Corneal Hysteresis
(a corneal biomechanical property)

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Leo Semes, OD

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Early attempt at characterizing the relationship between IOP and other biomechanical parameters of the eye.

Schiotz tonometry

Schiotz tonometry

Hjalmar August Schiøtz (1850-1927)

Scleral rigidity

Scleral rigidity ≠

Corneal Hysteresis

Goldmann tonometry then became the standard

1899-1991
The Cornea and Glaucoma

- CCT was the strongest independent indicator of conversion from ocular hypertension to POAG in the OHTS\(^1,2\)
- As a result, CCT has become an essential metric in glaucoma risk assessment
  - Not as an IOP correction factor
  - Low / Medium / High-risk stratification metric


The Cornea and Glaucoma

CH is related to CCT but... poorly correlated

CCT is a geometrical attribute. CH is a tissue property. CCT is NOT a surrogate for corneal biomechanical (i.e.: bending / strength) properties. The relationship between CCT and CH is weak and non-linear, especially when pathological eyes are included.

Why CCT-based IOP correction is flawed

Resistence to bending is not dependent thickness, but on material properties

What does CH measure?

- The bio-mechanical property of the cornea relating to its elasticity—specifically, the cornea’s relative ability to absorb pressure by bending when pressure is applied.

\[\text{CCT (stiffness)} \neq \text{CH}\]

Hysteresis: Not a New Concept

Sir James Alfred Ewing identified the phenomena of hysteresis and coined the term in 1890 while studying the magnetic properties of molecules in metals.

"Hysteresis, a measurement that characterizes response to application and removal of force (load/unload)\(^1\)"

- Various tissues and structures (tendon, lung, arteries, etc.)
- The importance of Corneal viscoelasticity had been discussed and explored (EX-VIVO) prior to the ORA\(^3\)

\(^2\) PubMed Search for “hysteresis” on October 3, 2014 returned 7696 results.
Corneal Hysteresis (CH) in vivo measurement of corneal/ocular biomechanics

- CH specifically refers to the output of the measurement process performed by the Ocular Response Analyzer (ORA)\(^1\)
- And reflects the ability of the corneal tissue to dissipate energy\(^1\)
- Function of viscoelastic damping\(^1\)
- Not a characterization of stiffness\(^3\) (CCT)
- Provides insight into ocular properties that were not previously considered


Ophthalmic Definition (CH)

Corneal hysteresis (CH) is defined as the difference in intraocular pressure recorded during inward and outward applanation and is therefore an indicator for the viscoelastic properties of the cornea.

Biomechanics and the Eye

- The globe is a viscoelastic tissue with complex, interconnected microstructure\(^2\)
- Geometrical attributes are not a surrogate for biomechanical properties
  - e.g.: CCT does not describe viscoelasticity stiffness(CCT) ≠ hysteresis
- The eye appears to be a mechanical structural continuum\(^2\)
- Tissue properties may provide additional diagnostic information


How is CH measured?

Commercially
- Ocular Response Analyzer (ORA).
- And the Corvis ST (Oculus)

Both use an airjet (puff) tonometer to measure pressure. Both FDA cleared

Jan 31, 2013

Ocular Response Analyzer Technology

The instrument

- Measures the biomechanical properties of the cornea in vivo
  - Corneal Hysteresis (CH)
  - Goldmann-correlated IOP (IOP\(_g\))
  - Corneal compensated IOP (IOP\(_cc\))

What happens during air applanation and rebound?
Method of operation – corneal deformation
Dynamic Bi-Directional Applanation

https://www.hightail.com/download/9XBhNWNeZv81R054TkU3Qw

What the ORA records
Applanation Signal Plot

Sample result

WS – waveform score (higher is better)
IOP (g) – Goldmann “equivalent”
IOP (cc) – Cornea Compensated (for biomechanical properties)
CH – corneal hysteresis (higher is better)
CRF – corneal resistance factor

Evidence for Corneal Hysteresis Clinical Utility in Glaucoma

CH is an Indicator of Susceptibility to glaucoma damage and Progression

Low Corneal Hysteresis (CH) has been demonstrated consistently to be strongly associated with or predictive of glaucoma progression - and more so than previous, established indicators such as IOP, CCT, and RNFL.

Clinical Evidence – Study 1
Corneal Hysteresis found to be associated with progression
• The first observational study to investigate the relationship of CH to a variety of other parameters in a glaucoma population
• 230 POAG or suspected POAG patients were included
  • POAG was defined by disc and VF changes consistent with glaucoma as judged by a fellowship-trained glaucoma specialist.
  • GAT, ORA, CCT and Axial Length measurements (IOL master) were recorded

Clinical Evidence – Study 1
Corneal Hysteresis found to be associated with progression
Progression criteria
- Among persons with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as
  - having achieved the OHTS standard of “conversion” (if previously normal),
  - or (if previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD.
- A stepwise model was not used nor were any hypothesis about interactions made.

Clinical Evidence – Study 2
CH associated with progression in NTG eyes
- A retrospective study to investigate the clinical significance of Corneal Hysteresis in patients with progressing normal tension glaucoma (NTG).
- 82 eyes of 82 NTG patients receiving topical anti-glaucoma medications were included.
- Subjects were included if they had an established diagnosis of NTG made by a glaucoma specialist based on glaucomatous optic disc damage and abnormal VF test results. Signs of glaucomatous optic disc damage were considered diffuse or localized intrascleral rim loss, excavation, and RNFL defects.
- An abnormal VF was defined as a pattern standard deviation outside of the 95% normal confidence limits or a Glaucoma Hemifield Test result outside normal limits.
- At least two consecutive abnormal VF examinations were required, with the most recent test performed within 12 months of enrollment.

Clinical Evidence – Study 3
CH associated with progression in NTG eyes
- NTG was defined by repeatable IOP ≤21 mm Hg, glaucomatous optic disc changes, and VF loss
- Patients were allocated to two groups based on the mean value of corneal hysteresis
  - Mean CH was 10.08 mmHg.
- Assessment of progression was based on the trend analysis using VF MD slope.
- Uni and multivariable analyses were constructed to identify factors associated with increased odds of progression, including CH, IOP, central corneal thickness (CCT), and RNFL thickness.

Clinical Evidence- Study 2
CH associated with progression in NTG eyes
- Of the 39 eyes with low CH, 26 (66.7%) showed progression of VF damage while 13 (33.3%) showed no progression.
- Of the 43 eyes with high CH, 15 (34.9%) showed progression of VF damage, whereas 28 (65.1%) showed no progression.

**These findings suggest that CH can be used as one of the prognostic factors for progression, independent of central corneal thickness or IOP**

Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression
- Investigated the relationship between CH and asymmetric POAG
- In a prospective cross-sectional study, ORA parameters were measured in 117 POAG patients with asymmetric visual fields.
  - 24–2 SITA-standard program.
- Asymmetry was defined as a 5-point difference between OD and OS using the (AGIS*) scoring system.

Pearson correlation coefficients were used to determine correlation of various parameters with the AGIS score. Receiver operating characteristic (ROC) curves were plotted for ORA and other glaucoma risk factors. Area under the curve (AUC) for each parameter was compared to determine the best predictor for the worse eye in POAG with asymmetric VF.
Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression

CH was a better identifier of the worse eye in asymmetric OAG.


Clinical Evidence – Study 4
CH Associated with Glaucoma Progression Rate

Retrospective study to investigate the correlation between CCT & CH and their relationship with the rate of VF progression
- Baseline characteristics included: age, ethnicity, sex, VF MD and PSD, CCT, and baseline IOP.
  - CCT was calculated as the average of 7 measurements
  - Baseline IOP was calculated by averaging the values taken during the first 4 office visits after the baseline VF. 

Because of the retrospective nature of the study and the fact that all patients were on glaucoma treatment by the time of the baseline VF test, this approach was chosen to minimize the limitations of using a single IOP measurement to reflect the baseline status of IOP control.


Clinical Evidence – Study 4
CH Associated with Glaucoma Progression Rate

- Only eyes with ≥5 reliable SITA Standard 24-2 visual field (VF) tests were included (N=153 eyes)
- Patients were typically seen at 3- to 12-month intervals and VF tests were repeated at the clinician’s discretion
- Automated pointwise linear regression analysis was used to determine VF progression

Determination of the mean follow-up IOP was calculated over the VF assessment period (from the baseline to the last VF test analyzed) excluding values obtained within 1 month after surgery, when frequent visits and unstable IOP control could bias the measurements.


Clinical Evidence – Study 4
CH Associated with Glaucoma Progression Rate

Time-adjusted Logistic Regression with VF Progression as Binary Outcome

- Univariate model: each 1 mmHg decrease in CH was associated with a 0.25%/year increase in rate of VFI decline (P<0.001)
- By comparison, each 1 mmHg higher baseline GAT IOP was associated with a 0.11%/year faster rate of VFI loss (P<0.001)
- In the multivariate model, CH was >3X more associated with rate of VF progression than CCT (17.4% vs 5.2%)
- The relationship between CH and IOP is complex:
  - For eyes with lower CH, the impact of IOP was significantly larger than in eyes with higher CH levels.

This prospective longitudinal study supports the role of CH as an important factor to be considered in the assessment of risk for glaucoma progression


Clinical Evidence – Study 5
CH as a Predictor of Progression in the DIGS Cohort

Study Overview and Design
- Previous retrospective studies suggested CH is associated with increased risk of glaucoma progression
- This investigation considered the relationship between baseline CH and rates of glaucoma progression in an observational study cohort to determine whether low CH is reflective of the disease process
- 68 glaucoma patients (114 eyes) were evaluated at 6-month intervals for 4 years Data collection included
  - CH (ORA), IOP (GAT), CCT (ultrasound pachymetry), VF (VFI)


Why is low CH associated with progression?

- The Structural Continuum: CH may represent a descriptor of ocular biomechanics and a therefore biomarker for glaucoma susceptibility likely due to a reduced ability for the eye to absorb increases in IOP.

CH and the structural continuum summarized

The Evidence suggests that CH is reflective of pressure-independent mechanisms involved in glaucoma pathogenesis and associated optic nerve damage.

Risk increases as IOP increases &
Risk is compounded with lower CH


Two illustrative cases

Case 1
62 WF

- Family Hx glaucoma-mother
- Baseline IOP 29/26 average (3)
- CCT 545 OD and 565 OS
- Refractive correction -4.00 D

Asymmetric ONH appearance
Case 2
43 WM

- Father with glaucoma
- Sleep apnea syndrome
- Baseline IOP 27/26
- Pach 556/552
As of January 1, 2015, the measurement of Corneal Hysteresis is reimbursable by Medicare in the USA

CPT code **92145**: Corneal hysteresis determination, by air impulse stimulation, unilateral or bilateral with interpretation and report.

The most common clinical indication for the CH measurement is the diagnosis and monitoring of glaucoma.

The CMS Physician Fee Schedule allowable for 92145 is $15.73.  
Technical $6.79  
Professional (i.e., interpretation).

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Thank you