Lower Corneal Hysteresis is Associated With More Rapid Glaucomatous Visual Field Progression

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Aim: We investigated the correlation between central corneal thickness (CCT) and corneal hysteresis (CH) and their relationship with the rate of visual field (VF) change.

Methods: Glaucoma patients who underwent complete ophthalmic examination and tonometry using both the Goldmann applanation tonometer and the Ocular Response Analyzer were prospectively enrolled. Only eyes with ≥ 5 SITA Standard 24-2 VF tests were included. Automated pointwise linear regression analysis was used to determine VF progression. One hundred fifty-three eyes (153 patients; mean age, 61.3 ± 14.0 y; mean number of VF, 8.5 ± 3.4; mean follow-up time, 5.3 ± 2.0 y) met the enrollment criteria.

Results: The mean global rate of VF change was -0.34 ± 0.7 dB/y. Twenty-five eyes (16%) reached a progression endpoint. Progressing eyes had lower CCT (525.0 ± 34.2 vs 542.3 ± 38.5 μm, $P = 0.04$) and lower CH (7.5 ± 1.4 vs 9.0 ± 1.8 mm Hg, $P < 0.01$) compared with nonprogressing eyes. CH and CCT correlated significantly ($r = 0.33$, $P < 0.01$). By multivariate analysis, peak intraocular pressure [odds ratio (OR) = 1.13 per mm Hg higher, $P < 0.01$], age (OR = 1.57 per decade older, $P = 0.03$), and CH (OR = 1.55 per mm Hg lower, $P < 0.01$) remained statistically significant.

Conclusions: Corneal biomechanical and physical properties, such as CH and CCT, are highly correlated and associated with VF progression. As CH may describe corneal properties more completely than thickness alone, it may be a parameter that is better associated with progression.

Key Words: corneal hysteresis, glaucoma, visual field, progression

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The major glaucoma clinical trials have provided valuable information on the role of intraocular pressure (IOP) reduction in preventing or delaying glaucoma onset or progression and have identified other risk factors, such as baseline optic disc and visual field status, older age, disc hemorrhage, low blood pressure, and lower central corneal thickness (CCT),[1–7] to be associated with greater risk of disease progression.

Why a smaller CCT increases the risk of progression remains to be explained. In the Ocular Hypertension Treatment Study (OHTS), eyes with thicker corneas had smaller measured IOP responses to topical medication than those with normal or thin corneas, and for every 40 μm lower CCT, the risk of developing a visual field (VF) defect increased by 71%, independent of IOP.[8,9] In the Early Manifest Glaucoma Trial, patients with newly diagnosed and established glaucoma, every 40 μm lower CCT independently increased the risk of future progressive VF loss by 25%.[10] These findings could be due to a tonometric artefact[8] or because corneal biomechanical properties may reflect altered biomechanics of the parapapillary region leading to an increased susceptibility of the optic nerve.[11,12]

Other variables, such as corneal curvature[13] and stiffness,[14] also influence Goldmann applanation tonometry (GAT). The Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments Inc., Depew, NY), a noncontact tonometer capable of measuring corneal viscoelasticity [corneal hysteresis (CH)] and other biomechanical features, provides IOP measurements that take this parameter into account.[15,16] We examined the relationship between CH and CCT to determine which of these parameters better correlates with VF progression in patients with established glaucoma.

MATERIALS AND METHODS

This retrospective study was approved by the New York Eye and Ear Infirmary Institutional Review Board and followed the tenets of the Declaration of Helsinki. Patients returning for routine office visits in a glaucoma referral practice underwent tonometric measurements with the ORA as part of their examination. VF, ORA, and clinical data were collected for patients examined between March and September 2009. Patients were typically seen at 3 to 12 months intervals and VF tests repeated at the clinicians' discretion, usually within the same interval. From this population, we included patients with established glaucoma with at least 5 SITA-Standard 24-2 fields (SITA-SAP, HFA II, Carl Zeiss Meditec, Inc., Dublin, CA) in either eye before the date of the ORA measurement. Glaucoma was defined by the presence of glaucomatous optic neuropathy associated with reproducible VF abnormalities on SITA-SAP on the date of baseline VF tests. Glaucomatous optic neuropathy was defined as a vertical cup-to-disc ratio > 0.6, asymmetry of the cup-to-disc ratio ≥ 0.2 between eyes, presence of localized retinal nerve fiber layer, and/or neuroretinal rim defects in the absence of any other retinal bnormalities that could explain such findings.

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The minimum criteria for a VF abnormality were a glaucoma hemifield test outside normal limits or a pattern standard deviation result < 5% on 2 consecutive reliable examinations. All baseline VF tests had reliability indices of < 25% fixation losses, false-positive responses, or false-negative responses. All eyes had visual acuities ≥ 20/40 and refractive errors < 8.00 diopters spherical equivalent.

We excluded patients with an insufficient number of VF for progression analysis or other ocular or neurological conditions likely to affect the VF. Eyes that underwent any type of intraocular surgery within 90 days of the ORA measurement were also excluded.[17] If both the eyes of the same patient were eligible, the eye with the largest number of VF tests and best ORA waveform score (WS, as described further) was included.

ORA

The ORA provides IOP and various corneal parameters. Details of the technology have been described elsewhere.[15] In brief, an air pulse against the cornea causes a minute inward deformation, after which the air pump shuts off and the cornea returns to its normal convex curvature. The device makes 2 measurements of the corneal response to the air pulse—the force necessary to flatten the cornea as the air pulse rises and the force at which the cornea flattens again after the air pump shuts off. The difference between the 2 pressures is the CH (mm Hg). Other parameters provided are the corneal resistance factor (CRF), Goldmann-estimated IOP (IOPg), and the IOP adjusted for the CH (IOPcc). The IOPg agrees well with GAT measurements, whereas IOPcc could reflect the true IOP after adjusting for corneal induced artefact.[15,16]

We measured the pressure of both the eyes of the same patient at least twice. If the difference between the 2 consecutive CH measurements was > 2 mm Hg, a third measurement was taken and the average was calculated. The device also provides a WS that ranges from 0 (worse) to 10 (better). Measurements below a WS score of 5 were not used.

VF Analysis

We evaluated VF progression using trend analysis. Automated pointwise linear regression analysis was carried out using Progressor software (Version 3.3, Medisoft, Ltd., Leeds, UK) providing slopes [decibels (dB)/y] of progression for each point based on threshold maps, and the significance of the slope (P values). Details of the software have been described elsewhere.[18] Progression was defined as the presence of a test point with a slope of sensitivity over time > 1.0 dB loss/y, with $P < 0.01$. For edge points, a stricter slope criterion of > 2.0 dB loss/y (also with $P < 0.01$) was used.[19,20] Edge points for the 24-2 field included the 2 outer nasal locations, 1 above and 1 below the horizontal midline. On account of using a single progressing point that meets the aforementioned criteria could result in high false-positive rates,[21] we increased the specificity of our analysis by requiring that at least 2 progressing points be adjacent and within the same hemifield to denote the eye as progressing. Global and localized rates of VF change are automatically provided by the software. Global rates correspond to the average of the slopes of all tested points in the field, whereas localized rates correspond to the average rate of those points that met our progression definition. The number of progressing points was also recorded.

Clinical Data

Baseline characteristics obtained on the date of the first VF test entered in the regression were age, ethnicity, sex, mean deviation (MD) and pattern standard deviation of the VF, CCT, and baseline IOP. CCT was calculated as the average of 5 measurements using ultrasonic pachymetry (DGH-550, DGH Technology Inc., Exton, PA).

Baseline IOP was calculated by averaging the values taken during the first 4 office visits after the baseline VF entered in the analysis. On account 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. Determination of the mean follow-up IOP was calculated over the VF assessment period (from the baseline to the last VF test analyzed) and excluded values obtained within 1 month after any incisional surgery, when frequent visits and unstable IOP control could have biased the determination of the mean follow-up IOP.

Statistical Analysis

Categorical data were compared between progressing and nonprogressing eyes using the χ^2 test. Continuous variables were compared using Student t test.

Logistic regression adjusted for follow-up time was performed using each variable to determine their association with the predefined progression outcome. Because some variables were derived from the same parameter and therefore presented a high interdependence (baseline, mean, and peak IOP; CH, CRF, and IOPg-IOPcc), multivariate models were first built to determine the most significant variable associated with each parameter using a stepwise approach, that is, significant variables (if $P < 0.05$) were entered sequentially; after a variable was entered in the model, variables that became non-significant were checked and removed (if $P > 0.10$). Then, a final multivariate model using the same stepwise approach, was built using the other clinical variables (age, sex, ethnicity, diagnosis, CCT, and baseline VF status) and the variables that remained statistically significant in the multivariate models described above (ORA and IOP-derived parameters). Statistical significance was defined at $P < 0.05$. Computerized statistical analyses were carried out using MedCalc software (MedCalc,Inc., Mariakerke, Belgium).

RESULTS

We enrolled 153 eyes of 153 patients (mean age 61.3 ± 14.0 y, mean number of VF tests 8.5 ± 3.4, and mean follow-up time 5.3 ± 2.0 y). A larger proportion of patients were women (56%) and of European ancestry (82%). Most patients had primary open angle glaucoma (44%), followed by normal-tension glaucoma (21%), exfoliative glaucoma (16%), angle-closure glaucoma (11%), juvenile glaucoma (7%), and pigmentary glaucoma (1%). The mean global rate of VF change was −0.34 ± 0.7 dB/y. Twenty-five eyes, 16% of those enrolled, reached our predefined progression endpoint. The mean number of progressing points among progressing eyes was 6.1 ± 4.7, and their mean rate of localized VF change was −2.5 ± 1.3 dB/y.

Data comparing progressing versus nonprogressing eyes are shown in Table 1.

There was a moderate and significant correlation between CH and CCT (Pearson's $r = 0.33$, $P < 0.01$). There

TABLE 1. Characteristics of the Study Population

Characteristics	Progressing N = 25	Nonprogressing N = 128	*P*
Age, y	67.7 ± 9.8	60.0 ± 14.1	0.01
Sex (Female)	11	75	0.26
Ethnicity (Caucasian)	21	104	0.96
Diagnosis			
POAG	11	56	0.98
NTG	5	27	
XFG	4	21	
ACG	3	14	
JOAG	2	8	
PG	0	2	
Baseline MD (dB)	−5.3 ± 4.1	−6.5 ± 6.8	0.43
Baseline PSD (dB)	4.7 ± 3.0	5.4 ± 4.3	0.48
Baseline IOP (mmHg)	15.3 ± 3.7	14.7 ± 3.9	0.47
Mean follow-up IOP (mmHg)	17.1 ± 2.6	14.8 ± 3.2	< 0.01
Peak IOP (mm Hg)	25.6 ± 5.2	20.5 ± 5.6	< 0.01
CCT (μm)	525.0 ± 34.2	542.3 ± 38.5	0.04
CH (mm Hg)	7.5 ± 1.4	9.0 ± 1.8	< 0.01
CRF (mm Hg)	7.6 ± 1.3	8.9 ± 2.0	< 0.01
IOPg (mm Hg)	14.2 ± 4.8	14.4 ± 5.0	0.86
IOPcc (mm Hg)	18.0 ± 5.3	16.5 ± 5.0	0.18
IOPcc-IOPg (mm Hg)	3.8 ± 1.4	2.1 ± 1.9	< 0.01
Follow-up time (y)	6.1 ± 1.7	5.2 ± 2.0	0.02
Number of VF tests	9.9 ± 3.2	8.2 ± 3.3	0.02

ACG indicates angle closure glaucoma; CCT, central corneal thickness; CH, corneal hysteresis; CRF, corneal resistance factor; IOP, intraocular pressure; IOPcc, corrected IOP; IOPg, Goldmann estimated IOP; JOAG, juvenile open angle glaucoma; MD, mean deviation; NTG, normal tension glaucoma; PG, pigmentary glaucoma; POAG, primary open angle glaucoma; PSD, pattern standard deviation; VF, visual field; XFG, exfoliative glaucoma.

was also a significant association between lower CH and worse baseline MD values ($r = 0.20$, $P = 0.01$).

Eyes that progressed had thinner central corneas compared with stable, nonprogressing eyes (525.0 ± 34.2 vs 542.3 ± 38.5 μm, $P = 0.04$), and lower CRF (7.6 ± 1.3 vs 8.9 ± 2.0, $P < 0.01$), greater difference between IOPcc and IOPg (3.8 ± 1.4 vs 2.1 ± 1.9 mm Hg), and lower CH (7.5 ± 1.4 vs 9.0 ± 1.8 mm Hg, $P < 0.01$). The median value (95% confidence interval) of CH of progressing eyes was 7.3 (6.5 to 8.7) mm Hg.

In the multivariate analysis that included only the IOP-derived parameters (baseline, mean, and peak) peak IOP remained statistically significant (OR = 1.14, $P < 0.01$). Similarly, in the multivariate analysis that included only the ORA parameters (CH, CRF, and IOPcc-IOPg) CH remained statistically significant after a stepwise multiple regression approach (OR = 1.72, $P < 0.01$) (Table 2). Therefore, peak IOP and CH were further entered in the final multivariate model along with the other clinical variables.

In the final multivariate model, peak IOP (OR = 1.13 per mm Hg higher, $P < 0.01$), age (OR = 1.57 per decade older, $P = 0.03$), and CH (OR = 1.55 per mm Hg lower, $P < 0.01$) remained statistically significant (Table 3).

DISCUSSION

We found a significant and moderate correlation between CH and CCT and that CH was the corneal parameter most strongly associated with VF progression.

In 1 other study, lower CH was more closely associated with progressing damage than was the CCT.[17] In that study, each mm Hg increase in CH decreased the association with progression by 20%, whereas CCT showed no association with progression. However, this association became nonsignificant after adjusting for the axial length, which could favor a potential association between CH and the elasticity of other ocular tissues. Similar to our study, the investigators found a significant role of older age (≥ 65 y) on progression. CCT and CH also presented a moderate and significant correlation ($r = 0.27$, $P < 0.01$). However, they did not find an association between elevated IOP and VF progression. Our study differs in various ways; we used automated pointwise linear regression to determine progression and rates of VF change both globally and locally. We also evaluated the role of other parameters provided by the ORA (CRF, IOPg, and IOPcc). Notably, despite losing their strength when compared with a stronger variable (CH), both CRF and the difference between IOPcc and IOPg were associated with progression in the univariable analyses. Moreover, peak pressure was also associated with progression.

It is worth noting that the IOP values used to determine the baseline, mean, and peak IOP were obtained with GAT during follow-up. The fact that we found a significant difference between IOPcc and IOPg, on average 3 mm Hg, may suggest that the IOP values obtained during follow-up were underestimated. The true mean and peak IOP responsible for damage to the optic nerve during this period could have been even higher, assuming that the CH remained stable during the entire period.

The use of CH as a measure of corneal biomechanical properties has been investigated in various studies.[11,12,22–24] However, the relationship between CH and VF progression remains obscure because data is sparse and a variety of confounding variables exist. First, as suggested by the OHTS,[9] a smaller CCT may result in underestimation of

TABLE 2. Stepwise Multivariate Models

Model Using IOP-related Variables			Model Using ORA-related Variables		
Variable	**OR (95% CI)**	***P***	**Variable**	**OR (95% CI)**	***P***
Baseline IOP (per mm Hg higher)	—	> 0.05	CRF (per mm Hg lower)	—	> 0.05
Mean IOP (per mm Hg higher)	—	> 0.05	IOPg-IOPcc (per mm Hg higher)	—	> 0.05
Peak IOP (per mm Hg higher)	1.14 (1.06-1.24)	< 0.01	CH (per mm Hg lower)	1.72 (1.27-2.35)	< 0.01
CCT (per 40 μ thinner)	1.69 (1.01-2.83)	0.04	CCT (per 40 μ thinner)	—	> 0.05

Left: intraocular pressure-related variables. Right: Ocular response analyzer-related variables. Central corneal thickness was included in both models.
CCT indicates central corneal thickness; CH, corneal hysteresis; CI, confidence interval; CRF, corneal resistance factor; IOP, intraocular pressure (mm Hg); IOPcc, corrected IOP; IOPg, Goldmann estimated IOP; OR, odds ratio; ORA, ocular response analyzer.

TABLE 3. Time-adjusted Logistic Regression With Visual Field Progression as Binary Outcome

	Univariate Model		Multivariate Model	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age (per decade older)	1.72 (1.15-2.59)	< 0.01	1.57 (1.03-2.38)	0.03
Sex (Female)	0.52 (0.21-1.25)	0.14	—	—
Ethnicity (non-Caucasians)	0.87 (0.35-3.77)	0.80	—	—
XFG presence	0.85 (0.26-2.80)	0.79	—	—
Baseline VF MD (dB)	1.02 (0.95-1.10)	0.53	—	—
Baseline VF PSD (dB)	0.96 (0.86-1.07)	0.47	—	—
Baseline IOP (per mm Hg higher)	1.04 (0.93-1.15)	0.46	—	—
Peak IOP (per mm Hg higher)	1.14 (1.05-1.23)	< 0.01	1.13 (1.04-1.23)	< 0.01
Mean follow-up IOP (mm Hg higher)	1.19 (1.03-1.36)	0.01	—	—
CCT (per 40 μ thinner)	1.68 (1.02-2.78)	0.03	—	0.41
CH (per mm Hg lower)	1.66 (1.22-2.24)	< 0.01	1.55 (1.14-2.10)	< 0.01
CRF (per mm Hg lower)	1.44 (1.10-1.88)	< 0.01	—	—
IOPcc-IOPg (per mm Hg higher)	1.59 (1.20-2.10)	< 0.01	—	—

Left: univariate model including each variable independently. Right: stepwise multivariate model including corneal hysteresis and intraocular pressure peaks along with the other clinical variables.

CCT indicates central corneal thickness; CH, corneal hysteresis; CI, confidence interval; CRF, corneal resistance factor; IOP, intraocular pressure; IOPcc, corrected IOP; IOPg, Goldmann estimated IOP; MD, mean deviation; OR, odds ratio; PSD, pattern standard deviation; VF, visual field; XFG, exfoliative glaucoma.

the transcorneal pressure gradient measured by GAT. As CCT often correlates with CH, the same argument also applies to the latter measurement and exposes the optic nerve to higher IOP than clinicians typically realize. Second, it could be that the corneal biomechanical properties may be a surrogate parameter of the susceptibility of the optic nerve to IOP-dependent and IOP-independent factors associated with glaucomatous loss. For instance, it has been suggested that CH may correlate with the viscoelasticity of ocular tissues[17] and the susceptibility of the optic nerve.[11,12] Wells et al[11] showed that CH but not CCT was associated with increased deformation of the optic nerve surface during transient elevations of IOP. Bochmann et al[12] showed in a prospective study that acquired pit-like changes of the optic nerve are more frequent in eyes with lower CH. Moreover, CH varies within the glaucoma spectrum, being higher in normals, ocular hypertensives and suspects, and lower in glaucomatous eyes.[16,25] It is possible, therefore, that decreased corneal stiffness may be either a primary or secondary event in the pathogenesis of glaucoma. This study added new information on the significant correlation between VF MD and CH. Our results also showed that hysteresis was lower in eyes with worse VF damage. Our observation that the VF MD was not associated with progression favors an independent association between CH and VF deterioration, regardless of how severe the VF was at baseline.

Aihara et al[26] showed in an experimental model that ocular hypertension can be induced with targeted type I collagen mutation and suggested there is an association between IOP regulation and fibrillar collagen turnover. The corneal stroma corresponds to approximately 80% of the corneal thickness and is consisted mostly of type I collagen fibrils. Daxer et al[27] found age-related changes in the collagen composition of the corneal stroma. In brief, there is increase of fibril diameter and expansion of the intermolecular spacing, which could explain the lowering of CH that occurs with aging.[28] As glaucoma is an age-related disease, it is reasonable to hypothesize that this degenerative aging process may lead to lower CH in glaucoma patients experiencing more rapid progression.

It is unclear whether the relationship between CH and VF progression is cause-effect or mere association. Perhaps corneal thinning and decrease of hysteresis could be a consequence of the glaucomatous process, similarly to optic disc cupping and nerve fiber layer loss. Ideally, prospective studies that assess the CH at baseline should address whether lower CH is indeed a risk factor for progression, as was shown with CCT in the OHTS.[9] Our study suggests that this may not only be true, but that CH may be a more specific predictor of progression than CCT. One should be reminded that there is a significant association between different variables related to CH, such as age, CCT, and IOP. Even though our study took these covariates into account in the statistical analyses, these interactions may have important clinical implications.

The retrospective nature of this study is limited with respect to how IOP variables were collected and analyzed. Unlike the major clinical trials in which patients are seen and VF tests are repeated at fixed intervals, our patients were seen and tested at the clinician's discretion. On one hand, this limitation could have influenced the role of each IOP parameter on the statistical analyses. In contrast, it resembles more closely how patients are typically seen in clinical practice. Nonetheless, future studies should verify our findings in a controlled, prospective design.

The main implication of this study is that in practice, patients with low CH should undergo more careful surveillance in search for past VF progression. Lower CH could, therefore, be (1) a marker of increased susceptibility of the optic disc to glaucomatous damage, or (2) may be the result of glaucomatous damage itself. To support these hypotheses, Leite et al[29] reported that healthy individuals of African ancestry, a group known to be at increased risk of glaucoma onset,[9] showed lower CH than healthy individuals of European ancestry. In addition, our group has recently showed that among eyes with asymmetric glaucomatous VF loss, CH was lower in eyes with worse VF damage independently of its effect on IOP measurements.[30] Moreover, our study adds information regarding rates of VF change and CH, showing that glaucomatous eyes with low CH not only reach event-based progression endpoints[17] but also progress more rapidly (in dB/y) than

those with statistically normal CH. As CH is currently not a modifiable risk factor, more aggressive IOP reduction may be indicated in these eyes to prevent future worsening of the VF.

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