Corneal Hysteresis but Not Corneal Thickness Correlates with Optic Nerve Surface Compliance in Glaucoma Patients

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PURPOSE. To investigate relationships between acute intraocular pressure (IOP)-induced optic nerve head surface deformation and corneal hysteresis and thickness in glaucomatous and nonglaucomatous human eyes.

METHODS. This was a prospective experimental study of 100 subjects (38 with glaucoma, 62 without glaucoma). Data collected included spherical equivalent, optic disc diameter, central corneal thickness (CCT), axial length, cylinder, Goldmann IOP, Pascal IOP, and ocular pulse amplitude and ocular response analyzer (ORA) measurements of corneal hysteresis (CH). Elevation of IOP was induced in the right eye of each subject with a modified LASIK suction ring to an average of 64 mm Hg for less than 30 seconds. Heidelberg Retina Tomography II (HRT) was used to map the optic nerve surface before and during IOP elevation. Mean cup depth was calculated using built-in HRT data analysis software. Change in optic disc depth during IOP elevation was calculated for all right eyes, and tests for correlation with the parameters listed were performed.

RESULTS. Both CH and CCT were lower in the glaucoma group (8.8 mm Hg and 532 μm) than in the control group (9.6 mm Hg, P = 0.012; 551 μm, P = 0.011, respectively). There were no statistically significant differences in spherical equivalent, cylinder, axial length, optic disc size, or ocular pulse amplitude between the glaucoma and the control groups. There was no difference between the amount of IOP elevation between the two groups (P = 0.41), and the average difference in mean cup depth between baseline (mean cup depth, 247 μm) and during IOP elevation was 33 μm (29.8 μm in glaucoma and 36.1 μm in control; P = 0.5). Multiple variable analysis, controlling for age and sex, showed that CH was correlated with mean cup depth increase (P = 0.032). This relationship persisted (P = 0.032) after controlling for glaucoma status in addition to age and sex. Other factors, including CCT (P = 0.3), axial length (P = 0.9), ocular pulse amplitude (P = 0.22), and spherical equivalent (P = 0.38), were not significant in this model.

CONCLUSIONS. In the glaucoma patients but not the control patients, CH but not CCT or other anterior segment parameters was associated with increased deformation of the optic nerve surface during transient elevations of IOP. (ClinicalTrials.gov number, NCT00328835.) (Invest Ophthalmol Vis Sci. 2008;49:3262–3268) DOI:10.1167/iovs.07-1556

It has been known since Goldmann first described what is currently the gold standard for intraocular pressure (IOP) measurement1 that the biomechanical characteristics of the cornea, especially central corneal thickness (CCT), play a role in the accuracy of IOP measurement. Particularly since the Ocular Hypertension Treatment Study (OHTS)2 brought CCT back into the limelight, there has been much discussion3–9 regarding the role that CCT has on the risk for glaucoma development or progression. Included in that discussion has been speculation that the biomechanical characteristics of the cornea might somehow reflect vulnerability of the optic nerve head to glaucoma, in addition to the well-described discrepancies between measured and true IOP. Corneal tissue properties may or may not be directly related to lamina tissue properties given that their embryological derivation is different, but there are also plausible connections.

First, corneal thickness might be associated with structural characteristics of the sclera and adjacent tissues and of the optic disc.3 Thinner corneas have been shown not to be associated with myopia or thinner anterior sclera,10 but there does seem to be a correlation between thinner corneas and larger optic discs.3 Larger optic disc diameters may be associated with increased vulnerability to pressure-induced deformation; Sigal et al.11 have described the importance of the peripapillary scleral stiffness and thickness and the optic canal diameter in determining lamina cribrosa strain. Bellezza et al.12 examined monkey eyes with and without induced glaucoma and found plastic expansions of the anterior scleral canal at Bruch membrane and anterior laminar insertions in glaucomatous eyes but not in control eyes.

Second, the corneal tissue characteristics themselves, such as the ability to resist deformation, might reflect the constitution of the extracellular matrix (ECM). This is supported by suggestions that corneal hysteresis (CH) is lower in patients with Marfan syndrome, a systemic connective tissue disorder (Gatinel D, personal communication, 2008), and in pregnancy (Sousa AK, et al. IOVS 2007;48 ARVO E-Abstract 3144), which has hormonally mediated systemic effects on connective tissues.
Given that the cornea, sclera, peripapillary ring, and lamina cribrosa in an individual eye are essentially made from ECM constituents coded for by the same genes, it is plausible, but unproven, that their biomechanical characteristics might be similar. It has been speculated that an eye with a more deformable cornea, or one with less viscous damping, might also have an optic disc that is more vulnerable to glaucoma damage from raised IOP. Both the cornea and the lamina tend to become more rigid with age and to become stiffer, less resilient structures. Age-related stiffening of connective tissues is possibly similar in the cornea and lamina, and, because CH declines with age, it is possible that the lamina and peripapillary sclera behave similarly.

Structural changes at the optic nerve head are pivotal to the diagnosis of glaucoma and may be implicated in the pathogenesis of glaucoma. Biomechanical responses of the optic nerve head to elevations of IOP have been studied in several models, including monkey eyes, human eyes, and computer modeling techniques. There are deformations of the lamina cribrosa in human and monkey eyes in response to transient IOP increase. However, finite element analysis suggests that a significant proportion of the change measured by scanning laser ophthalmoscopy, such as Heidelberg Retina Tomography II (HRT), may be in the prelaminar tissues, including the neuroretinal rim, rather than in the lamina.

Recently, the introduction of the ocular response analyser (ORA) has allowed the measurement of CH. Hysteresis of the cornea is correlated with CCT but only weakly. CH has been associated with progressive visual field worsening in glaucoma patients, and hysteresis is lower in patients who have glaucoma.

In this study, we investigated changes in optic disc cup depth in a large group of patients, with and without glaucoma, during a transient IOP rise and compared them with measurements of their CCT and CH.

**METHODS**

**Patients**

One hundred patients older than 18 years of age who had attended a specialist appointment in the preceding 12 months were recruited from general ophthalmology and glaucoma clinics in Wellington, New Zealand. All had best-corrected visual acuities of at least 6/12. Patients were assigned to either the glaucoma or the control group based on their clinical findings on previous visits (Table 1). Those included in the glaucoma group had been diagnosed as having glaucoma by a glaucoma specialist (APW) and had documented glaucomatous optic disc appearance over at least two specialist visits. At study entry, the glaucoma group had a mean deviation (MD) of $-3.2 \pm 5.52$ dB and a pattern standard deviation (PSD) of $4.2 \pm 1.9$ dB on Humphrey Matrix perimeter. As a control group, we recruited patients with healthy eyes and others referred to our clinic as glaucoma suspects who had no evidence of glaucomatous optic neuropathy.

Patients with known or suspected ocular perfusion abnormalities were excluded from the study because of the potential effects of the high induced IOP on retinal circulation. Patients were also excluded if changes had been made to their treatment regimen or if they had undergone either intraocular surgery or laser trabeculoplasty within the preceding 3 months. Glaucoma patients with advanced disease, defined as any documented visual field defects within 5° of fixation, or inadequate control on maximal medical therapy requiring glaucoma filtration surgery, were excluded from the study.

More than half the patients in the control group were glaucoma suspects referred to our clinic with dysmorphic but nonlumacomatic disc appearances, visual fields within normal limits at study entry (MD, $-0.5 \pm 3.2$, PSD, $3.0 \pm 1.0$; Humphrey matrix), IOP less than 20 mm Hg, and no documented disc changes on subsequent visits (Table 1). The rest of the control group consisted of patients with signs that might increase the risk for glaucoma, such as narrow angles and pseudoxefiolation, but normal optic discs at specialist review. Four patients in the control group were recruited from general ophthalmology clinics after being seen with problems unrelated to glaucoma.

**Corneal Hysteresis Measurement**

Hysteresis was measured using an ORA (Reichert Corp., Buffalo, NY). This device has been described in detail previously. It uses an air puff to deform the cornea into slight concavity and an optical sensor to measure the deflection of the cornea, which is timed to the pressure applied by the air puff. From these data, the pressures at which the

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POAG, primary open angle glaucoma; PXF, pseudoxefiolation; NTG, normal tension glaucoma; NAG, narrow angle glaucoma; PDS, pigment dispersion syndrome; SLT, selective laser trabeculoplasty; YAG PI, YAG peripheral iridotomy; OHTN, ocular hypertension; other: eyelid abnormalities (2), trochlear nerve palsy (1), vitreous detachment (1).
After successful local anesthesia, the lid speculum was placed and left in situ to reduce the potential membrane distortion effects from the speculum. Artificial tears were administered to maximize image quality.

**IOP Elevation**

Transient IOP elevation was induced in the right eye of each subject by a modified laser-assisted in situ keratomileusis (LASIK) automated corneal shaper (Chiron; Hansa Research & Development, Miami, FL) after the administration of local anesthesia. Because LASIK suction rings can potentially produce IOPs in excess of 100 mm Hg, the rigid plastic tubing connecting the suction ring to the main pump had been punctured by two 18-gauge needles that were left in situ to reduce the potential intraluminal negative pressure produced and, therefore, limit the peak IOP elevation that could be generated. Elevation of IOP lasted up to a maximum of 30 seconds. IOP measurement during the procedure was obtained with a rebound tonometer (iCare; Tiolat, Helsinki, Finland). Measurements were taken with the rebound tonometer because technical difficulties made measurement with other available devices (including Goldmann IOP, Tono-Pen [Reichert Corp.], Pascal IOP, dynamic contour tonometer, and pneumotonometer) impossible. Because we did not have access to a rebound tonometer, the procedure was performed on subsequent images. The lid speculum was closed so that the previous image was not visible, and then the same procedure was performed on subsequent images.

**Optic Nerve Imaging and Data Collection**

The right eye of each patient was imaged before and during IOP elevation using HRT II. Three scans were averaged, combined into a single mean topography image, using the standard HRT data acquisition process. Imaging was performed with an eyelid speculum in place before and during IOP elevation to control for refractive or ocular distortion effects from the speculum. Artificial tears (Bion Tears; Alcon, Fort Worth, TX) were used to lubricate the cornea and to maximize image quality.

Contour lines were drawn by an experienced operator using the built-in HRT II software for each of the 200 scans (100 right eyes before and during IOP elevation). A masked operator drew the contour lines at an interval of some hours after image acquisition. The automated contour line import function in HRT II scales the contour line in proportion to the scaling inherent in sequential image alignment. Given that we were examining changes to the optic nerve as a response to raised IOP and that there would likely have been a differential between stretch of the optic nerve head and that of the surrounding retinal features, contour lines were placed manually for each image. The contour line was drawn, the average optic disc depth was recorded, and the contour line was deleted before the image window was closed so that the previous image was not visible, and then the same procedure was performed on subsequent images.

**Statistical Analysis**

Data were collated using commercial software (Excel 11.1 [Microsoft, Redmond WA, www.microsoft.com]) and analyzed (Excel [Microsoft] and SPSS 11.04 [SPSS Inc., Chicago, IL, www.spss.com]). Patient characteristics were analyzed using $\chi^2$ tests and two-tailed Student’s $t$ tests. Parametric data obtained before and after the procedure within each group were tested for relationships using Pearson correlation coefficients, and nonparametric data were investigated using Spearman rank correlation coefficient. Multiple variable analyses were performed using the general linear model in SPSS.

**RESULTS**

There was no significant difference in the ages of subjects in the glaucoma and control groups. Significantly more male subjects were recruited in the glaucoma group, whereas the male/female balance was almost even in the control group (Table 1). Male CH and CCT were lower in the glaucoma group (8.8 mm Hg and 532 $\mu$m) than in the control group (9.6 mm Hg; $P = 0.012$ and 551 $\mu$m; $P = 0.011$, respectively; Figs. 1, 2). CCT was associated with CH ($P = 0.005$; Fig. 3). There were no statistically significant differences in spherical equivalent, cylinder, axial length, optic disc size, or ocular pulse amplitude between the glaucoma and the control groups. There was also no statistically significant difference in pre-procedure IOP in either eye between the two groups, although the glaucoma group did have thinner corneas ($P < 0.011$). Mean topography standard deviations for the HRT scans were similar between the glaucoma and control groups for both baseline (25.0 and 24.4, respectively; $P = 0.7$) and raised IOP (36.8 and 38.3, respectively; $P = 0.46$).

**IOP Elevation**

IOP during suction application was recorded in 17 patients in the glaucoma group with an average of 66.6 mm Hg and 34 patients in the control group with an average of 63.2 mm Hg ($P = 0.4$). Rebound tonometry may overestimate IOP compared with Goldmann tonometry,$^{24,25}$ therefore, Goldmann IOPs during pressure elevation—if they could have been measured—might have been approximately 2 mm Hg lower.

**Correlations with Changes in Optic Disc Cup Depth**

Mean cup depth is the mean of the distances below the reference plane for each pixel that is enclosed by the contour line.
and is below the reference plane. For the entire group, the average difference in mean cup depth between baseline (247 ± 109 μm) and during IOP elevation was 33 μm (29.8 μm in glaucoma and 36.1 μm in control; \( P = 0.5 \)). Multiple variable analysis, controlling for age and sex, showed that CH was correlated with mean cup depth increase \( (P = 0.032; \text{Fig. } 4) \). This relationship persisted \( (P = 0.032) \) after controlling for glaucoma status, in addition to age and sex. Other factors including CCT \( (P = 0.3, \text{Fig. } 5) \), axial length \( (P = 0.9) \), ocular pulse amplitude \( (P = 0.22) \), and spherical equivalent \( (P = 0.58) \) were not significant in this model.

When the whole group was subdivided according to glaucoma status, neither the glaucoma nor the control group showed associations between CCT and mean cup depth. Similarly, the control group did not show an association between CH and change in mean cup depth \( (P = 0.5; \text{Fig. } 6) \), but CH was significantly associated with change in mean cup depth for the glaucoma group \( (P = 0.047; \text{Fig. } 6) \).

**DISCUSSION**

Results from this study suggest that optic disc surface compliance may have a relationship with corneal hysteresis, a parameter of ocular biomechanics that is easily and noninvasively measurable at the front of the eye. Optic disc compliance was not associated with CCT in this study. If optic disc compliance, as measured by the amount of deepening of the optic cup during an acute rise in pressure, is associated with increased risk for glaucoma, it is possible that CH might provide further information about glaucoma risk and pathogenesis. It is possible that CH had a relationship to change in mean optic disc depth in this study because it represents properties of the rest of the eye rather than just the cornea.

The relationship between hysteresis and optic nerve surface compliance observed in this study occurred only in patients with glaucoma, suggesting that glaucoma patients have altered ocular tissue biomechanics.

Nicolela et al. described 23 glaucoma patients in whom topography was performed before and after glaucoma medica-
tion was stopped in one eye, and they did not detect a change in stereometric or topographic change analysis parameters with an IOP shift of 5 mm Hg. This might have been too small an IOP change to deform the optic nerve surface, or the number of patients might have been too small to detect a very small change.

Lesk et al. lowered IOP in 32 patients with glaucoma or ocular hypertension through medication, laser trabeculoplasty, or trabeculectomy by a mean of 35% and split the cohort in half on the basis of CCT. Patients with thin CCT had larger decreases in Goldmann-measured IOP than the patients with thick CCT (mean 38% vs. 30%; \( p = 0.09 \)) and also had statistically significant differences in the change in mean (\(-36 \pm 32 \text{ vs. } -4 \pm 36 \text{ mm}; \ p = 0.003 \)) and maximum (\(-73 \pm 107 \text{ vs. } -4 \pm 89 \text{ mm}; \ p = 0.02 \)) cup depth. CH was not assessed. Those results suggested that thicker corneas are associated with a less compliant optic nerve surface, a finding not replicated in our study. Possible explanations include the fundamentally different nature of the intervention, raising the IOP in our study compared with lowering it in the Lesk et al. study, the possibility that a few patients in the Lesk et al. study with postintervention low IOP might have had distorted topography results, and the possible overestimation of IOP in eyes with thicker corneas. If the latter, the measured IOP would have changed less, because of the larger contribution of corneal stiffness to the measurement, and subsequent changes in the optic cup would have been correspondingly smaller.

**Study Limitations**

The task of outlining the optic nerve head in the HRT software was subjective; we attempted to minimize the impact of this by using a relatively large number of subjects. Similarly the relatively high topography standard deviations for the baseline tests, as well as the raised pressure tests, reflected the decision to standardize scans as much as possible by performing all imaging with the speculum in place. Again, the large number of subjects should have minimized the impact of this. It is possible that the method of raising IOP might itself have altered the structural characteristics of the eye during IOP elevation, though the built-in image alignment algorithm in the HRT software would have compensated for minor changes in image refraction.

We also drew the contour lines separately rather than using the automated contour line import function between image series to eliminate the possibility that errors in the automated importing of the contour line could affect the results. In particular, this allowed us to control for possible changes in disc size, which would not have been possible using the automated contour line alignment.

The control cohort had similar numbers of male and female patients, but the glaucoma cohort of the study group had a strong sex bias toward male patients. Some studies have found a correlation between male sex and higher CCT values, but others have not. We controlled for sex in addition to age and glaucoma status in our model; therefore, it is unlikely that the sex bias in the glaucoma group had a tangible influence on the results.

Although the amount of suction applied was constant and a single device was used throughout, we have no way of knowing whether the IOP responses were uniform across the eyes. In addition, when IOP was measured, this was measured using an external device, so true IOP was not known. IOP was transiently raised to high levels—approximately 64 mm Hg—in this study. We might have achieved similar deformations at lower IOPs, but the design and methods of the study made investigation of a dose–response relationship impossible. It is also unknown whether the corneal biomechanical properties might have influenced the magnitude of IOP elevation obtained by the method used. The duration of IOP elevation in this study was less than 1 minute, which might not have allowed enough time for the response to raised IOP to fully equilibrate, described in ex vivo studies, to take up to several minutes. Our inclusion of glaucomatous eyes made us reluctant to adopt an approach with more sustained IOP elevations.

**Hysteresis, Central Corneal Thickness, and Glaucoma**

Hysteresis is a physical term describing a property of a physical system that does not instantly follow an applied force but that reacts slowly. It can be thought of, in simple terms, as energy absorption or damping effect. An analogy for hysteresis is that of a damper (shock absorber) on an automobile: The faster the damper is pushed, the more it resists the force. Using the ORA,
the CH value is expressed as the difference between inward and outward application pressures on either side of the applied pressure curve, a measure of the response to the applied pressure. Understanding of the direct relevance of CH to glaucoma, especially as it relates to CCT, is still in evolution. CH is a direct measurement of an aspect of ocular biomechanics measured at the cornea, whereas CCT represents only one parameter that affects the biomechanics. CCT has been associated with the risk for progression of OHT to glaucoma and of progression of existing glaucomatous visual field loss. Recently, in a clinic-based retrospective observational study, Congdon et al. found lower CH values were associated with progression of glaucomatous visual fields independent of CCT.

Ridley described in 1930 that glaucomatous eyes are less distensible than nonglaucomatous eyes. More recently, Downs et al. have described changes in the viscoelastic properties of the peripapillary sclera in normal monkey eyes and those with early glaucoma and have suggested that tissue viscoelastic properties change in the optic disc region of eyes exposed to chronic elevations in intraocular pressure. These findings may reflect an underlying predisposition to glaucoma change or a change that has occurred as a result of part of the glaucoma process, or they may reflect contributions from both.

Woo et al. analyzed stress and strain characteristics of sections from different regions of whole human globes and found, using finite-element analysis, that the biomechanical characteristics of the anterior segment approximated that of the whole globe. A similar result was reported recently by Starck Johnson, who demonstrated that the pressure-volume curves of a corneoscleral shell had the same shape as a whole globe.

The association between CH and optic disc surface compliance described in this article runs counter to the simplistic concept that a so-called floppy cornea would be associated with floppy lamina cribrosa and peripapillary connective tissue structures. Hysteresis refers to the ability of the ocular connective tissues to dampen pressure changes rather than having characteristics of floppiness or rigidity. We found that higher hysteresis values were associated with more optic nerve deformation under acute IOP elevation, but only in our patients who had diagnoses of glaucoma. This would appear to support the notion proposed by Downs that glaucoma itself may modify the biomechanical properties of tissues supporting the optic nerve head. Downs showed that peripapillary sclera from eyes with early glaucoma exhibited an equilibrium modulus that was significantly greater than that measured in normal eyes.

Optic Disc Surface Compliance

Early glaucoma in experimental monkeys produced an increased compliance of the optic nerve head in the monkey glaucoma model described by Bellezza. This may represent an initial response. Previously, Burgoyne et al. had demonstrated that in a similar model, optic disc compliance initially increased for 1 to 2 weeks before decreasing again to the original level. In a study before that, IOP-induced optic nerve deformation was noted in the nonglaucomatous monkey model over much longer periods, usually more than 10 minutes.

If the optic nerve head were more rigid, a given applied force would produce less lamina movement, which ought to be seen through the methods used in this study as decreased surface compliance. If optic nerve head rigidity were related to cross-linking between collagen fibrils in the laminae, then one might expect greater stiffness to be associated with lower hysteresis and the findings of this study would be consistent with this hypothesis. We did not find a link between CH and cup change in the control eyes; hence, one might speculate that glaucoma-related changes to the ocular tissues might result in a stiffer, but less viscoelastic, material.

The importance of the measurable biomechanical parameters of the cornea, such as CH, remains to be fully elucidated. The ability for the sclerocorneal shell to dampen brief IOP fluctuations, such as the 10 mm Hg spike from blinking or perhaps significantly larger pressures from eye rubbing or Valsalva, may protect eyes with glaucoma from sudden pressure spikes. From this study and others, it appears that CH in particular may have relevance to glaucoma that is separate from that of CCT.

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References


