differ among these populations. It indicates that CH may be related to endocrine, microenvironment and other body factors [11].
2. Binocular asymmetric POAG: Some scholars have carried out a study on whether there was a difference in CH between two eyes with different glaucoma conditions. Anand et al. [12] found that

for glaucoma patients with little intraocular pressure difference, but poor visual field in both eyes, CH in lower visual field defect was found to be lower. However, the results of Hirneiss et al. [13] showed there was no significant statistically difference between two eyes in patients with only one eye diagnosed with open-angle glaucoma.

Glaucoma is a binocular disease, and the incidence of both eyes is often inconsistent [14], if there is a certain correlation between asymmetric glaucoma and CH in the prospective study. CH without any doubt can be a good screening index of glaucoma. Early detection of glaucoma may be found in patients, and we can find these patients and treat them earlier. A large number of relevant researches should be carried out to explore.

3. Primary angle-closure glaucoma (PACG): In a prospective study of angle-closure glaucoma, open-angle glaucoma and healthy eyes, Dascalu et al. [15] found that open-angle glaucoma and angle-closure glaucoma have roughly the same CH value, but they are all lower than normal people.
4. Normal intraocular pressure glaucoma and ocular hypertension: A large number of studies have shown that CH of normal-tension glaucoma was also reduced to some extent. But CCT is normal [16, 17]. CH in normal-tension glaucoma, although lower than healthy eyes, is significantly higher than open-angle glaucoma. The characteristic of CH is an important differentiating point between normal-tension glaucoma and open-angle glaucoma [17].
5. Congenital glaucoma: Doozandeh et al. [18] and Gatziofias [19] found that CH in congenital glaucoma patients was lower than healthy eyes, which may be related to the progression of the eye structure. Congenital glaucoma, also known as the water eye, will result the eyeball volume to increase, due to the embryonic eye structure dysplasia. So the biomechanical characteristics of the cornea will change accordingly, which reduce the ability to resist external forces, following by a corresponding reduction in CH.

The above results show that CH in all types of glaucoma patients is lower than healthy people [20]. CH is therefore a good indicator of glaucoma

diagnosis and screening. Intraocular pressure (IOP) fluctuated within 24 h, and the associated CH changes within 1 day; it will result in some interference to the diagnosis and screening of glaucoma. Related studies have shown no significant change in CH in 1 day, which has no correlation with 24 h IOP fluctuation [21]. Presumably, the mechanism of intraocular pressure fluctuations is due to the dynamic equilibrium of aqueous humour production and discharge; CH is the nature of the cornea and has nothing to do with aqueous humour.

Relationship between CH and other structural indexes of glaucoma

Many studies have found that there was a certain correlation between CH and optic disc morphology [22]. Park et al. [23] conducted a retrospective study and found that lower CH is significantly associated with a thinner RNFL (retinal nerve fibre layer) and a larger LCCR (linear cup/disc ratio), independent of disc size, corneal thickness, intraocular pressure, and age. Khawaja et al. [24] combined Heidelberg retinal tomography examination and found that CH was positively correlated with the optic disc defect of the optic disc and negatively correlated with the linear optic disc ratio ($P < 0.001$) and was correlated with the thickness of the nerve fibre layer ($P = 0.006$). Long-term oppression of the optic nerve can result in a structural change, and these studies suggest that changes in CH may be somewhat consistent with this point.

In 2010, Prata et al. [25] identified the relationship between CH and the depth of optic disc depression and further found that CH was associated with the morphological changes in the optic disc after rapid decompression. Low CH is associated with the change in optic disc area ($r^2 = 0.17$, $P < 0.01$). Wells et al. [26] found that low CH was associated with speed of disc depression ($P = 0.032$). Compared with eyes of low CH, eyes with high CH can better deal with changes in optic disc microcirculation and intraocular pressure, this may be related to the higher viscoelasticity of the eyes with high CH, which can better protect the retinal nerve fibres.

The correlation between CH and visual field loss

In 2006, Congdon et al. [27] first discussed the potential of CH in the treatment of glaucoma. The study found that 230 cases of glaucoma patients with 5-year progressive loss of vision have low CH. Medeiros et al. [28] conducted a prospective study to investigate whether CH baseline values in patients with glaucoma correlate with a decrease in visual field index and found that CH and intraocular pressure can affect the rate of loss of visual field. For each 1 mmHg reduction of baseline, loss of visual field would be faster (visual field index of 0.25%/year); CH and the basic intraocular pressure have a synergistic effect on the process of loss of vision. Baseline IOP in subjects with low CH had a significant effect on visual field damage. Consequently, the patients with low CH and high intraocular pressure will increase the loss of vision. Chee et al. [29] analyse a large number of fundus photographs and found that CH and glaucomatous optic nerve morphological changes have a significant correlation.

CH and IOP control

CH and the basic intraocular pressure play a synergistic role in the progression of glaucoma; this study found that CH can change with changes in basic intraocular pressure, and CH increases when intraocular pressure decreases, while the CH decreases conversely when intraocular pressure increases [30]. Meda et al. [31] hold a prospective, interventional case–control study, 70 eyes from 35 patients with POAG. One eye per patient underwent prostaglandin analogue (PGA) to control intraocular pressure for 6 weeks. The conclusion is that topical PGAs induce reversible increase in CH. On the other hand, Bolívar et al. [32] observed sixty-eight eyes of 68 patients and found that treatment with prostaglandin analogue after 6 months increases CH. However, it should be noted that although the eye CH increased after treatment, it was still lower than healthy eyes.

Pakravan et al. [33] observed trabeculectomy in 23 eyes, glaucoma phacoemulsification cataract surgery in 23 eyes, glaucoma valve implantation in 17 eyes and non-glaucoma phacoemulsification cataract surgery in 26 eyes and found that CH was significantly increased ($P < 0.001$) 3 months later after glaucoma

surgery, and especially after IOP decreased > 10 mmHg, CH increased more pronounced. However, some scholars find different results; in a retrospective study of 57 patients (109 eyes) with POAG, Agarwal et al. [34] found that a low baseline CH was associated with a significant reduction in intraocular pressure after PGA control of IOP. Statistical analysis results show that intraocular pressure was reduced by 29% when CH P25 (25 points, which means that 25% of the surveyed population has data smaller than this value) was 7 mmHg, and by 7.6% ($P = 0.06$) when CH P75 (75 points, which means that 75% of the surveyed population has data smaller than this value) was 11.9 mmHg. Multivariate analysis after controlling for baseline IOP showed that baseline CH values were able to predict a decrease in IOP in PGA regimens ($\beta = 3.5$, $P = 0.01$). In addition, Hirneiss et al. [35] consider that low CH correlates with greater antihypertensive ability of laser trabeculectomy. Linear regression analysis showed that CH, corneal resistance factors and baseline IOP were correlated with the antihypertensive ability of laser trabeculectomy.

In the above studies, both studies found that intraocular pressure of eyes with low CH baseline decreased more significantly. This cannot be explained by the degree of absorption of the drug, but rather the ability of the measuring instrument or the greater antihypertensive ability of low CH. At present, most research data show that intraocular pressure of high CH glaucoma patients can be reduced more after treatment [36]. However, high intraocular pressure (CH) during intraocular pressure test may lead to measurement deviation in Goldman tonometer. Therefore, the research must be carried out under the same conditions and repeated in order to distinguish the opposite results.

CH is a risk factor for the progression of glaucoma

Not long ago, Susanna et al. [37] conduct a prospective longitudinal study to investigate corneal hysteresis as a risk factor for predicting progression of glaucoma. They followed two hundred and eighty-seven eyes of 199 patients suspected of having glaucoma for an average of 3.9 ± 1.8 years. During follow-up, repeatable visual field defects occurred in 54 eyes (19%). Patients with glaucoma have significantly lower CH measurements at baseline compared with those who

Table 1 The main research about corneal hysteresis

Author	Publication time	The main research results	Topic of literature
HeM	2017.09	The cornea has the properties of viscoelastic material and certain degree of hysteresis when they in contraction or diastole. Such hysteresis is not an inherent or constant property, but rather an ability to remove its force when stimulated by external forces	Corneal Biomechanical Properties in High Myopia Measured by Dynamic Scheimpflug Imaging Technology
Al-ArfajK	2016.07	Normal person's CH average value is 11 mmHg	Corneal biomechanics in normal Saudi individuals
Martin R	2014.05	CH is determined by the individual's corneal shape	Corneal assessment technologies: current status
Salman AG	2016.03	CH in patients with keratoconus and glaucoma will change, often lower than healthy people	Corneal Biomechanical and Anterior Chamber Parameters Variations after 1-year of Transepithelial Corneal Collagen Cross-linking in Eyes of Children with Keratoconus
Ramesh PV	2017.08	CCT is related to glaucoma	Comparison of Central Corneal Thickness using Anterior Segment Optical Coherence Tomography Versus Ultrasound Pachymetry
Hussnain SA	2015.12	Patients with POAG had a significantly greater rate of CH decline compared to normal person.	Change in corneal hysteresis over time in normal, glaucomatous and diabetic eyes
Castro DP	2010	Patients with diabetes mellitus had a significantly higher CH than patients with open-angle glaucoma, whereas CCT did not differ among these populations. It indicates that CH may be related to endocrine, microenvironment and other body factors.	Corneal viscoelasticity differences between diabetic and non-diabetic glaucomatous patients
Anand A	2010	Glaucoma patients with little intraocular pressure difference, but poor visual field in both eyes, CH in lower visual field defect was found to be lower	Corneal hysteresis and visual field asymmetry in open-angle glaucoma
Dascalescu D	2016.10	Open-angle glaucoma and angle-closure glaucoma have roughly the same CH value, but they are all lower than normal people.	The importance of assessing corneal biomechanical properties in glaucoma patients care—a review
Chen M	2018.03	CH of normal-tension glaucoma was reduced to some extent. But it is significantly higher than open-angle glaucoma	The role of corneal hysteresis during the evaluation of patients with possible normal-tension glaucoma
Doozandeh A	2017.11	CH in congenital glaucoma patients was lower than healthy eyes, which may be related to the development of the eye structure	Corneal profile in primary congenital glaucoma
Oner V	2016.07	CH in all types of glaucoma patients is lower than healthy people	Influence of Pterygium on Corneal Biomechanical Properties
Taylor DA	2015.03	There was a certain correlation between CH and optic disc morphology	Corneal hysteresis and its relevance to glaucoma
Park K	2018.01	Lower CH is significantly associated with a thinner RNFL, and a larger LCDR, independent of disc size, corneal thickness, intraocular pressure, and age	Relationship between corneal biomechanical properties and structural biomarkers in patients with normal-tension glaucoma: a retrospective study
Khawaja AP	2014	CH was positively correlated with the optic disc defect of the optic disc and negatively correlated with the linear optic disc ratio and was correlated with the thickness of the nerve fibre layer	Corneal biomechanical properties and glaucoma-related quantitative traits in the EPIC-Norfolk Eye Study

Table 1 continued

Author	Publication time	The main research results	Topic of literature
Wells AP	2008	Low CH was associated with speed of disc depression. Compared with eyes of low CH eyes with high CH can better deal with changes in optic disc microcirculation and intraocular pressure; this may be related to the higher viscoelasticity of the eyes with high CH.	Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients
Medeiros FA	2013	CH and intraocular pressure can affect the rate of loss of visual field, for each 1 mmHg reduction of baseline, loss of visual field would be faster (visual field index of 0.25%/year); CH and the basic intraocular pressure have a synergistic effect on the process of loss of vision	Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study
Neuburger M	2010	CH can change with changes in basic intraocular pressure, CH increases when IOP decreases, while the CH decreases conversely when intraocular pressure increases	Recovery of corneal hysteresis after reduction of intraocular pressure in chronic primary angle-closure glaucoma
Meda R	2017.02	Opical PGAs induce reversible increase in CH	The impact of chronic use of prostaglandin analogues on the biomechanical properties of the cornea in patients with primary open-angle glaucoma
Pakravan	2014	CH was significantly increased 3 months later after glaucoma surgery, especially after IOP decreased > 10 mmHg	Corneal biomechanical changes following trabeculectomy, phaco-trabeculectomy, ahmed glaucoma valve implantation and phacoemulsification
Agarwal	2012	Low baseline CH was associated with a significant reduction in intraocular pressure after PGA control of IOP	The relationship between corneal hysteresis and the magnitude of intraocular pressure reduction with topical prostaglandin therapy
Hirneiß C	2013	Low CH and laser trabeculoplasty can be greater to reduce intraocular pressure. CH, corneal resistance factors and baseline IOP were correlated with the antihypertensive ability of laser trabeculoplasty	Corneal biomechanics predict the outcome of selective laser trabeculoplasty in medically uncontrolled glaucoma
Arutyunyan LL	2015.09	Intraocular pressure of high CH glaucoma patients can be reduced more after treatment	Influence of antihypertensive therapy on morphofunctional and biomechanical parameters of eyes
Bagga H	2009	No significant change in CH in 1 day, and it has no correlation with 24 h IOP fluctuation	Intraocular pressure measurements throughout the 24 h
Avetisov SE	2016	Decrease in CH and IOP after Lasik surgery	Intraocular pressure, ocular blood flow, and corneal biomechanics changes after LASIK surgery for myopia
Zhang J	2016	Decrease in CH after post-LASER refractive surgery	Corneal biomechanics after small-incision lenticule extraction versus Q-value-guided femtosecond laser-assisted in situ keratomileusis

did not (9.5 ± 1.5 mm Hg vs 10.2 ± 2.0 mm Hg; $P = .012$). Each 1 mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during follow-up. It can be seen that baseline lower CH measurements were significantly associated with increased risk of developing glaucomatous visual field defects over time.

Limitation of CH

CH is a biological characteristic of the cornea, which is closely related to corneal integrity and biological activity. After corneal injury or corneal surgery, CH will be a corresponding change. Therefore, in the clinical diagnosis and treatment process, the feasibility

of using CH to evaluate the indexes should be paid attention to; we should pay attention to the status and function of the cornea. Using ORA to measure CH is also influenced by the method of operation and the patient's own factors. CH should be repeated for long-term monitoring, in order to assess the patient's condition. At the same time, we also look forward to find better inspection methods; a better instrument can exclude the interference of external factors; the formula algorithm can be used to eliminate the influence of diabetes and other factors and more objectively describe the CH.

Changes in CH before and after post-LASER refractive surgery

Laser-assisted in situ keratomileusis (LASIK) is primary procedure for correction of refractive error. However, it can lead to corneal biomechanical changes. Zhang et al. [38] conducted a prospective study about corneal biomechanics changes after femtosecond laser-assisted in situ keratomileusis. They studied 80 patients (80 eyes) allocated to FS-LASIK. The mean preoperative CH value was 10.83, and the mean CH value on the first postoperative day was 7.95. The decreases subsequently stabilized with no further deteriorations compared to postoperative day 1, 2 week, 1 month and 3 month. Avetisov et al. [39] held a study about intraocular pressure and corneal biomechanics changes after LASIK surgery for myopia. They concluded that postoperative CH value ($P < 0.001$) and intraocular pressure were both lower than before surgery. It is hypothesized that the decrease in biomechanical properties and CH value of the cornea may be related to postoperative corneal dilatation.

Summary

Corneal biomechanical properties can affect the accuracy of Goldman and other tonometer measurements. Although the CCT value can be used to correct IOP measurements during glaucoma risk assessment, the correction formula is not perfect and is only an estimation. CH is used as a predictor of glaucoma risk and may help to assess the effect of corneal thickness

on intraocular pressure, in order to better assess glaucoma status.

Corneal biomechanical properties can provide important information for the clinical diagnosis of glaucoma and may predict the efficacy of various glaucoma treatments. In recent years, research on CH has been increasing, and its relationship with glaucoma and the impact of decreasing pressure after treatment is attracting more and more attention. The study found CH relative to CCT, and its progression with glaucoma is closer. CCT has become an important indicator of glaucoma in clinical practice. The clinical significance of CH in the diagnosis and efficacy of glaucoma will become more explicit and clear as the technology of inspection equipment improves. In the near future, CH can also play an important role in the diagnosis and treatment of glaucoma and benefit glaucoma patients (Table 1).

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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