Association of Corneal Hysteresis With Lamina Cribrosa Curvature in Primary Open Angle Glaucoma

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PURPOSE. To investigate whether corneal biomechanical properties are associated with the lamina cribrosa (LC) curvature in eyes with primary open angle glaucoma (POAG).

METHODS. Corneal biomechanical properties and LC curvature were assessed in 65 treatment-naive POAG patients. Corneal biomechanical properties, including corneal hysteresis (CH), corneal resistance factor (CRF), and corneal-compensated intraocular pressure (IOPcc), were measured using an ocular response analyzer (ORA; Reichert Ophthalmic Instruments). LC curvature was assessed by measuring the LC curvature index (LCCI) on B-scan images obtained using spectral-domain optical coherence tomography (OCT). The LCCI was determined by measuring LC curve depth on the anterior LC surface and the width of the reference line.

RESULTS. The LCCI was correlated with CH (P = 0.001), CRF (P = 0.012) and IOPcc (P = 0.001) in the univariate analysis. To adjust multicollinearity, principal component analysis was performed, and multivariate regression analyses were conducted using one variable from each component. The larger LCCI was associated with larger IOPcc (P < 0.001), smaller CRF (P = 0.001) and smaller CH (P < 0.001).

CONCLUSIONS. Lower CH was associated with a more posteriorly curved LC in treatment-naive POAG patients. This finding may provide a basic explanation for the reported association between CH and an increased risk for glaucoma development and progression, and support a potential value of CH for risk assessment for glaucoma.

Keywords: Corneal hysteresis, ocular response analyzer, lamina cribrosa, spectral-domain optical coherence tomography

Intraocular pressure (IOP) plays a pivotal role in glaucomatous optic nerve damage, and the lamina cribrosa (LC) is a key structure for understanding IOP-related mechanical damage of the optic nerve. An experimental study demonstrated that the LC deforms posteriorly upon IOP elevation prior to detectable retinal nerve fiber layer (RNFL) loss. Because optic nerve axons pass through laminar pores, LC deformation may induce stress and insult to the axons. This stress, in turn, may initiate or accelerate retinal ganglion cell apoptosis through various mechanisms, including blockade of axoplasmic flow.

Studies have shown that LC position and curvature change in accordance with changes in IOP. Reduction in IOP, either through surgery or medication, was shown to result in anterior shift of the LC position and flattening of the LC curve. In addition, re-elevation of IOP, due to a decrease in bleb function, in patients who underwent trabeculectomy resulted in the posterior movement of anteriorly-shifted LC. These findings suggest that IOP-related stress is a key driving force that induces and maintains posterior LC bowing. However, the degree of posterior LC deformation is not simply dependent on IOP level but is influenced by other factors, including the material properties of the LC.

Because both sclera and cornea have a similar collagen content, their material properties may be related. It would, therefore, be of interest to determine whether corneal properties, such as corneal hysteresis (CH), are associated with the configuration of LC, which also has a collagenous part. The purpose of the study was to determine whether CH is associated with posterior bowing of the LC, as assessed by the LC curvature index (LCCI), in eyes with treatment-naive primary open angle glaucoma (POAG).
Corneal Hysteresis and the Posterior Bowing of the LC

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Corneal material properties were measured by the ORA. To minimize the effects of topical anesthetics, measurements in all eyes were performed at least 10 minutes before Goldmann applanation tonometry. As the software generates a waveform score of 0 to 10, with higher values representing more accurate measurements, only readings with waveform scores $\geq 7$ were included in the data analysis. At least two measurements were obtained per eye, with the highest waveform scores used for the analysis.

Details of the operation of the ORA have been described previously. Briefly, the ORA emits collimated air pulses, converting convex to concave corneas, with these corneas recovering their original convexity within milliseconds. During this process, corneal flattening is observed at two pressure levels: from convex to concave ($P_1$) and from concave to convex ($P_2$). The difference between these pressure levels ($P_1 - P_2$) was defined as the CH, a measure of the energy dissipated by the material properties of the cornea during the stress-strain cycle.

The ORA also measures several other parameters. The corneal resistance factor (CRF) was calculated as $P_1 - k \times P_2$, with $k$ derived from empirical evaluation of $P_1$, $P_2$, and CCT. This modified parameter was found to be more strongly associated with CCT than with CH and it is relatively unaffected by IOP. CRF is thought to reflect overall resistance against stresses that are relatively unaffected by changes in IOP, whereas CH is affected by both IOP and tissue resistance. The ORA also provides an estimate of IOP that is less influenced by corneal properties than that provided by Goldmann applanation tonometry, with this ORA-estimated IOP called corneal-compensated IOP (IOPcc). IOPcc is regarded as being better able to predict clinically relevant outcomes than conventional IOP measurement.

Enhanced Depth Imaging SD-OCT of the Optic Disc

The optic nerve head (ONH) of each eye was imaged by OCT (Heidelberg Engineering) using the EDI technique. The details and advantages of this technology for evaluating the LC have been described previously. Imaging was performed using a $10^\circ \times 15^\circ$ rectangle covering the optic disc. Scanning of this rectangle consisted of approximately 70 sections, located 30 to 54 $\mu$m apart, with the slicing distance determined automatically by the machine. The average number of frames per section was 42, which provided the best tradeoff between image quality and patient cooperation. Corneal curvature was entered into the OCT system (Heidelberg Engineering) prior to scanning, thus removing any magnification error. To enhance the visibility of the peripheral LC, all images were post-processed using adaptive compensation.

Quantification of the LC Curvature

LC curvature was quantified using the LC curvature index (LCCI), which was defined as the inflection of a curve representing a section of the LC. The LCCI of each eye was measured on horizontal B-scan images at seven locations equidistant across the vertical optic disc diameter. The measurements obtained from these seven B-scans were used to calculate the mean LCCI of the eye. To enhance the visibility of the peripheral LC, all images were post-processed using adaptive compensation and measurements were determined using ImageJ software (version 1.51, http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) by two glaucoma specialists (KML, EJL) who were blinded to patients’ clinical information.

To measure the LCCI, a reference line was drawn on each B-scan by connecting the two points on the anterior LC surface that met the lines drawn from each termination point at Bruch’s membrane (BM), perpendicular to the reference line.
for the BM opening. The length of this reference line was defined as the width (W), the maximum depth from this reference line to the anterior LC surface was defined as the LC curve depth (LCCD; Fig. 1), and the LCCI of each eye was calculated as (LCCD/W) \times 100. Because the curvature was normalized to the LC width, it describes the shape of the LC independent of the actual size of the ONH. Similar normalization was also used in the measurement of iris curvature.25 Only the LC within the BM opening was considered, because the LC was often not clearly visible outside this opening. In eyes with LC defects, the LCCI was measured using a presumed anterior LC surface that best fit the curvature of the remaining part of the LC or excluding the area of LC defect.

To evaluate the interobserver reproducibility of this method, 20 randomly selected SD-OCT datasets were evaluated by two independent examiners (KML, EJL), who calculated the intraclass correlation coefficient (ICC) and limit of agreement using Bland-Altman analysis.

### Data Analysis

Linear regression analysis and Pearson’s correlation analysis were used to evaluate the associations between the LCCI and ORA parameters. Due to the multicollinearity of ORA parameters, principal component analysis was utilized to reduce the number of dimensions. The threshold for statistical significance was set at \( P < 0.05 \). All statistical analyses were performed with commercially available software (Stata version 14.0; StataCorp, College Station, TX, USA) and R statistical package version 3.4.3 (available at http://www.r-project.org; assessed December 5, 2017). Except where indicated otherwise, all data are presented as mean \pm standard deviation (SD).

### RESULTS

The study initially enrolled 87 eyes of 87 treatment-naïve POAG patients. Of these, 22 eyes were excluded, 10 because they had undergone prior corneal refractive surgery, 9 because their optic discs were tilted, 2 because B-scan image quality was poor, and 1 because of coexisting corneal dystrophy. Thus, 65 eyes of 65 subjects were evaluated; their demographic and clinical characteristics are summarized in Table 1.

The LCCI measurement showed excellent intraobserver reproducibility (ICC = 0.985 [95% confidence interval: 0.942–0.995], two-way mixed-effects model, absolute agreement) and interobserver reproducibility (ICC = 0.975 [95% confidence interval: 0.939–0.990], two-way random effects model, absolute agreement) reproducibility. The intraobserver and interobserver limits of agreement for measurements of the LCCI were –0.3 (lower, 95% confidence interval: –0.5 to –0.1) and 0.6 (upper, 95% confidence interval: 0.4 to 0.8), and –0.8 (lower, 95% confidence interval: –1.1 to –0.5) and 0.7 (upper, 95% confidence interval: 0.4 to 1.0), respectively (Supplementary Fig. S1).

CH was correlated with IOPcc (\( r = 0.300, P = 0.015 \)), CRF (\( r = 0.899, P < 0.001 \)), and CCT (\( r = 0.531, P < 0.001 \)). CRF was correlated with CCT (\( r = 0.605, P < 0.001 \)). IOPcc was not correlated with CRF (\( r = 0.148, P = 0.240 \)) or CCT (\( r = 0.111, P = 0.378 \); Fig. 2A). Principal component analysis was used to identify basic components from ORA parameters and CCT. The two principal components (PCs) explained 88% of the total variance in the data (59%, PC1; 29%, PC2; Fig. 2B). Among them, IOPcc was exclusively dependent on PC2, CRF and CCT were exclusively dependent on PC1, whereas CH was dependent on both PC1 and PC2 (Fig. 2B).

Linear regression analysis was performed based on this reduction of dimension. Univariate analysis showed that higher LCCI was significantly associated with higher IOPcc (\( P = 0.001 \)), lower CRF (\( P = 0.012 \)), and lower CH (\( P < 0.001 \); Table

### Table 1. Patient Clinical Demographics

<table>
<thead>
<tr>
<th>Study Population (( n = 65 ))</th>
<th>D, diopters; dB, decibel.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.7 ± 14.1</td>
</tr>
<tr>
<td>Male/female</td>
<td>26/39</td>
</tr>
<tr>
<td>Spherical equivalent, D</td>
<td>–2.15 ± 2.96</td>
</tr>
<tr>
<td>Central corneal thickness, ( \mu )m</td>
<td>550.5 ± 40.9</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>24.55 ± 1.63</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.4 ± 6.0</td>
</tr>
<tr>
<td>IOPcc, mm Hg</td>
<td>15.5 ± 3.6</td>
</tr>
<tr>
<td>CH, mm Hg</td>
<td>10.8 ± 2.3</td>
</tr>
<tr>
<td>CRE, mm Hg</td>
<td>10.7 ± 2.7</td>
</tr>
<tr>
<td>LCCI</td>
<td>9.5 ± 2.0</td>
</tr>
<tr>
<td>RNFL thickness, ( \mu )m</td>
<td>76.4 ± 14.8</td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>−5.05 ± 5.92</td>
</tr>
</tbody>
</table>
(PC2) explains 59.3% and 28.5% of total variance of ORA parameters, respectively. The relation of each ORA parameter to both components is drawn up side along PC2. This indicates that more curved LC is associated with smaller PC1, which is correlated with smaller CH, CRF, and CCT (resistance indicates the 95% probability area of each group. Despite many overlaps, the more curved LC tends to locate on the left side along PC1 and on the up side along PC2. This indicates that more curved LC is associated with smaller PC1, which is correlated with smaller CH, CRF and CCT (resistance component), and larger PC2 which is correlated with IOPcc (pressure component).

In this study, we investigated whether the degree of LC deformation was associated with CH in treatment-naïve POAG patients. We found that patients with lower CH had more curved LC. In addition, the LCCI was positively correlated with IOPcc and inversely correlated with CRF. This study was novel in its assessment of LC curves and corneal biomechanical properties in treatment-naïve POAG patients.

LCCI was used to measure the degree of LC curvature. The validity of LCCI for evaluating LC morphology is supported by several studies. The change of LC morphology after IOP lowering surgery was well characterized using LCCI. In addition, LCCI was excellent in differentiating between glaucomatous and healthy eyes, and was able to predict the rate of future RNFL thinning in glaucoma suspects. More recently, a correspondence between larger regional LCCI and location of RNFL defects was reported in POAG eyes with hemifield defects. These results indicate that LCCI is a valid parameter to evaluate IOP-related glaucomatous LC strain or morphology.

Experimentally, posterior bowing of the LC has been demonstrated after IOP elevation. Conversely, reduction of LC curvature occurred after IOP lowering treatment in glaucoma patients. Moreover, interindividual variation of LCCI of healthy subjects were confined within a certain range (95th percentile was 9.51). These findings suggest that the innate LC is slightly curved and elastic, thereby being posteriorly bowed when IOP increases and becoming less curved when IOP decreases. Therefore, although the possibility of an inborn large curvature cannot be ruled out completely, an eye with a relatively large LCCI is more likely to have experienced a certain degree of posterior LC deformation.

Ideal elastic tissue will return to its original configuration once the external stress has been removed. However, connective tissues, such as cornea and LC, have elements of both elasticity and viscosity, with some energy being dissipated when a stress is applied. This loss of dissipated energy during the stress-strain cycle is defined as hysteresis. The degree of hysteresis is determined by both the applied pressure and the material properties that dissipate stress in response to elastic changes. Similarly, IOP-induced stress applied to the LC would
partly dissipate. When the dissipation is large, only a small fraction of energy would be involved in LC deformation. Therefore, LC hysteresis may play a significant role in the posterior bowing of the LC.

The association between LC and corneal hysteresis could be understood in two ways. First, cornea and sclera have a similar collagen content, and LC is also rich of collagen. It is possible that the collagen in LC may have similar material property with that in the corneal and scleral collagen within an individual. The embryologic origins of them, however, are complicated, and the relationship of their material properties are not certain yet. Alternatively, it may also be hypothesized that association between LC and corneal hysteresis have been acquired after birth at least in part. Internal pressure within the globe would affect both ends of the scleral canal (i.e., LC and cornea). In this situation, LC and corneal hysteresis are both affected by the same pressure, true IOP, thereby they might be correlated.

Energy dissipation may also be relevant not only with the static IOP level but also with dynamic IOP changes induced by ocular perfusion, blinking, etc. However, Agoumi et al. demonstrated that anterior LC surface was noncompliant to acute IOP elevation induced by ophthalmodynamometry. Therefore, it is likely that the degree of energy dissipation during dynamic IOP change may not be a predominant factor for determining the LC morphology. Nonetheless, cumulative effect of energy dissipation upon instant IOP change over long time may have some influence on the LC morphology.

Univariate analysis showed that CCT was not associated with LCCI. CCT was only associated with LCCI when considered together with IOPcc in the multivariate analysis (model 2). At a given level of measured IOP, variation in CCT can reflect variation in “true IOP.” This finding suggests that LCCI is influenced by true IOP. In addition, statistical significance ($P = 0.012$) of CCT in the multivariate analysis was less than that of CH ($P < 0.001$). This finding signifies that CH could be more practical parameter than CCT via reflecting both material properties (e.g., CCT and corneal stiffness) and internal globe pressure (true IOP). This does not necessarily mean that lower CH is a causal factor to induce greater posterior LC deformation. It is possible that eyes with lower CH may have higher true IOP. Currently, CCT is measured routinely in clinical practice as a measure to correct the IOP and as a potential factor related with glaucoma progression. CH may have additional clinical value over CCT in predicting the development and progression of glaucoma.

CH has been shown to predict glaucoma development and progression. The association between CH and LCCI provides a plausible explanation for the association of CH with glaucoma progression. In eyes with smaller hysteresis, pressure would not be dissipated too much. Thus, a higher proportion of IOP-derived energy would be used in elastic changes resulting in greater LC deformation (Fig. 4). This, in turn, would likely promote axonal damage through diverse mechanisms.

The LCCI was not correlated with the disease severity parameters such as mean deviation of visual field test or average RNFL thickness. This is consistent with our previous study. An experimental study demonstrated that LC bowing occurs earlier than RNFL loss. This indicates that the RNFL loss occurs with time after the LC deformation. Therefore, the degree of RNFL loss is likely dependent both on the duration of LC deformation and the degree of LC deformation. In addition, glaucoma is a multifactorial disease in which non-IOP related factors (e.g., vascular factors) may also play a role in the optic nerve damage. Therefore, severe optic nerve damage may be
Corneal Hysteresis and the Posterior Bowing of the LC

**Figure 4.** Schematic diagram suggesting two components affecting the LCCI. The posterior bowing of LC would be the product of given pressure and tissue resistance, which comprised two principal components: (PC2 and PC1 in Fig. 2B, respectively). Hysteresis represents the energy dissipated by material property of connective tissue during the stress-strain cycle. Therefore, hysteresis is a parameter related both pressure and tissue resistance. Assuming that corneal hysteresis is associated with LC hysteresis, smaller CH could imply that LC is more prone to deform when IOP-induced stress is applied.

found without a large degree of LC deformation if non-IOP related factors play a predominant role in a given patient.66

This study had several limitations. First, due to its cross-sectional design, the prognostic value of higher LCCI and lower CH could not be addressed. Second, the LCCI reflects the loading of the LC along the axial direction, while there might be another source of LC deformation including tensile stiffening associated with scleral canal expansion.57-58 Third, we used linear regression model even though stress/strain curves of cornea and LC might be nonlinear. Fourth, because of tilted discs and eyes previously treated for glaucoma with antiglaucoma medications and/or surgery were excluded, our results cannot be applied to such eyes. Finally, we could not determine whether CH and CRF represent true hysteresis or resistance of LC because no method is currently available to directly measure the material properties of the LC.

In conclusion, CH was correlated with LC curvature in treatment-naïve POAG patients, suggesting that both IOP and material property of LC are involved in the posterior LC deformation. This finding may provide a basic explanation for the reported association of CH with an increased risk for glaucoma development and progression, and support a potential value of CH for risk assessment for glaucoma.

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