Taking Glaucoma Risk Assessment to the Next Level:
The Role of CORNEAL HYSTERESIS

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Taking Glaucoma Risk Assessment to the Next Level:

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INTRODUCTION

Glaucoma is a complex, multifactorial disorder that affects the optic nerve and can lead to functional vision loss or blindness if not treated. Reduction of intraocular pressure remains the only established form of therapy to slow or halt the progression of glaucoma. The aggressiveness of therapy is often based on a global risk assessment. Risk factors for glaucoma are well established and include intraocular pressure, age, central corneal thickness, and ethnicity, among others. Corneal hysteresis—a measure of the viscoelastic biomechanical properties of the eye—is emerging as an additional important risk factor for glaucoma progression. Corneal hysteresis is easily measured in a noninvasive fashion in the office, and emerging data support its importance in the process of global risk assessment for glaucoma. In 2015, hysteresis was given a reimbursable CPT code.

Recently, a group of glaucoma specialists gathered in San Francisco to review and interpret the data supporting the role of corneal hysteresis in glaucoma risk assessment. This gathering was supported by Reichert—manufacturer of the Ocular Response Analyzer, the only device that measures corneal hysteresis.

This monograph is intended to share the key take-home messages derived from that meeting. These include a basic understanding of corneal hysteresis and its relationship to ocular biomechanics, familiarity with the data supporting the importance of hysteresis in glaucoma risk assessment, and guidance on incorporating hysteresis in the clinical management of glaucoma patients.

What is Corneal Hysteresis? Historical Perspectives of Central Corneal Thickness and Corneal Hysteresis as Risk Factors for Glaucoma

Robert N. Weinreb: Corneal hysteresis (CH) has been of great interest in glaucoma for more than ten years. There now are several hundred publications, many of which validate and support its use in glaucoma care. In clinical research studies, there is compelling evidence that CH is a powerful tool for predicting the development of glaucoma and its progression as well. Today’s discussion discusses the use of CH in clinical glaucoma care.

Dr. Brandt: The emergence of CH as a risk factor for glaucoma is reminiscent of the path that central corneal thickness (CCT) followed in becoming a validated risk factor for glaucoma. The influence of CCT in IOP measurement had been recognized since the 1950s. Its widespread acceptance and use in risk modeling did not occur until the Ocular Hypertension Treatment Study (OHTS) provided strong evidence of its importance and practical guidance on how to incorporate it into the risk assessment process. Many of us were surprised that CCT was such a strong risk factor in OHTS, and it was helpful in establishing CCT’s credibility that the European Glaucoma Prevention Study (EGPS) confirmed this finding.

Dr. Weinreb: We began to evaluate the role of CCT in glaucoma in the Diagnostic Innovations in Glaucoma Study (DIGS), which began in 1986. One early analysis from DIGS involved 98 patients with suspected preperimetric glaucoma—their optic nerves looked suspicious but their visual fields were full. After a follow-up period of about eight years, 60% had converted to glaucoma. But when the subjects were stratified into two groups based on thin or thick corneas, the rate of conversion to glaucoma was 46% in eyes with thin corneas compared to 11% in eyes with thicker corneas.¹

Dr. Brandt: The question that arose then was this: is CCT truly a risk factor or is it merely a source of error in intraocular pressure (IOP) assessment? One possibility is that eyes with thin CCT have higher IOP than we measure using Goldmann tonometry; and that is why these eyes fare less well. An alternate possibility is that CCT is an indicator of more global ocular biomechanics. Several lines of research suggest that CCT is an important risk factor indepen-
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Dr. Radcliffe: CCT as a biomechanical indicator has limitations, and chief among them is that most models relating CCT and IOP assumed that the cornea is a purely elastic structure. In fact, the cornea is viscoelastic. To understand this difference, consider the shock absorbers in your car. On a bumpy road, they dampen the bumps and smooth out the ride. If you had only springs, which are elastic—and not shock absorbers, which are viscoelastic—you would feel every bump much more significantly. The shock absorbers dissipate energy. In terms of the eye, the cornea’s response to deformation (for instance, applanation) is rate dependent: when moved rapidly like a car wheel hitting a bump, it dissipates some of the energy absorbed during the deformation. This differential tissue response to the load/unload of stress is called hysteresis, a term that was coined in the 19th century. CH is not a measure of the stiffness of the cornea, but rather a measure of how corneal tissue absorbs and dissipates energy during deformation and return. It can be considered a measure of tissue function rather than a geometrical attribute. There are correlates to CH in other bodily systems. The ascending aorta exhibits viscoelastic behavior with every heartbeat, expanding to accept blood from the heart and absorbing energy in the process, then rebounding and dissipating that energy as that blood flows more distally.

Dr. Brandt: Because both CCT and CH are biomechanical parameters of the cornea, they tend to be weakly correlated. Data suggest, however, that CH may be a better predictor of glaucoma than CCT. These data will be reviewed in the next section. So in summary, CH has followed a similar path as CCT in becoming recognized as a risk factor for glaucoma. CH may be more closely related to glaucoma risk than CCT. This likely relates to its functional nature (how the eye responds to dynamic changes in IOP compared to CCT’s more structural nature (how thick it is).

Corneal Hysteresis as an Indicator for Glaucoma Progression Risk

Dr. Radcliffe: It is useful to review the key studies supporting the clinical utility of CH as a risk factor for glaucoma and its progression.

Among the first studies to demonstrate this was a retrospective report of 230 glaucoma patients and suspects with the goal of identifying associations with progression. The study utilized the OHTS criteria for the determination of both the presence of glaucoma and the progression of glaucoma. Among the associations for progression were patient age, lack of treatment, and CH. Of note, neither IOP nor CCT were found to be significant associations of progression. This study concluded that CH was the only ocular parameter associated with progression.

CH has also been associated with the risk of progression in normal-tension glaucoma (NTG). A retrospective study of 82 eyes being treated for NTG included an assessment of CH. The average value of CH in the group was 10.1 mmHg. The study sample was then divided into two groups: those with CH higher than the mean and those with CH lower than the mean. The risk of progression of NTG was 67% in the 39 eyes with low CH, and only 35% in the 43 eyes with high CH. In a multivariate model of visual field progression, CH was highly predictive while CCT was not significantly predictive at all. This study demonstrated that CH can be utilized independently of IOP and CCT as a prognostic factor for glaucoma progression.

Asymmetry of primary open-angle glaucoma (POAG) may also be explained, at least in part, by CH. One hundred seventeen POAG patients with asymmetric glaucoma (with...
asymmetry defined as an inter-eye difference in AGIS visual field score of >5 points) were observed in a prospective cross-over study to evaluate factors associated with asymmetry of glaucoma severity. Among the potential factors evaluated were Goldmann IOP, CCT, the number of IOP-lowering medications used, and CH. Of these, only CH was significantly different between the fellow eyes, being lower in worse eyes (mean 8.2 versus 8.9 mmHg, p<0.001). This study demonstrated that CH offered the best discriminative power for discerning the worse eye in asymmetric POAG.

The rate of visual field progression may also be related to CH. A recent retrospective study of 152 glaucomatous eyes evaluated the correlation between CH and CCT and their relationship with the rate of visual field change over time. This study found that rapidly progressing eyes had lower mean CCT and CH than stable or slowly progressing eyes, and that CH and CCT were modestly correlated (r=0.33). In a multivariate model of visual field progression, only age, peak IOP, and CH were predictive; CCT was not. This study demonstrates that glaucomatous eyes with low CH are at higher risk for progression and progress faster.

The Diagnostic Innovations in Glaucoma Study has been ongoing since the mid-1980s. Its goals are to develop better methods for detecting glaucoma progression, to characterize the rate of progression, and to identify risk factors for progression of glaucoma. Enrolled subjects were either healthy glaucoma suspects or established glaucoma patients. They underwent full eye examinations every six months. This database of patients provides a wealth of

Case 1. Progression Despite Low IOP

Dr. Radcliffe: One of my patients is a 54-year-old Hispanic lady with recently-diagnosed POAG. Her IOP on treatment is 10 mmHg. Her CCTs are in the 540s, her vertical cup-disc ratio is 0.8, and her optic nerves and visual fields are shown in the figure.

Most of us would be satisfied that, with an IOP lowered to 10 mmHg, we have this patient’s glaucoma adequately controlled. However, over the next several years, her visual field continues to progress despite maintaining an IOP in the 9-11 mmHg range. We measured her CH before we initiated treatment at the time of her diagnosis, and it was 6.1 mmHg. That’s well below the normal range. That CH value indicates that she is at high risk for progression, and that is exactly what happened.

Figure. Optic nerve photographs (top) and visual fields (middle) from the patient described in Case 1. Visual field progression was noted over time (bottom).
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information about glaucoma, progression, and risk factors. A recent analysis of a subset of 68 glaucoma patients followed for four years revealed that Goldmann IOP was significantly influenced by CCT but not by CH, and that CH and CCT were modestly correlated (r=0.48). In a multivariate model of glaucoma progression, CH was three times more strongly associated with the rate of progression than CCT. This study was among the first prospective studies to confirm the relationship between CH and the risk of glaucoma progression.

Dr. Brandt: There are convincing data that CH is related to glaucoma risk and to progression risk. CH is lower in patients with glaucoma than in healthy subjects, and it is lower in glaucoma patients who progress than in glaucoma patients who remain stable. Is this association due solely to CH’s effect on IOP measurement, or does CH also tell us something about the biomechanics of the eye? Can CH be a biomarker for optic nerve damage in glaucoma?

Dr. Radcliffe: There are some interesting studies that give in-

Is Corneal Hysteresis a Biomarker for Susceptibility to Glaucoma Damage?

The Reichert Ocular Response Analyzer

How It Works

Dr. Radcliffe: Corneal hysteresis is easily and noninvasively measured in the office. CH can only be measured using the Reichert Ocular Response Analyzer (ORA). This device functions very much like a noncontact tonometer. A metered puff of air is delivered to the cornea, flattening it into an applanation configuration, much like Goldmann tonometry (see figure). The air puff deforms the cornea past the applanation point, making it briefly concave. As the pressure of the air puff diminishes, the cornea returns to its normal configuration, passing through the applanation position a second time on its rebound. Interestingly, the pressure of the air puff at the point of the first and second applanations is different (being lower on rebound than it was upon initial applanation), as the cornea’s viscoelastic nature dissipates some of the energy. The difference in IOP at each of these two applanation points is defined as the corneal hysteresis. If the cornea were perfectly elastic and did not dampen some of the energy, the two applanation points would occur at the same IOP level.

BELOW: Schematic diagrams of ORA measurement procedure.
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Corneal Compensated IOP (IOPcc) Accuracy and Safety Advantages

**Dr. Radcliffe:** In addition to CH, the ORA provides two other parameters, both estimates of IOP. One is a Goldman equivalent IOP (IOPg), which is designed to match Goldmann values. The second is a cornea compensated IOP (IOPcc), which is an estimate of true IOP taking the biomechanics of the cornea into account.

**Dr. Medeiros:** Goldmann tonometry remains the clinical standard for IOP measurement in most parts of the world. There are some limitations to Goldmann tonometry. Goldmann IOP is not objective—deciding when the mires are aligned is subjective. An objective tonometer that returns a value digitally without a subjective interpretation could make IOP measurement more objective. Likewise, a device that is fast and technician-friendly would be of value. If IOPg reasonably estimated Goldmann tonometry, the ORA could have value in clinical glaucoma management.

**Dr. Radcliffe:** There is definitely less random variability with IOP measured by the ORA compared to Goldmann tonometry. My experience has been that IOPg provides cleaner data than Goldmann IOP in mathematical models that incorporate IOP. Frankly, if I had an ORA in every one of my exam rooms, I would be comfortable using IOPg in place of Goldmann IOP in clinical practice.

**Dr. Realini:** The IOPcc measurement is interesting to me. Certainly the biomechanical properties of the cornea affect our IOP measurements regardless of the tonometer we use. None measures true intraocular pressure, and the difference between our measurement and true IOP is likely highly dependent upon corneal biomechanics. Before we had CH, we used CCT as a surrogate measure of corneal biomechanics. But CCT is not a measure of the functional biomechanical properties of the cornea—it is a structural measurement of corneal thickness. Not all thick corneas are stiff, and not all thin corneas are flipp. This is why I have never been a believer in the practice of correcting IOP based on CCT. They are— as Dr. Brandt pointed out—indeed independent risk factors. Correcting Goldmann IOP based on CCT is akin to adding 5 mmHg to IOP for a positive family history—why would you combine two independent risk factors into one? However, CH is different from CCT in that it is a measure of the functional biomechanical structure of the cornea—it tells us how that individual cornea responds to being applanated. It makes far more sense to correct an IOP measurement based on CH than on CCT.

**Dr. Fingeret:** But the data also show that CH and IOP are independent risk factors, so doesn’t the same logic apply? Wouldn’t this approach also be combining two independent risk factors into one?

**Dr. Realini:** That’s a valid point. Once we correct IOP based on CH, we have incorporated the component of CH’s risk associated with IOP measurement error. Is there also a structural component to CH as a risk factor? Does it both affect our IOP measurement and tell us something about the susceptibility of the optic nerve head and lamina cribrosa to glaucoma damage? It would be interesting to know if CH remains significant in a model of glaucoma progression that includes IOPcc. This would tell us whether CH still brings relevant information to the table after a CH-based IOP correction.

**Dr. Brandt:** The IOPcc measurement may also be useful in eyes that have previously undergone refractive procedures. LASIK both flattens the cornea and dramatically changes its biomechanical properties. An IOP measurement that takes the altered biomechanics into consideration would be of value. In coming years more and more patients will have had corneal refractive procedures decades earlier and will forget to tell you or your technician about them.

**Safety Advantages**

**Dr. Flanagan:** The ability to obtain a Goldmann equivalent IOP using noncontact tonometry offers a variety of important safety issues. Obviously, the risk of corneal abrasion—although very small to begin with—is eliminated. Also, there is no need for anesthesia or fluorescein dye, so we also eliminate possible adverse reactions to these products as well. But perhaps the biggest advantage is the elimination of the risk of infection.

**Dr. Coleman:** There have been a number of significant outbreaks of epidemic keratoconjunctivitis in eye clinics. Among the methods by which microbes are transmitted from one patient to the next is the incomplete sterilization of the tonometer tip between patients. There are a variety of ways to clean the Goldmann tonometer tip. They can be soaked in bleach or alcohol for five to 20 minutes. Also, it requires that every room have multiple tips, which is costly. A more extreme approach is to sterilize them the same way we do our surgical instruments, but this can lead to cracking of the tip over time. These methods are most likely to be effective, but they come with inconveniences. There are more pragmatic approaches. They can be wiped off with an alcohol pad, or washed by hand with soap and water, or soaked in hydrogen peroxide, although the infection control experts are uncertain that these are adequate.

**Dr. Liebmann:** There are disposable Goldmann tonometer tips, but they cost approximately $1.25 apiece, which adds considerable expense to every eye examination.

**Dr. Flanagan:** In the United Kingdom, they have the added concern about prion-based diseases such as Creutzfeldt-Jakob disease. The use of reusable Goldmann tonometer tips ended in the UK more than 10 years ago—everything is now disposable.
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**Case 2: Progression with Thick Cornea**

**Dr. Medeiros:** This patient from my practice also illustrates how CH might be useful in identifying the patients at risk for progression. This 70-year-old man with POAG has a CCT of nearly 600, which would suggest a relatively low risk of progression. Yet he is clearly progressing by both visual field and OCT criteria (figure). His CH, however, is 8.6, which is not as low as the CH in Dr. Radcliffe’s patient, but is still moderately low. This is an eye in which CH revealed a propensity for progression that was in contrast to the CCT.

Dr. Brandt: We conducted a study in which we measured axial length in glaucomatous eyes before and after trabeculectomy. We also measured CCT and CH preoperatively. We found that CH was significantly associated with the shortening of axial length, while CCT was not. This study was confirmed by other investigators. These data suggest that the biomechanical responses of an eye to significant IOP reduction can be predicted in part by the CH measurement.

Dr. Radcliffe: There was also a study in which patients with and without glaucoma underwent optic nerve imaging before and after an induced IOP rise. In this study, the higher the CH, the more the lamina cribrosa was deformed backward in response to the pressure. In other words, eyes with higher CH were able to adapt to the IOP change and absorb it, while eyes with lower CH had less of a tissue adaptation to deal with the elevated IOP.

Dr. Brandt: Think of it as optic nerve head compliance. Eyes with higher CH were better able to buffer the IOP rise. As more indirect evidence of this, a study demonstrated that CH but not CCT was correlated with the structural parameters of glaucoma damage measured by confocal scanning laser ophthalm-
moscopy, with lower CH being associated with worse nerve damage.\textsuperscript{12}

**Dr. Realini:** The question is: are these eyes progressing because they have low CH, or do they have low CH because they have glaucoma? Does glaucoma lead to a reduction in CH? In cross-sectional studies, this cannot be determined. A longitudinal study will be necessary to see if CH diminishes as patients progress from early glaucoma to moderate or advanced glaucoma.

**Dr. Myers:** This is an important point. In response to stress, bone creates more bone. In response to chronic hypertension, arteries produce more collagen and become stiffer and less compliant. Does a glaucomatous eye undergo connective tissue responses that would change its compliance and thus its hysteresis?

**Dr. Realini:** Either way, low CH is a sign of high risk for progression.

**Dr. Radcliffe:** The evidence supports a role for measuring CH in our patients with POAG. There is now a CPT code for the measurement and interpretation of CH. It is 92145. This is for one or both eyes. The frequency—one per year? once per lifetime?—has not been established, nor have the diagnostic codes that will support the test been established.

**Dr. Gross:** I suspect that even though Medicare has assigned the code and seems to be paying for it, that, like with many new codes, most private insurance providers will initially not pay for the service. But we need to bill for it anyway in order to demonstrate a volume of use that will play a role in making it payable eventually by private payers.

**Dr. Brandt:** As we move toward greater and greater office efficiency, we spend more time thinking about workflow. How can we best incorporate CH assessment into our clinical workflow? There are several issues. Who are the optimal patients for CH assessment—and who are not? How often does it need to be done? At what point in the workflow should it be done?

**Dr. Myers:** I think patient selection for measuring CH will be similar to that for CCT when it first emerged. We would want to know CH in patients who are glaucoma suspects to assess their risk of developing glaucoma. We would want it in treated patients who are progressing despite what appears to be adequate IOP control. We might want it in those odd patients who have markedly high IOP but no evidence of damage in order to better understand how the eye is tolerating the IOP.

**Dr. Coleman:** We should consider getting it in all of our established glaucoma patients if helps us decide which of them is at high risk for progression.

**Dr. Brandt:** I would add that patients who have undergone refractive surgery such as LASIK might be good candidates. The CH value may not be useful—it would be a measure of their altered cornea and not of their native eye. But the ORA IOP measurement (IOPcc) might be useful. We know that these
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procedures alter the accuracy of Goldmann tonometry by altering corneal biomechanics in a way that the Goldmann tonometer cannot compensate for. IOPcc may be a better measure of IOP than Goldmann IOP in these eyes.13

Dr. Radcliffe: Eyes with IOP over 30 mmHg may not be good candidates for CH measurement. In these eyes, the ORA will underestimate CH in order to avoid hitting the eye with an air puff strong enough to measure it accurately. This is not a significant limitation, however, because once the IOP is above 30, the need for IOP reduction is usually evident.

Dr. Realini: In those ocular hypertensives with high IOP and normal nerves, it might still be useful. If CH is underestimated in high-IOP eyes, an elevated CH in such an eye would be particularly compelling given that the true CH might be even higher.

Dr. Weinreb: In our 24-hour study, short-term variability of CH was not seen.14 In studies by our group and others, CH does tend to diminish with age, by approximately 0.2 mmHg per decade.15 But other studies suggest that CH may be a more dynamic measurement than CCT, especially when pathology is present.

Dr. Brandt: As for when to do it, I would ideally like to have it available when I see the patient. It should be available when I see the IOP, so I can use these two pieces of data together. It is not feasible to put an ORA into every exam room. One way to incorporate CH assessment into practice is to have a work-up area that all patients come through for their vision, pressures, and CH, then come to the exam room to be seen by the doctor.

Dr. Realini: That’s a good point. Pachymeters are easily portable. But the ORA cannot come to the patient—the patient has to come to the ORA.

Dr. Brandt: Many of our devices are moving toward DICOM compatibility, so that they interface with our electronic health record. Therefore EHR software should have fields for corneal hysteresis. It is not clear yet whether EHR companies are incorporating this parameter.

Dr. Liebmann: One potential solution is to integrate this test in combination with our other standard glaucoma tests. Get CH after your visual fields, or after your OCT. Make it an automatic part of the process until you’ve gotten CH on all your patients.

Dr. Coleman: Once we have

Normal Values for CH

Dr. Radcliffe: In studies including healthy subjects from the United States, United Kingdom, South America, Europe and Asia, normal values for CH fall in the range of 10.1 to 10.9 mmHg.

Dr. Weinreb: We conducted a study several years ago in which 15 healthy subjects underwent 24-hour assessment of IOP, CCT and CH in our sleep laboratory at the Hamilton Glaucoma Center, University California San Diego. Both IOP and CCT demonstrated significant 24-hour variability, with highest values recorded during the nocturnal period. In contrast, CH was quite stable throughout the 24-hour period, with no significant variation at all.14 Children tend to have high hysteresis (around 12 mmHg),16,17 and our group and others have also demonstrated that CH does decrease slightly with age.18,19 The significance of age-dependent decreases in CH is unknown.
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Points of Consensus on Corneal Hysteresis

- CH is associated with the risk of glaucoma progression.
- CH measurement would be valuable in assessing the risk of glaucoma suspects progressing to glaucoma, and in assessing the risk of progression of established glaucoma.
- At present, CH should be considered a semi-quantitative risk factor: low (CH <8 mmHg), medium (CH 8-12 mmHg) or high (CH >12 mmHg).
- Future research will enhance our understanding of how to best utilize CH in glaucoma risk assessment.

incorporated the testing process into our workflow, how do we incorporate the data into our patient management? What is the normal value for CH? What is the normal range? At what CH level should I consider my patient to be at increased risk of progression?

Dr. Radcliffe: The mean value in most normal populations is between 10 and 11 mmHg. The normal range is typically be-
tween 8 and 14 mmHg.

Dr. Brandt: I don’t think we have adequate data yet to es-

tablish the risk of progression associated with specific values of CH. My approach will be to use the same approach I do with CCT. I think of the values as low, medium or high, and I think of the associated risk in the same way. A low CH with no other risk factors is no more compelling than a low CCT with no other risk factors. But in a patient you are already worried about—say, they have already gone blind in one eye or they have a strong family history of glaucoma blindness—in these patients, a low CH might be the straw that breaks the camel’s back and prompts you to be more aggressive to prevent progression, while a normal or high CH might make you decide to maintain your current therapy and watch closely.

References


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A sea change in glaucoma care.

The tide is changing. A superior test for the evaluation of glaucoma risk is rising to the surface.

Corneal Hysteresis is more associated with visual field progression than CCT or IOP.

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