Changes in Corneal Biomechanics and Applanation Tonometry with Induced Corneal Swelling

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PURPOSE. To investigate the changes in Goldmann applanation tonometry (GAT) and Ocular Response Analyzer (ORA) measurements with corneal edema induced by contact lenses.

METHODS. Twenty-five healthy, normal subjects (age, 23 ± 2 years) had central corneal radius (CCR), ORA, GAT, and central corneal thickness (CCT) measurements performed in both eyes before a thick, soft hydrogel contact lens was worn with eye closure for 2 hours in one eye. Measurements were repeated immediately after lens removal and every 20 minutes thereafter for the following hour.

RESULTS. The experimental and control eyes behaved asymmetrically over time (repeated measures analysis of variance [RMANOVA]; $P < 0.05$) for all variables except CCR. GAT, ORA Goldmann-correlated intraocular pressure (ORAg), and ORA corneal-compensated intraocular pressure (ORAcc) showed comparable overestimations, whereas corneal hysteresis (CH) and corneal resistance factor (CRF) responded to corneal swelling in dissimilar ways (RMANOVA; $\alpha = 0.05$). The variation in GAT in experimental eyes could be predicted by changes in CRF (0.85 [0.23] mm Hg ΔGAT/mm Hg ΔCRF; $P < 0.001$), but not by CCT or CH. The covariation of both CH and CRF with CCT was influenced by the presence of corneal swelling (Eye×ΔCCT interaction, $P < 0.001$ and $P = 0.003$, respectively).

CONCLUSIONS. The GAT overestimation caused by small amounts of corneal swelling represents an overall increase in corneal rigidity, which is partially characterized by CRF. In contrast, CH does not appear to usefully quantify biomechanical changes induced by corneal swelling. The accuracy of ORAcc is affected by corneal swelling. (*Invest Ophthalmol Vis Sci.* 2011;52:3207–3214) DOI:10.1167/iovs.10-6754

The Goldmann applanation tonometer (GAT) is the gold standard instrument for intraocular pressure (IOP) measurement.[1] However, its accuracy is affected by variation in corneal properties such as its thickness,[2-5] curvature,[6,7] and material stiffness.[8-12]

Variation in corneal hydration also affects the accuracy of applanation tonometry. Gross underestimations occur in extremely edematous corneas—for instance, those observed postmortem or with induced endothelial damage.[13-15] In contrast, tonometric overestimation has been reported with up to 13.1% corneal swelling in most studies,[16-19] with one exception finding no effect.[20] Therefore, corneal geometry cannot linearly describe the corneal-hydration–related tonometric error. A change in corneal rigidity associated with the variation in corneal water content is the likely cause of the IOP measurement inaccuracy.

Young's modulus (*E*) is the most relevant corneal biomechanical property involved in errors in tonometry,[8-12] but unfortunately it is not possible to determine corneal biomechanical properties in vivo. However, the commercially available Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY) is believed to measure the overall biomechanical response of the cornea to the noncontact tonometry (NCT) process.[21]

The ORA reports two corneal parameters termed corneal hysteresis (CH) and corneal resistance factor (CRF). CH is intended to quantify the viscoelastic mechanical damping ability of the cornea, whereas CRF is thought to describe its overall viscoelastic resistance.[21,22] The ORA also calculates Goldmann-correlated and corneal-compensated IOP estimates (ORAg and ORAcc, respectively). ORAg is analogous to standard NCT IOP measurements, whereas ORAcc is an IOP estimate that uses a mathematical correction to minimize its corneal dependence.[22] However, the definitions and validity of CH, CRF, and ORAcc have not been convincingly demonstrated, despite the increasing use of the ORA in glaucoma,[23,24] keratoconus,[25,26] and refractive surgery.[27,28]

This study had three purposes: first, to evaluate the descriptions of CH and CRF with reference to small increases in corneal hydration and any related GAT error; second, to identify corneal parameters that could predict such errors, if detected; and third, to compare GAT, ORAg, and ORAcc readings in swollen corneas.

METHODS

Participants

Twenty-five volunteers (mean age, 22.6 ± 1.7 years; 14 women) from the student population at the University of New South Wales (UNSW) participated. Informed consent was obtained from the subjects after an explanation of the nature and possible consequences of the study. The project was approved by the Human Research Ethics Committee, UNSW, and was conducted according to the tenets of the Declaration of Helsinki. Subjects were eligible if they had good general and ocular health, the mean sphere of their refraction was within ±6.00 D, and their corneal and refractive astigmatism was within ±2.50 D cylinder. Participants were excluded if they had any ocular abnormalities, had a history of ocular surgery, were taking any medications, or had a history of full-time soft or any rigid contact lens wear. Part-time soft contact lens wearers (≤2 days per week) were permitted to participate if their lenses had not been worn during the previous 2 days. All measurements were taken at least 2 hours after awakening, to ensure the initial absence of closed-eye corneal swelling.[29-31]

To ensure the participant's eligibility, a preliminary screening was performed. The screening consisted of a brief interview and eye examination including refraction, autokeratometry (Reichert EyeChek autokeratometer; Reichert Ophthalmic Instruments), slit lamp biomicroscopy, visual fields screening (Humphrey Matrix; Carl Zeiss Meditec, Dublin, CA), and undilated ophthalmoscopy.

Measurement Sequence

The central corneal radius (CCR) was measured first with the autokeratometer. The mean sphere of two readings was averaged and used for analysis. Corneal biomechanics and the IOP were then estimated with the ORA. Initially, four readings with acceptable waveforms were taken,[32] where each ORAg value was to be within 2.4 mm Hg of their mean. This intrasession repeatability criterion was based on an unpublished pilot study performed by the authors and calculated using the procedure described by Bland and Altman.[33] However, the mean of the best three readings were selected for analysis to avoid inclusion of borderline waveforms, as the evaluation of measurement quality is subjective. According to pilot study data, a slightly different repeatability criterion was applicable with the exclusion of a measurement. Each of the three readings used was to have its ORAg value within 2.3 mm Hg of their mean; an additional measurement was taken to meet this requirement if it was not met. The cornea was then anesthetized and the tear film stained using 1 drop of 0.5% proxymetacaine hydrochloride (Alcaine; Alcon Laboratories, Frenchs Forest, NSW, Australia) and 2% sodium fluorescein (Minims; Bausch & Lomb, North Ryde, NSW, Australia), respectively, before the IOP was measured with the Goldmann AT 900 (Haag-Streit, Bern, Switzerland). The average of three readings, within ± 2 mm Hg (i.e., one scale division) of their mean, was used for analysis. Finally, the CCT was measured using an ultrasonic pachymeter (Pocket II Precision; Quantel Medical, Clermont-Ferrand, France). Three consecutive readings within ± 5 μm of their average were taken and the mean analyzed.

A contact lens was then inserted in the right eye, and the eyelid was taped shut (as described in the following subsection) for 2 hours. The series of measurements as described above was repeated immediately after lens removal (time [hours:minutes], 2:00) and every 20 minutes for the next hour (times, 2:20, 2:40, and 3:00).

The measurements were performed on both eyes, with the participants' preferred eye being measured first. The left eye was the control. Each instrument was designated to a single, trained observer who was masked to the results from the other instruments. An exception was made that the investigator performing GAT was also masked to his own measurements, as recommended by Kass.[34] An assistant recorded GAT results and turned the measurement drum away from the recorded value after each attempt.

Participants were free to leave the clinic and continue with their daily routines between measurements. However, strenuous activity, napping, and the consumption of caffeine, alcohol, or large amounts of food or fluid were not permitted.

The calibration of the autokeratometer, GAT and ultrasonic pachymeter was checked before the first and after the last measurements taken on each day on which data were collected. The ORA cannot be calibrated without special equipment. Therefore, it was returned to its distributor (BOC Instruments, Silverwater, NSW, Australia), where its function was verified before the study.

Contact Lenses and Eyepads

Custom-made hydroxyethyl methacrylate (38% water) contact lenses (Ciba Vision, Bella Vista, NSW, Australia) were used. The lenses were parallel in profile, with a diameter and thickness of 14.0 and 0.3 mm, respectively. Base curves of 8.1, 8.4, 8.7, and 9.0 mm were available. The oxygen transmissibility of the lenses was 2.8×10^{-9} cm $\cdot$ mL O_2/s $\cdot$ mL $\cdot$ mm Hg.

Contact lens– and eyepad-related duties were delegated to the assistant performing autokeratometry. The contact lenses were inserted in right eyes only. With a satisfactory fitting lens in place, the eyelid was closed and taped shut with 2.5-cm-wide medical tape (Dermicel Hypo-Allergenic Cloth Tape; Johnson & Johnson Medical, Arlington, TX). A gauze eyepad (Livingstone Eye Pad; Livingstone International, Rosebery, NSW, Australia) was then lightly taped over the eye. Care was taken to ensure firm application without unnecessary pressure. The lenses were sterilized after each use by autoclaving.

Statistics

Statistical significance was set at the 0.05 level (SPSS ver. 16.0.2; SPSS Inc., Chicago, IL). Normality was evaluated by the Shapiro-Wilk test and visual inspection of probability–probability plots. When appropriate, parameters are reported with a standard deviation (SD) in parentheses or standard error (SE) in square brackets or parentheses.

Means were compared by repeated-measures analysis of variance (RMANOVA). The Greenhouse-Geisser correction was applied to the degrees of freedom if sphericity was violated. To protect against the inflation of the family-wise error rate, planned contrasts were performed only if a statistically significant experimental effect was confirmed by the omnibus test. Where corrected means are reported, these figures were calculated by subtracting the changes in the control eyes from the experimental eyes at each time point.

This study was designed to detect a 1.5-mm Hg change in GAT assuming an SD of 2.5 mm Hg between paired measurements.[18] For a statistical power of 80%, a required sample size of 24 was calculated with G*Power (ver. 3.0.10).[35] This power calculation was based on the paired *t*-test rather than RMANOVA, because the latter requires a priori knowledge of sphericity and the correlation between measures.

Linear mixed models (LMM) were used to assess the ability of corneal changes to explain the variation in GAT, CH, and CRF. Least-squares regression could not be used because it is unable to account for the nonindependence of the data resulting from repeated measurements. All changes were calculated from baseline and are prefixed with the delta symbol (Δ). Measured parameters were treated as fixed effects. The random variance of intercept was modeled between subjects; however, these data are not reported. Maximum-likelihood estimation was used, and model fit was assessed by Hurvich and Tsai's corrected Akaike's Information Criterion (AICc). Initially, predictors were identified as potentially important if their interaction with eye tested was statistically significant in exploratory models. An interaction indicates a between eye difference, and regression coefficients were then obtained in each eye separately when this occurred. Unstandardized beta values for corneal parameters without a significant interaction are statistically similar between eyes and therefore are calculated using pooled data.

RESULTS

Means

Figures 1, 2, and 3 show the variation of each measured parameter over time. There were statistically significant differences between the changes observed in the experimental versus control eyes for all variables (RMANOVA 2-way interaction, $P < 0.05$) except CCR. The true experimental effect was therefore considered to be the variation in the right eye after correcting for the fluctuations in the left eye (Table 1).

Predictors of ΔGAT

Table 2 shows that the ability of ΔCRF to predict the ΔGAT was significantly different between eyes.

In experimental eyes, the coefficient for ΔCRF was statistically significant (0.85 [0.23] mm Hg ΔGAT/mm Hg ΔCRF, $P < 0.001$). The improvement in model fit (ΔAICc) compared with
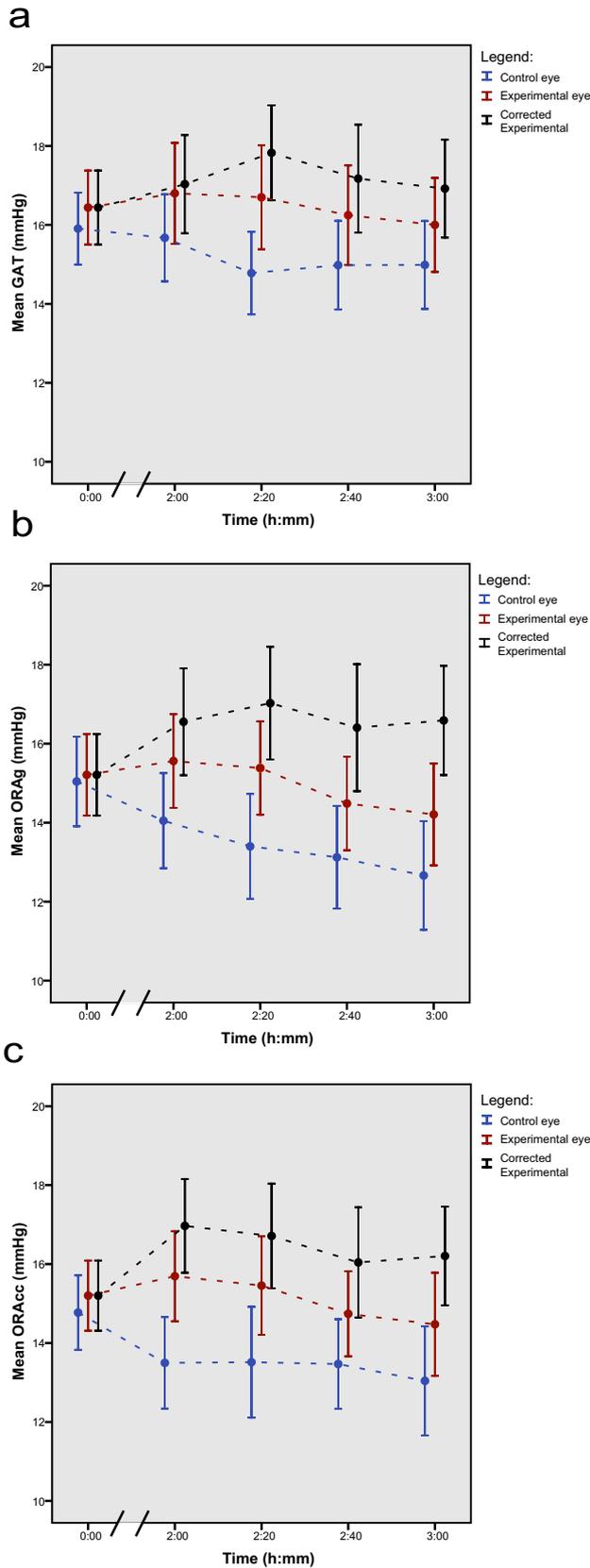
FIGURE 1. Mean values for (**a**) GAT, (**b**) ORAg, and (**c**) ORAcc at each measurement time. Error bars, ±2 SE of the mean.

the null model (AICc = 405.3) was −10.8. In the control eyes, ΔCRF could not predict ΔGAT (0.24 [0.16] mm Hg ΔGAT/mm Hg ΔCRF; $P = 0.129$).

ΔCCT and ΔCH showed similar behavior in control and experimental eyes (Table 2). With eyes pooled, neither ΔCCT nor ΔCH predicted ΔGAT (0.14 [0.12] mm Hg ΔGAT/10 μm ΔCCT; $P = 0.212$ and −0.06 [0.14] mm Hg ΔGAT/mm Hg ΔCH; $P = 0.680$).

Corneal Geometric Predictors of ΔCH and ΔCRF

The ability of ΔCCT to predict both ΔCH and ΔCRF was significantly different between the eyes (Table 3).

As a predictor of ΔCH, ΔCCT was statistically significant in control, but not experimental, eyes (0.58 [0.14] and 0.00 [0.01] mm Hg ΔCH/10 μm ΔCCT; $P < 0.001$ and $P = 0.366$ respectively). In control eyes, the ΔAICc improved −12.0 units compared with the null model AICc of 253.0. With ΔCRF as the outcome variable, ΔCCT was statistically significant in both eyes (0.72 [0.15] and 0.14 [0.05] mm Hg ΔCRF/10 μm ΔCCT, $P < 0.001$ and $P = 0.010$ in control and experimental eyes, respectively). The ΔAICc improvements

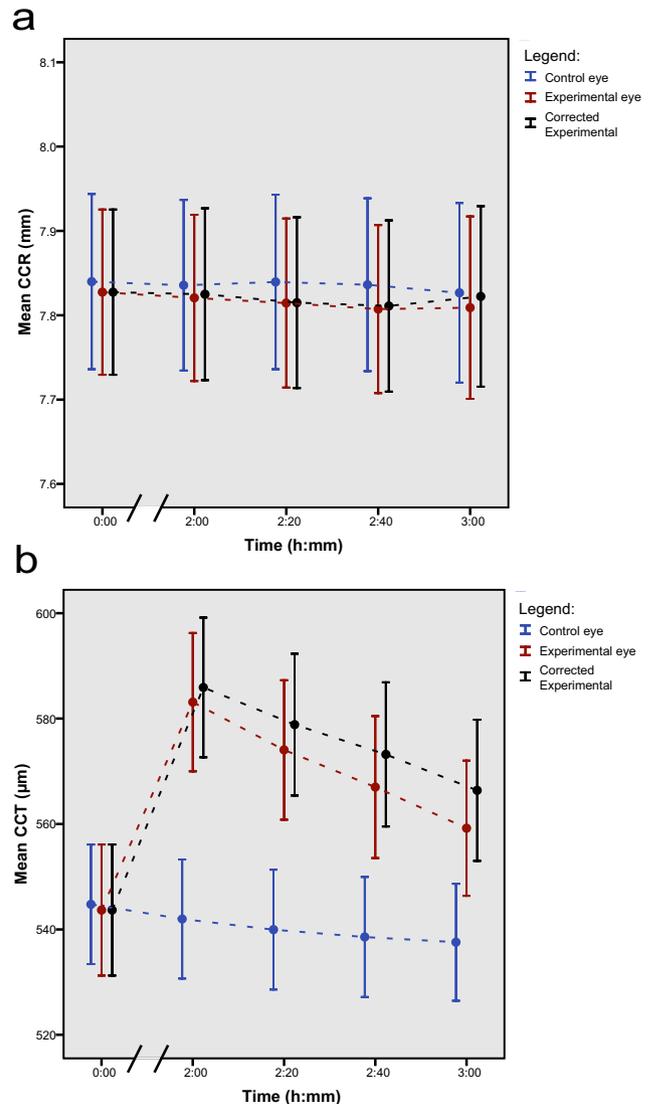**FIGURE 2.** Mean values for (**a**) CCR and (**b**) CCT at each measurement time. Error bars, ±2 SE of the mean.
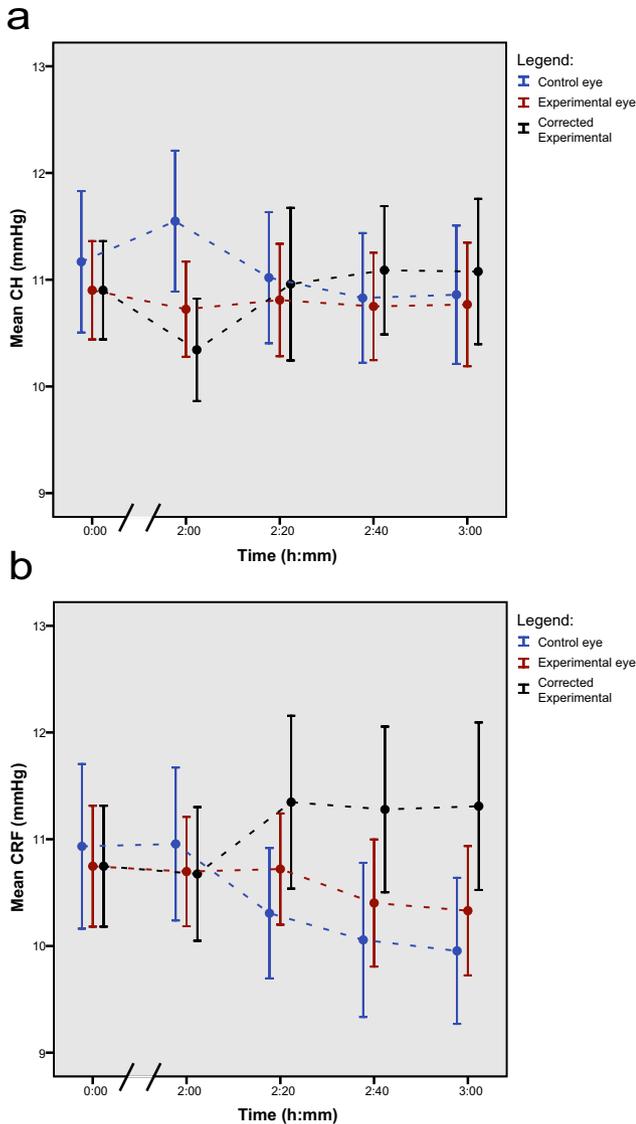
a

b

FIGURE 3. Mean values for (**a**) CH and (**b**) CRF at each measurement time. Error bars, ± 2 SE of the mean.

for control and experimental eyes were -17.9 and -4.1 compared with the null model AICc values of 265.7 and 222.7, respectively.

TABLE 2. Exploratory LMM Assessing the between-Eye Difference in the Predictors of ΔGAT, with CH and CRF Evaluated Separately in Models 1 and 2

Predictor*	Model 1	Model 2
Eye$\times\Delta$CCT	0.435	0.314
Eye$\times\Delta$CH (model 1 only)	0.310	—
Eye$\times\Delta$CRF (model 2 only)	—	**0.003**

* Eye as a predictor refers to experimental versus control eyes.
† Predictors essential for model; *P*-values unimportant.

DISCUSSION

Means

The asymmetric trends observed were attributed to the monocular closed-eye contact lens wear. This interpretation assumes that symmetrical behavior would have occurred in the absence of the experimental intervention.

The experimental increase in CCT is readily explained by hypoxia-induced stromal swelling caused by low-oxygen-transmissible contact lens wear.[36–38] In contrast, the lack of an experimental response in the anterior CCR is consistent with corneal swelling in the posterior direction only.[39,40]

Each corrected IOP estimate was elevated after contact lens wear. Because the experimental intervention is not believed to affect the true IOP, these elevations are attributed to corneal changes causing tonometric overestimation.[16–19] GAT, ORAg, and ORAcc behaved similarly over time (RMANOVA two-way interaction; $P > 0.05$). ORAcc readings therefore cannot be accurate in eyes with swollen corneas. This finding is consistent with previous work.[17]

The maximum GAT overestimation of 1.4 (0.4) mm Hg is in agreement with previous work. Hamilton et al.[16,18,19] found respective GAT overestimations of 2.7 (1.6), 2.8 (2.2), 1.3 (3.0), and 1.5 (2.8) mm Hg with 10.0%, 7.4%, 7.8%, and 8.9% corneal swelling, whereas Lu et al.[17] detected ORAg and ORAcc elevations of 1.5 and 1.4 mm Hg, respectively, with 13.1% corneal edema. In contrast, Oh et al.[20] reported a null result; however, this finding is probably explained by the much lower corneal swelling induced (3.9%).

The peak GAT overestimation did not coincide with the greatest amount of corneal swelling. This finding is supported by the literature. Corneal edema on the order of hundreds of micrometers, such as seen postmortem or with a pathologic source, causes a substantial tonometric underestimation.[13–15] In contrast, 7.4% to 13.1% corneal swelling has been observed to cause IOP overestimation.[16–19] Therefore, the relationship

TABLE 1. Corrected Means for the Experimental Eye*

Time (h:min)	Intraocular Pressure†			Corneal Geometry		ORA Corneal Parameters†	
	GAT (mm Hg)	ORAg (mm Hg)	ORAcc (mm Hg)	CCR (mm)	CCT (μm)	CH (mm Hg)	CRF (mm Hg)
0:00	16.4 (2.3)	15.2 (2.4)	15.2 (2.1)	7.83 (0.24)	543.7 (30.1)	10.9 (1.1)	10.7 (1.3)
2:00	17.0 (3.0)	**16.6 (3.2)**	17.0 (2.8)	7.82 (0.25)	**585.9 (32.1)**	**10.3 (1.1)**	10.7 (1.5)
2:20	**17.8 (2.9)**	**17.0 (3.4)**	16.7 (3.1)	7.81 (0.25)	**578.9 (32.6)**	11.0 (1.7)	**11.3 (1.9)**
2:40	17.2 (3.3)	16.4 (3.8)	16.0 (3.3)	7.81 (0.25)	**573.2 (33.1)**	11.1 (1.4)	11.3 (1.8)
3:00	16.9 (3.0)	**16.6 (3.3)**	16.2 (3.0)	7.82 (0.26)	**566.4 (32.4)**	11.1 (1.6)	**11.3 (1.9)**
P‡	**0.043**	**0.037**	**0.046**	0.279	**<0.001**	**0.010**	**0.006**

Data are the mean (SD).
* Bold data are significantly different compared to their corresponding baseline means (pair-wise contrast, $P < 0.05$).
† The profiles observed for the IOP estimates were similar; however, the trend for CH variation over time was different from that for CRF (repeated-measures ANOVA two-way interaction, $\alpha = 0.05$).
‡ Repeated-measures ANOVA.

TABLE 3. LMM Interactions Assessing the between-Eye Difference of ΔCCT in Predicting ΔCH and ΔCRF

Predictor*	Outcome	
	ΔCH	ΔCRF
Eye×ΔCCT	<0.001	0.003

* Eye as a predictor refers to experimental vs. control eyes.

between the tonometric error and corneal hydration must be nonlinear (Fig. 4).

A stationary point was not detected in published studies involving periodic tonometry, because the contralateral eye was not used as a control.[17,19] If only the uncorrected data from the present study were considered, the maximum GAT in the right eye would have apparently occurred at time 2:00 (Fig. 1).

CH and CRF showed dissimilar experimental responses (RMANOVA two-way interaction, $P < 0.05$). Possible reasons for this result are discussed in relation to their covariation with other measured parameters in the after subsections. Immediately after lens wear, CH was reduced by 0.6 (0.2) mm Hg before returning to baseline. The only other study involving ORA measurements and induced corneal edema found no change in CH with up to 13.1% corneal swelling[17]; however, measurements were taken on the lens-wearing eye only. Again, the experimental changes in CH were only statistically significant in the present study if controlled for fluctuations in the control eye (Fig. 3). In contrast, CRF was elevated by a maximum 0.6 (0.3) mm Hg. This maximum did not occur concur-
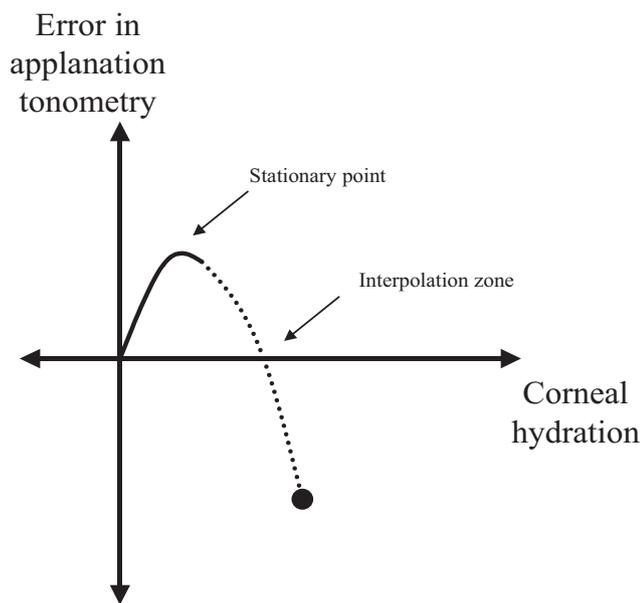

FIGURE 4. The postulated relationship between corneal hydration and tonometric error (not to scale). Let the origin represent 0 hydration-related error for the normally hydrated cornea; small amounts of swelling result in tonometric overestimation. Grossly edematous corneas cause underestimation errors (●), and hence the interpolation zone (*dotted line*) can be inferred. Note that the extent of underestimation may be limited by the true IOP (not shown). The stationary point corresponds to the maximum overestimation, which occurred between 5.4% and 7.8% swelling in this study. There is little or no data on the accuracy of applanation tonometry in eyes with slightly dehydrated corneas; hence, the function is not extrapolated to the left of the ordinate.

rently with the greatest amount of corneal swelling; the trends for CCT and CRF over time were also dissimilar. Lu et al.[17] also found a rise of 0.6 mm Hg; however, it occurred immediately after lens removal and was followed by a gradual decrease, which was not observed in the present study. The use of uncorrected data and the substantially greater amount of corneal swelling (13.1%) reported by Lu et al.[17] are likely contributors to the differences in the results between studies.

Predictors of ΔGAT

ΔCRF was statistically significant in experimental eyes only (0.85 [0.23] mm Hg ΔGAT/mm Hg ΔCRF; $P < 0.001$). To our knowledge, no other studies have examined the role of ΔCRF in predicting GAT errors induced by corneal swelling. However, a weak relationship between ΔGAT and ΔCRF is suggested by the modest improvement in model fit (ΔAICc = −10.8), and their relatively dissimilar mean profiles (Table 1).

CRF is intended to quantify corneal viscoelastic resistance,[22] which should be related to the thickness and material stiffness of the cornea. However, corneal biomechanical properties such as E were not considered in its derivation.[22] Thus, the theoretical basis for CRF to extract information on overall corneal rigidity from the bidirectional applanation process of the ORA[21] is not entirely specific. In fact, the ability for such information to be obtained using NCT has not been proven. Therefore, ΔCRF being at least a weak predictor of ΔGAT in this study is an important finding, because it supports the description of CRF. The GAT overestimation was essentially a physical response suggesting increased corneal rigidity, which covaried modestly with corneal resistance or CRF. However, the minor effect size of this relationship (ΔAICc = −10.8) indicates that CRF may not precisely represent corneal rigidity, which may be a limitation arising from the NCT method.

The similar coefficient between eyes for ΔCCT indicates that the level of corneal swelling cannot predict the GAT error. In other words, ΔCCT is not related to the change in corneal rigidity, unlike ΔGAT and ΔCRF. The association between corneal thickening and tonometric error has been previously studied; however, comparison with the literature is difficult because the earlier data analyses were not robust. For instance, Hamilton et al.[18] reported that the GAT overestimation correlated with the CCT increase ($r = 0.500$ and 0.399 for two different contact lenses; both $P < 0.05$). However, data from the control eyes were inappropriately included in their analysis. The resulting issues include violation of independence and heteroscedastic data, which were apparent in the scatterplots that they presented. If the data are reanalyzed using experimental eyes only, respective correlations of $r = -0.032$ and -0.197 (both $P > 0.05$) are obtained. Lu et al.[17] described significant associations for both ORAg and ORAcc with corneal swelling ($r = 0.32$ and 0.29, respectively) using least-squares regression, which does not account for the violation of independence in their analysis. Hamilton and colleagues[19] correctly identified LMM as an appropriate statistical method for a repeated measures design; however, they erroneously applied general linear model statistics. The error is evidenced by their regression equations containing fixed factors only, and their model fits being based on the usual variance-explained approach of least-squares regression. They reported a statistically significant correlation between ΔGAT and ΔCCT of 0.84, which is extremely inconsistent with the effect sizes quoted above.

The independence of ΔGAT and ΔCCT in the present work is not necessarily inconsistent with the postulated nonlinear relationship between the increase in corneal hydration and tonometric error (Fig. 4). For relatively low amounts of corneal swelling, this diagram suggests that a linear correlation be-

tween ΔGAT and increases in corneal hydration may exist; however, CCT was measured rather than the actual corneal water content. Although corneal thickening is a widely accepted surrogate for increases in corneal hydration, it may not have been specific enough to yield a statistically significant effect.

To our knowledge, the effects of corneal hysteretic behavior or viscoelasticity on GAT accuracy have not been studied, nor has the relationship between CH and corneal hydration–related GAT error. It is difficult to infer whether the inability of ΔCH to predict ΔGAT supports or refutes the validity of CH.

Corneal Geometric Predictors of ΔCH and ΔCRF

In the control eyes, small to moderate associations between ΔCCT and ΔCH (0.58 [0.14] mm Hg ΔCH/10 μm ΔCCT; $P <$ 0.001; ΔAICc = −12.0) and ΔCCT with ΔCRF (0.72 [0.15] mm Hg ΔCRF/10 μm ΔCCT; $P <$ 0.001; ΔAICc = −17.9) were observed. These relationships were weakened in swollen corneas (Eye×ΔCCT interaction for outcome variables ΔCH and ΔCRF; $P <$ 0.001 and $P =$ 0.003, respectively), which supports the description of CH and CRF as corneal parameters. This interpretation assumes that the role of CCT as an indicator of corneal biomechanical behavior is different in normally hydrated and edematous corneas, as discussed below.

CRF was developed to have a strong correlation with baseline CCT[22]; however, the attenuation of their experimental relationship (0.14 [0.05] mm Hg ΔCRF/10 μm ΔCCT; $P =$ 0.010; ΔAICc = −4.1) indicates that it is not simply CCT per se that is related to CRF. Concomitant biomechanical changes present with corneal swelling also require consideration and are most likely responsible for the ΔCCT coefficient difference between eyes. The lower coefficient and reduced model fit in swollen corneas suggest that variation in other factors such as corneal E may have better predicted ΔCRF. Essentially, ΔCRF was influenced by corneal swelling and was able to partially predict the induced GAT error (0.85 [0.23] mm Hg ΔGAT/mm Hg ΔCRF; $P <$ 0.001 in experimental eyes; ΔAICc = −10.8), which infers that CRF does quantify corneal rigidity to some extent. This study therefore provides experimental evidence to help clinicians interpret CRF readings.

ΔCH could not be predicted by ΔCCT in experimental eyes (0.00 [0.01] mm Hg ΔCH/10 μm ΔCCT; $P =$ 0.366), which is consistent with results in a previous contact lens study.[17] How this finding relates to the validity of CH as a measure of viscoelasticity is unclear, because there are few data on how the corneal hysteretic response varies with stromal hydration. In theory, the hysteresis may decrease with small amounts of corneal swelling as stromal fibril spacing increases slightly, whereas collagen cross-link damage associated with high levels of edema may elevate hysteresis (Elsheikh A, personal communication, 2010). This theory suggests a nonlinear association between hydration and viscoelasticity, but a linear relationship in the present study could have been observed because maximum corneal swelling was relatively low (7.8%). Changes in corneal material properties associated with corneal swelling (which may or may not necessarily relate to viscoelasticity) most likely account for the disruption in the usual correlation between ΔCH and ΔCCT. However, CH does not appear to usefully quantify these hydration-induced effects.

Study Limitations

The tonometric error was calculated as the difference from baseline because manometry to determine the true IOP was too invasive to be performed. Other tonometers such as the Pascal dynamic contour tonometer (DCT), which may be less affected by the cornea,[41–43] were not used because of the finite time needed to perform the measurement sequence.

Nevertheless, it is unclear whether DCT IOP estimates are affected by corneal swelling. Hamilton et al.[16] reported an underestimation of −0.7 (1.1) mm Hg ($P <$ 0.001) with 8.9% swelling, but this value should be viewed with caution, given that its interaction with the relatively similar control eye changes (−0.3 [0.9] mm Hg; $P =$ 0.085) was not reported. In other words, the lens wearing and control eyes may have had a statistically identical DCT change.

In theory, ultrasonic pachymetry may be inaccurate in swollen corneas, because the speed of sound through the cornea varies with its hydration.[44] However, the results and conclusions of this study should be unaffected, given that recent work predicts that 20% edema is necessary to cause an overestimation of 7 μm in CCT.[44]

The ORA corneal parameters could not be compared to corneal biomechanical properties such as E. Determination of the latter cannot be performed in vivo due to limitations in technology. Other novel approaches, such as holographic interferometry,[45] dynamic corneal imaging,[46] or ultrasound methods,[47–49] were not used because they are not widely used or commercially available.

The behavior of the ORA corneal parameters in response to corneal swelling in the present work may not be applicable to cases of ocular pathology, and thus the present study provides a useful reference. Corneal swelling in this study caused the mean values of CH and CRF to deviate in opposite directions and weakened their usual positive correlations with CCT. In contrast, both mean CH and CRF were both reduced and at least showed a trend to correlate negatively with CCT in eyes with 12.6% corneal edema caused by Fuchs' dystrophy.[50] Although these dissimilar results may be due to differences in the level of corneal swelling, it is more likely that incomparable changes to the stromal microstructure determining biomechanical behavior occurred. In particular, the chronic nature of corneal edema in Fuchs' dystrophy may have caused biomechanical effects which would not be present with the acute induction and resolution of contact lens–related corneal swelling. Diabetes is another condition associated with poor corneal hydration control.[51] There is disagreement on whether CH and CRF are elevated or reduced in diabetics, including on whether these parameters are affected similarly or not.[52–54] It is difficult to relate these findings with the present study, because of several factors including the degree of swelling, its duration and level of diabetic stromal cross-linking, plus their possible interactions.

Future Work

Although corneal swelling appears to affect GAT in young and more elderly adults in a similar way,[18,19] it is unclear whether the ORA would provide similar results between these age groups. However, a more relevant direction for future work could be to investigate how corneal swelling affects tonometry in patients with ocular hypertension, glaucoma, and suspected glaucoma. Although the maximum GAT increase averaged only 1.4 mm Hg in this study, greater overestimations of up to 2.8 mm Hg have been observed in healthy eyes.[18] Given that the tonometric error caused by the variation in CCT may be more than twice as great in glaucomatous than in normal eyes,[2] it is possible that the same may apply to corneal hydration–related GAT errors. The implications of this possibility would be clinically significant for glaucoma patients, particularly those with conditions such as Fuchs' dystrophy.

Characterization of the probable nonlinear relationship between corneal swelling and the related GAT error would also be of particular interest (Fig. 4). Future studies may therefore be designed for a greater maximum and range of swelling. ORA measurements should be included to assess the association of

ΔCRF with the GAT error over the larger range of corneal swelling; a significant covariation would further support the validity of CRF. Care should be exercised when inducing high levels of corneal edema. Possibly irreversible microstructural damage such as lamellar disorganization has been observed in grossly edematous corneas,[55,56] and there are few data to suggest a safe cutoff point. It may be preferable to conduct an ex vivo investigation, which has the advantage that manometry can be performed.

Conclusions

The overestimation in applanation tonometry caused by small amounts of corneal swelling cannot be predicted by the increase in CCT. The GAT error represents an overall increase in corneal rigidity associated with an elevation in corneal hydration, which is partially characterized by CRF. In contrast, CH does not appear to usefully quantify biomechanical changes induced by corneal swelling. GAT, ORAg, and ORAcc are influenced by corneal swelling to a similar degree.

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