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An Ultra-High-Speed Scheimpflug Camera for Evaluation of Corneal Deformation Response and Its Impact on IOP Measurement

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PURPOSE. To investigate the test-retest variability of and factors associated with the corneal deformation response, and evaluate its impact on IOP measurement.

METHODS. Forty normal and 140 glaucoma suspect/glaucomatous eyes of 104 individuals were prospectively included for repeated measurements of corneal deformation response by an ultra-high-speed Scheimpflug camera, followed by corneal hysteresis and corneal resistance factor measurements by the ocular response analyzer, and dynamic contour tonometry (DCT) (the reference standard) and Goldmann applanation tonometry (GAT) during the same visit. The test-retest variability of corneal deformation response was evaluated. Univariate and multivariate linear mixed models were used to identify factors (age, manifest spherical refractive error, axial length, IOP, central corneal thickness [CCT], corneal curvature, corneal hysteresis, and corneal resistance factor) associated with corneal deformation response and the difference between DCT and GAT measurements.

RESULTS. Corneal deformation amplitude (CDA) had an intraclass correlation coefficient of 0.86. There was no difference in CDA between the glaucoma and nonglaucoma groups. A higher IOP, a younger age, and a greater CCT were associated with a smaller CDA (P ≤ 0.002) (n = 180). In the univariate analysis (n = 180), the difference between DCT and GAT measurements was associated with spherical refractive error (P = 0.037), CCT (P = 0.004), and CDA (P < 0.001) after adjusting the effect of IOP (DCT). In the multivariate analysis, the only factor associated with the IOP difference was CDA (P = 0.003).

CONCLUSIONS. CDA was a reliable indicator to quantify corneal deformation response. CDA, rather than CCT, was the key source of measurement error of GAT.

Keywords: ultra-high-speed Scheimpflug camera, intraocular pressure, corneal deformation response

Goldmann applanation tonometry (GAT) is the reference standard for measurement of IOP in clinical practice and clinical trials.1 Although GAT overestimates IOP in healthy eyes with thick corneas and underestimates IOP in healthy eyes with thin corneas, the corneal biomechanical response has been suggested to be more influential than central corneal thickness (CCT) in measuring IOP.2 In a mathematical simulation model, Liu and Roberts2 examined the association between IOP and corneal parameters, including CCT, corneal curvature, and corneal elasticity. They showed that normal variation of CCT (443–629 μm) contributed to a difference of only 2.87 mm Hg of predicted GAT IOP measurements. By contrast, variation of corneal elasticity, measured in Young’s modulus with an estimated normal range between 0.1 and 0.9 MPa, accounted for a difference of 17.26 mm Hg. This is supported by an experimental study by Dupps and colleagues3 using sonic wave propagation velocity on the corneal surface as a measure of corneal stiffness. They showed that corneal stiffening after cross-linking in two human globes resulted in a dramatic increase in IOP measured by pneumotonometer (Mentor O&O, Inc., Norwell, MA) and TonoPen (Medtronic Solan, Jacksonville, FL) despite a relatively low intravitreal pressure. These studies indicated that the biomechanical properties of the cornea are more important than CCT in determining GAT measurement.

Clinical investigation of the stress and strain response of the cornea has been obfuscated by the lack of instrumentation to capture the dynamic behavior of the cornea. Although the ocular response analyzer (ORA) (Reichert, Inc., Depew, NY) provides a measure of corneal hysteresis and corneal resistance factor,4 direct measurement of the corneal dynamics, such as the displacement of the cornea (strain) in response to an external pressure (load) has not been attainable in vivo. The recent introduction of an ultra-high-speed Scheimpflug imaging device (Corvis ST; Oculus, Arlington, WA) has allowed visualization and measurement of corneal deformation response to a standardized air-puff pressure. The instrument captures the corneal deformation response at a rate of 4330 image frames per second. With frame-by-frame analysis of the corneal images, parameters, including corneal deformation amplitude, corneal applanation length, and corneal velocity, can be quantified and analyzed, providing insights into the biomechanical properties of the cornea. Using the ultra-high-speed Scheimpflug camera, we evaluated the test-retest repeatability of the parameters describing the corneal defor-
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MOTION RESPONSE: Identified factors determining the corneal deformation response, and investigated the impact of corneal deformation response on GAT IOP measurement.

METHODS

Subjects

One hundred eighty eyes, including 40 normal, 39 glaucoma suspect, and 101 glaucomatous eyes of 104 individuals were prospectively examined at the University Eye Center, the Chinese University of Hong Kong. They underwent a complete ophthalmic assessment, including visual acuity, manifest autorefraction, axial length, corneal curvature, CCT measurement, and fundus examination. All subjects had visual acuity of at least 20/40, manifest spherical error within the range of -4.00 and -8.00 diopters, and with no clinical evidence of ocular disease other than mild cataract and/or glaucoma. Subjects with corneal refractive surgery were excluded. Glaucoma patients had narrowing of the neuroretinal rim and/or thinning of the retinal nerve fiber layer (RNFL) evident in clinical examination with corresponding visual field defects (described below). Glaucoma suspects had either a history of IOP of 22 mm Hg or higher during three separate visits or evidence of narrowing of the neuroretinal rim and/or thinning of the RNFL but without visual field defects. Healthy subjects had no record of GAT IOP of 22 mm Hg or higher, and no evidence of glaucomatous optic disc or visual field changes. All participants had repeated corneal deformation response measurements by Corvis ST (Oculus), and corneal hysteresis and corneal resistance factor measurements by ORA (Reichert, Inc.). This was followed by dynamic contour tonometry (DCT, Pascal; Swiss Microtechnology AG, Port, Switzerland) and GAT during the same visit. The study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki with approval obtained from the local ethics committee. Informed consent was obtained from all participants.

Measurement of Corneal Deformation Response

The Corvis ST (Oculus) is an ultra-high-speed Scheimpflug camera imaging the corneal deformation response to a symmetrically metered air puff (size: 3.06 mm; pressure: 60 mm Hg) at a rate of 4330 image frames per second covering a horizontal distance of 8 mm. A total of approximately 140 images of the cornea on one two-dimensional cross-section were collected over a constant metered collimated air puff for 30 ms. By tracing the anterior and posterior corneal boundaries at individual image frames, parameters describing the corneal deformation response were automatically measured by the built-in software. These include (1) corneal deformation amplitude; (2) inward and (3) outward corneal applanation lengths; and (4) inward and (5) outward corneal velocities at the time of applanation (the study was conducted at a time when the Corvis ST was not capable of analyzing “corneal curvature at the maximum deformation” and “peak distance”). Although the Corvis ST also measured the IOP and CCT, we used only DCT and GAT for measurement of IOP, and ultrasound pachymetry for measurement of CCT. Corneal deformation amplitude was the maximum displacement of the corneal apex in response to the air puff (Fig. 1C). The inward and outward applanation lengths represented the distance of the cornea flattened by the air puff at the time of inward and outward applanation, respectively (Figs. 1B, 1D). The Corvis ST recorded the movement of the cornea at high temporal resolution and the velocity was calculated by tracking the corneal displacement with time. All participants had two consecutive measurements for each eye during the same visit.

Measurement of IOP

The systolic IOP was recorded for both GAT and DCT. The systolic diastolic IOP variation can be estimated from the GAT by observing the relative movement of the upper and lower semicircular rings during the pulsation. The systolic IOP was obtained when the force of applanation was adjusted so that the rings did not cross each other and the diastolic pulsation rested on the touching of the inner rings. The working principle of DCT has been described. In brief, the matching of the contour of the tonometer and the contour of the cornea allows the IOP to be measured by a pressure sensor located at the tip of the tonometer. In this study, the recording duration of each measurement was approximately 5 seconds. Measurement with a quality score higher than 3 (scale 1–5) was repeated until two measurements of quality score of 3 or lower (as recommended by the manufacturer) were obtained in each eye. Likewise, two consecutive IOP measurements were obtained with GAT. For both DCT and GAT, if the difference between the first and second readings were greater than 2 mm Hg, a third measurement would be obtained, and the average of two measurements was calculated.

Measurement of Corneal Hysteresis and Corneal Resistance Factor

Each ORA measurement generates a signal profile with 2 distinct peaks corresponding to the first (P1) and second (P2) applanation pressures. A quality score was provided by the instrument with reference to the signal profile. Only measurements with a quality score (waveform score) greater than 4 were included. Four parameters were derived from each ORA signal profile: (1) corneal compensated IOP, (2) Goldmann-correlated IOP, (3) corneal hysteresis, and (4) corneal resistance factor. Corneal hysteresis is an indicator of viscous dampening effect of the cornea and corneal resistance factor is an indicator of the overall resistance of the cornea. These parameters are derived from the difference between the 2 applanation pressures using the formula P1 – kP2 + c, where P1 and P2 are the first and second applanation pressures, respectively, and k and c are constants. Only corneal hysteresis and corneal resistance factor were analyzed in the study.

Visual Field Testing

The diagnostic groups were defined with reference to visual field results. Standard visual field testing was performed using static automated white-on-white threshold perimetry (SITA Standard 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec, Dublin, CA). A visual field was defined as reliable when fixation losses, and false-positive and false-negative rates were less than 20%. Only reliable tests were included in the analysis. A visual field defect was defined as having three or more significant (P < 0.05) nonedge contiguous points with at least one at the P less than 0.01 on the same side of horizontal meridian in the pattern deviation plot. Further, it had to be classified as outside normal limits in the glaucoma hemifield test and confirmed with at least two consecutive visual field tests.

Statistics

Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX). Test-retest variability was quantified with
FIGURE 1. Serial images of the cornea captured by an ultra-high-speed Scheimpflug camera at 0.000 ms (A), 7.623 ms (B), 18.018 ms (C), 22.407 ms (D), and 32.109 ms (E) after a symmetrically metered air puff (size: 3.06 mm; pressure: 60 mm Hg) was ejected. The inward and outward corneal applanations are indicated in (B) and (D).
repeatability coefficient (RC), coefficient of variation (CV), and intraclass correlation coefficient (ICC). RC, defined as “2.77 times within subject standard deviation (Sw),” is an estimated average of measurement variability in a population. The Sw is the square root of the within-subject mean square of error (the unbiased estimator of the component of variance due to random error) in a one-way random effects model. The sample size required for a repeatability study depends on the estimated confidence interval of Sw (1.96/√[2n(m − 1)]), where n is the number of subjects and m is the number of observations. Depending on the stringency for accuracy, the confidence interval is usually set as 10% to 20% either side of Sw. With a sample size of 180 eyes with two observations in each eye, the confidence interval was estimated at 12.7%. Coefficient of variation (CVw) was defined as 100 × Sw/overall mean. ICC was interpreted as follows: less than 0.75 represents poor to moderate reliability; 0.75 to 0.90 represents good reliability; greater than 0.90 represents excellent reliability for clinical measures. Univariate and multivariate linear mixed models were used to investigate the associations between corneal deformation amplitude (the average of two measurements during the same visit was analyzed) and each of the following: age, spherical error, axial length, DCT, CCT, corneal curvature, corneal hysteresis, corneal resistance factor, use of topical IOP-lowering medication, use of topical prostaglandin analogue, and diagnosis (normal, glaucoma suspect, glaucoma). Likewise, factors associated with the difference in DCT and GAT measurements were examined with univariate and multivariate linear mixed models. P less than 0.05 was considered statistically significant.

**RESULTS**

The mean (SD) and the range of age, spherical error, axial length, DCT IOP, GAT IOP, CCT, corneal curvature, corneal hysteresis, corneal resistance factor, and corneal deformation response measurements are shown in Table 1. Except for IOP measurements (P = 0.004), there were no significant differences between the normal and glaucoma suspect/glaucoma groups (P ≥ 0.064, linear mixed modeling with adjustment of correlation between fellow eyes).

**Test–Retest Variability of Corneal Deformation Measurements**

The test–retest variability of corneal deformation amplitude was low and the RC, CV, and ICC were 0.13 mm (95% confidence interval [CI]: 0.12–0.14 mm), 4.29% (95% CI: 3.85%–4.73%), and 0.86 (95% CI: 0.82–0.89), respectively (Table 2). However, the inward and outward corneal applanation lengths and corneal velocities had high test–retest variabilities. The values of ICC were less than 0.60 and the CVs were greater than 10%. For this reason, in the analyses of determinants of corneal deformation response and its impact on IOP measurement, we included only corneal deformation amplitude.

**Determinants of Corneal Deformation Amplitude**

In the univariate analysis, corneal deformation amplitude was significantly associated with IOP (DCT), CCT, and age (all with P ≤ 0.006) (Table 3). Spherical error, axial length, corneal curvature, corneal hysteresis, corneal resistance factor, use of topical IOP-lowering medication(s), and diagnosis (normal, glaucoma suspect, glaucoma) were not associated with corneal deformation amplitude (P ≥ 0.116). Multivariate analysis revealed that a higher IOP a younger age, and a greater CCT were associated with a smaller corneal deformation amplitude (all with P ≤ 0.002). Figure 2 illustrates the dynamic corneal response in an eye with a high IOP and an eye with a low IOP. The movie captures are shown in Supplementary Movies S1 and S2.

**Impact of Corneal Deformation Amplitude on IOP Measurement**

DCT measures IOP largely independent of CCT and corneal biomechanical properties and closely approximates the true IOP. Using DCT IOP as a reference standard, the difference between DCT and GAT measurements increased with increasing IOP (P < 0.001) (Fig. 3). After adjusting the effect of IOP (DCT), the IOP difference (DCT − GAT) was significantly associated with spherical error (P = 0.037, R2 = 0.295), CCT (P = 0.004, R2 = 0.509), and corneal deformation amplitude (P <
Table 2. RC, CV, and ICC of Corneal Deformation Response Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RC</th>
<th>CV (%)</th>
<th>ICC</th>
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<tbody>
<tr>
<td>Corneal deformation amplitude, mm</td>
<td>0.13</td>
<td>4.29 (3.85–4.73)</td>
<td>0.86 (0.82–0.89)</td>
</tr>
<tr>
<td>Inward corneal applanation length, mm</td>
<td>0.74 (0.67–0.82)</td>
<td>15.36 (13.77–16.95)</td>
<td>0.01 (–0.14–0.15)</td>
</tr>
<tr>
<td>Outward corneal applanation length, mm</td>
<td>1.21 (1.08–1.33)</td>
<td>23.19 (20.79–25.58)</td>
<td>–0.05 (–0.19–0.10)</td>
</tr>
<tr>
<td>Inward corneal velocity, m/s</td>
<td>0.08 (0.07–0.09)</td>
<td>22.84 (20.48–25.20)</td>
<td>0.17 (0.03–0.31)</td>
</tr>
<tr>
<td>Outward corneal velocity, m/s</td>
<td>0.16 (0.14–0.17)</td>
<td>–17.11 (–15.35 to –18.88)</td>
<td>0.59 (0.49–0.68)</td>
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The Corvis ST ultra-high-speed Scheimpflug camera is a new technology to evaluate the dynamic corneal biomechanical response. Investigating its measurement variability is of fundamental importance. It is notable that although corneal deformation amplitude can thus provide insights into the biomechanical property of the cornea and its impact on IOP measurement, corneal deformation amplitude had the highest repeatability (ICC = 0.86), which was followed by outward corneal velocity (ICC = 0.59). Inward corneal velocity and inward/outward corneal applanation lengths had poor repeatabilities (ICC ranged between –0.05 and 0.17). Such disparity can be explained by the differences in clarity and definitiveness of the landmarks used in the measurements. The well-defined corneal apex is used for measurement of the corneal deformation amplitude (Fig. 1C). However, determining the ends of the flattest portion of the cornea for measurement of corneal applanation length could be less consistent (Figs. 1B, 1D). Microsaccadic eye movement may add variations to the measurement of corneal velocity analyzed in a relatively short time frame (30 ms).

We showed that corneal deformation amplitude was negatively associated with IOP (Table 3). A higher IOP renders the cornea less likely to deform in response to stress (Fig. 2). Of note, the association between corneal biomechanical response and IOP has been previously reported in porcine and human eyes ex vivo. Examining 17 porcine eyes under inflation conditions, Bao and colleagues measured the corneal deformation with a laser displacement sensor, estimated Young’s modulus of the cornea, and found a linear relationship between Young’s modulus and IOP. Elsheikh and colleagues measured the corneal stiffness (expressed in Young’s modulus) in 37 human donor corneas using inflation tests and demonstrated that there was a positive linear relationship between Young’s modulus and IOP. These ex vivo studies signify that the cornea is less likely to deform when the IOP is high. The implication is that corneal deformation amplitude should always be interpreted with reference to the level of IOP. After adjusting the effect of IOP in the multivariate model, CCT and age were also associated with corneal deformation amplitude (Table 3). Although it is conceivable that the cornea would deform less in eyes with a greater CCT, the positive association between age and corneal deformation amplitude is unexpected. Previous ex vivo studies suggest that
corneal stiffness increases with age. Notably, these studies examined corneoscleral buttons only, and the measurement of pressure deformation response may not reflect the actual corneal biomechanical response in an intact globe. Although there was no significant difference in age between the glaucoma and normal groups (Table 1), glaucomatous eyes may exhibit different corneal biomechanical properties compared with normal eyes, confounding the analysis between corneal deformation amplitude and age. More investigation is needed to validate the present finding.

CCT impacts Goldmann applanation tonometry. Although a number of correction formulas have been proposed to adjust
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GAT IOP readings with reference to CCT, such adjustment is not recommended in clinical practice. In fact, adjusting GAT IOP using CCT-based correction formula results in poorer agreement with DCT IOP compared with unadjusted GAT IOP. CCT-based correction formulas are not applicable to individual corneas because factors other than CCT can influence IOP measurement. In this study, in addition to CCT, corneal deformation amplitude was a significant factor accounting for the difference between GAT and DCT IOP measurements. In fact, corneal deformation response is more instrumental than CCT in determining the IOP measurement obtained with GAT. This is supported by the finding that although CCT was associated with the difference between DCT and GAT measurements, it became insignificant in the multivariate model when corneal deformation amplitude was also included (Table 4). The relative impact of corneal deformation amplitude and CCT on GAT IOP measurement can also be inferred from the respective univariate analyses (Table 4). With a range of CCT between 425 and 637 μm (Table 1), the estimated variation in IOP is 2.65 mm Hg (0.0125 \( \times \) 210). By contrast, with a range of corneal deformation amplitude between 0.790 and 1.795 mm, the estimated variation in IOP is 2.65 mm Hg (0.0125 \( \times \) 210). This observation supports the mathematical simulation study by Liu and Roberts demonstrating that corneal biomechanical property is more influential than CCT in GAT. Although clinical measurement of corneal elasticity is not yet feasible, corneal deformation amplitude can serve as a useful indicator of corneal biomechanical response. In fact, it is a direct measurement of strain, in response to a fixed load. For a given level of IOP, a smaller corneal deformation response may signify a “stiffer” cornea. Measurement of the corneal deformation amplitude with the ultra-high-speed Scheimpflug camera can contribute to a better understanding of the corneal biomechanical properties. Incorporation of individualized corneal deformation amplitude in GAT may provide a more accurate estimation of IOP.

Corneal deformation amplitude measured by the ultra-high-speed Scheimpflug camera is different from corneal hysteresis measured by the ORA, although both instruments measure the corneal response to a fixed load of air puff. The former directly measures the strain response (displacement, expressed in mm), whereas the latter (expressed in mm Hg) represents the difference between the two peak applanation pressures. Hysteresis is defined by the area bounded by the load-unload displacement curve. Because the ORA does not measure corneal displacement, the biomechanical implication of "corneal hysteresis" reported by the ORA remains ambiguous. In this study, corneal hysteresis and corneal resistance factor were not associated with corneal deformation amplitude, nor accounted for the IOP difference between GAT and DCT (Tables 3, 4).

There are limitations in the measurement of corneal deformation response. Similar to the ORA, the load-unload (pressure) displacement relationship cannot be determined by the Corvis ST. The Corvis ST measures only corneal displacement, but not the corresponding load during the deformation. In other words, direct measurement of corneal elasticity and corneal hysteresis would not be possible with the Corvis ST. As corneal deformation response was significantly related to IOP (Table 3), we investigated only intravisit repeatability, but not intervisit reproducibility. IOP readings likely varied from visit to visit, rendering determination of the variability of corneal deformation responses impractical. To investigate the impact of corneal deformation amplitude on IOP measurement, we maximized the range of IOP in the analysis by including both healthy subjects and glaucoma patients. Notably, there was no significant difference in corneal deformation amplitude between the normal and glaucoma groups even after adjustment of IOP age, and CCT (Table 4). The role of measurement of corneal deformation response in risk assessment of the development and progression of glaucoma requires further investigation. Last, it is worth noting that high-quality standards were imposed on data collection, including IOP, ORA, and Corvis ST measurements. Our finding may not be generalized to other populations.

To summarize, the ultra-high-speed Scheimpflug camera provides a novel approach to quantify the corneal deformation response. The corneal deformation amplitude had a low test-retest variability, associated with age, IOP, and CCT, and was more influential than CCT in GAT measurement. This new measure would be pertinent to evaluating GAT IOP measurement and investigating the biomechanical properties of the cornea.

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**References**


