A Clinical Description of Ocular Response Analyzer Measurements

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PURPOSE. To examine the interrelationships among the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY), Goldmann applanation tonometer (GAT), and corneal geometry measurements in a young, healthy sample.

METHODS. Central corneal radius, ORA, GAT, and central corneal thickness (CCT) measurements were taken in 99 subjects (age, 21 ± 2 years) who were free of ocular and systemic disease.

RESULTS. The mean ± SD corneal hysteresis (CH) and corneal resistance factor (CRF) were 10.4 ± 1.2 and 10.1 ± 1.5 mm Hg, respectively. The Bland-Altman 95% limits of agreement of ORA Goldmann-correlated IOP (ORAg) and ORA corneal-compensated ORAcc were −4.5 to +6.0 and −4.1 to +6.8 mm Hg, respectively. The full equations used by the ORA to calculate ORAcc and CRF were reconstructed. The statistically significant effect of CCT on GAT became redundant if CRF was included in a multivariate regression analysis. Both CH and CRF were associated with CCT ($R^2 = 0.252$ and 0.290, respectively).

CONCLUSIONS. Sample CH and CRF were consistent with those reported in the literature. ORAg and ORAcc agreed poorly without GAT. CRF appears to be at least a partial description of corneal rigidity. The ocular determinants of CH are unclear. (Invest Ophthalmol Vis Sci. 2011;52:2911–2916) DOI: 10.1167/iovs.10-6763

The Goldmann applanation tonometer (GAT) is the reference instrument for clinical measurement of intraocular pressure (IOP).¹ However, its accuracy is affected by the inter-individual variation in corneal geometric properties, such as thickness²–⁵ and curvature.⁶–⁷ Corneal biomechanical properties such as Young’s modulus are also believed to influence GAT readings.⁸–¹² but the traditional methods used to determine these properties (strip extensiometry and membrane inflation) cannot be performed in vivo.

A commercially available clinical instrument called the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY) has been proposed to characterize corneal biomechanical responses using the noncontact tonometry (NCT) process.¹³,¹⁴ An air pulse of increasing force lasting approximately 20 ms is directed onto the eye, causing progressive corneal deformation through a first, inward applanation state (P1) to indentation. A second, outward applanation (P2)

is achieved as the cornea returns to its original shape. Infrared light is used to determine the point of corneal flattening by using the cornea as a mirror, as previously described.¹⁵ The air pulse force is noted at P1 and P2 for use in calculating four parameters, as discussed below.

The ORA reports two corneal parameters termed corneal hysteresis (CH) and corneal resistance factor (CRF).¹⁵,¹⁶ The former is intended to quantify the viscoelastic mechanical damping ability of the cornea, whereas the latter is thought to describe its overall viscoelastic resistance.¹⁵,¹⁶ Neither of these variables can be considered corneal properties, because they are responses that are specific to the ORA measurement process. In contrast, true properties such as thickness and Young’s modulus are ideally invariant to the measurement technique.

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.¹³,¹⁶ However, the definitions and validity of CH, CRF, and ORAcc have not been convincingly demonstrated. The goals of this study were to collect normative ORA data in young normal subjects and to evaluate the descriptions of the ORA parameters based on their intercorrelations and associations with other clinically measured variables.

METHODS

Participants

Volunteers between 18 and 30 years of age 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 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 or a history of ocular surgery, any medications, or full-time soft or any rigid contact lens wear. Part-time 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 absence of closed-eye corneal swelling.¹⁷–¹⁹

To ensure participant 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 field screening (Humphrey Matrix; Carl Zeiss Meditec, North Ryde, NSW, Australia), and undilated ophthalmoscopy.

Protocol

The central corneal radius (CCR) was measured first using the autokeratometer (Eyecheck; Reichert Ophthalmic Instruments). The mean...
sphere of two readings in millimeters was averaged and used for analysis. Corneal biomechanics and the IOP were then estimated by the ORA. Initially, four readings with acceptable signal waveforms were taken, where each ORAg value was to be within 2.4 millimeters of mercury (mm Hg) of their mean. This latter figure was based on an unpublished pilot study performed by the authors. However, the mean of the best three readings was selected for analysis, to avoid inclusion of borderline waveforms, as the evaluation of measurement quality is subjective. Each of the three readings used was to have its ORAg within 2.3 mm Hg of the mean (also based on pilot study data). Additional readings were taken to meet these requirements, if necessary. The cornea was then anesthetized and the tear film stained with 1 drop of 0.5% proxymetacaine hydrochloride (Alcaine; Alcon Laboratories, Bausch & Lomb, North Ryde, NSW, Australia) respectively, before the IOP was measured (Goldmann AT 900; Haag-Streit, Bern, Switzerland). The average of three readings, within ±2 mm Hg of their mean, was used for analysis. Last, the CCT was measured by ultrasonic pachymeter (Pocket II Precision Pachymeter; Quantel Medical, Clermont-Ferrand, France). Three consecutive readings within ±5 μm of their average were taken, and the mean analyzed. Measurements were taken in both eyes in random order; however, only data from the right eyes were analyzed. 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. An assistant recorded GAT results and turned the measurement drum away from the recorded value after each attempt.

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

Statistics

This study was designed to detect a moderate standardized coefficient of 0.3 in a linear regression analysis at 80% power and α of 0.05. G*Power (ver. 3.0.10) was used to calculate the required sample size, which was 82.

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

Parametric means were compared by using repeated-measures analysis of variance (RMANOVA). The Greenhouse-Geisser correction was applied to the degrees of freedom if sphericity was violated.

Table 1. Central Tendency and Spread of the Variables of Interest

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>Intraocular pressure</td>
<td></td>
</tr>
<tr>
<td>GAT, mm Hg</td>
<td>13.9 (2.9)</td>
</tr>
<tr>
<td>ORAg, mm Hg</td>
<td>14.7 (5.2)</td>
</tr>
<tr>
<td>ORAcc, mm Hg</td>
<td>15.3 (2.9)</td>
</tr>
<tr>
<td>Corneal geometry</td>
<td></td>
</tr>
<tr>
<td>CCR, mm</td>
<td>7.80 (0.24)</td>
</tr>
<tr>
<td>CDT, μm</td>
<td>546.0 (29.9)</td>
</tr>
<tr>
<td>Corneal biomechanics</td>
<td></td>
</tr>
<tr>
<td>CH, mm Hg</td>
<td>10.4 (1.2)</td>
</tr>
<tr>
<td>CRF, mm Hg</td>
<td>10.1 (1.5)</td>
</tr>
<tr>
<td>Basic ORA applications</td>
<td></td>
</tr>
<tr>
<td>P1, mm Hg</td>
<td>19.9 (3.3)</td>
</tr>
<tr>
<td>P2, mm Hg</td>
<td>9.5 (3.1)</td>
</tr>
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</table>

Comparison of the IOP Estimates

There was an overall difference in the means of the IOP estimates (RMANOVA, P < 0.001; Table 1, Fig. 1). Planned contrasts indicated that ORAg and ORAcc were significantly greater than GAT by 0.7 [0.3] (P = 0.010) and 1.3 [0.3] mm Hg (P < 0.001), respectively.

With respect to GAT, the Bland-Altman 95% limits of agreement were −4.5 to +6.0 mm Hg and −4.1 to +6.8 mm Hg, respectively, for ORAg and ORAcc (Fig. 2). For both comparisons, the correlation between the difference and mean of the IOP estimates was statistically significant (Pearson r, both P > 0.05).

Calculation of the ORA Parameters

P1 and P2 correlated very strongly (r = 0.951, P < 0.001). With the current data, each ORA parameter could be virtually entirely predicted by P1 and P2, by using linear regres-
sion (\(R^2 \approx 0.999\)). These equations were algebraically rearranged to the form presented by Reichert, and are shown in equations 1 to 4:

The calculation of ORAg from P1 and P2:

\[
\text{ORAg} = \frac{(P1 + P2)}{2} \quad (1)
\]

The calculation of CH from P1 and P2:

\[
\text{CH} = P1 - P2 \quad (2)
\]

The calculation of ORAcc from P1 and P2:

\[
\text{ORAcc} = 1.51(P2 - 0.43 \cdot P1) + 13.82 \quad (3)
\]

The calculation of CRF from P1 and P2:

\[
\text{CRF} = (P1 - 0.70 \cdot P2) - 3.08 \quad (4)
\]

Corneal Effect on Tonometry

The regression models used to describe the variance of the IOP estimates associated with corneal geometry are summarized in Table 2.

If CH was included in each model, its coefficient did not gain statistical significance for outcome variables GAT and ORAg (0.05 [0.28] mm Hg GAT/mm Hg CH, \(P = 0.868\) and -0.05 [0.30] mm Hg ORAg/mm Hg CH, \(P = 0.879\)). For ORAcc, CH was a significant predictor and also caused CCT to gain significance (-1.11 [0.26] mm Hg ORAcc/mm Hg CH, \(P < 0.001\), and 0.29 [0.10] mm Hg ORAcc/10 \(\mu\)m CCT, \(P = 0.006\), respectively). The final model \(R^2\) was 0.185.

CRF was statistically significant when included in each of the models described in Table 2 (1.02 [0.20], 1.69 [0.17] and 0.83 [0.22] mm Hg IOP/mm Hg CRF for the outcome variables GAT, ORAg, and ORAcc, respectively; all \(P < 0.001\)). Where applicable, its inclusion also caused CCR and CCT to lose their significance in each model (all \(P > 0.05\)). The respective \(R^2\) values were 0.266, 0.552, and 0.152.

Corneal Geometry, CH, and CRF

The influence of corneal geometry in determining the ORA corneal biomechanical responses is described in Table 3.

DISCUSSION

Mean CH and CRF

The average CH and CRF were consistent with other normative data. In studies involving at least 100 normal eyes, both mean CH and CRF ranged between 10.0 and 11.0 mm Hg.25–30 These citations also report the SD for CH and CRF to lie between 1.3 and 2.0, and 1.5 and 2.0 mm Hg, respectively.25–30 Only the seminal paper was an exception, which reported a mean CH of 9.6 mm Hg.14 Slight modifications to the ORA before its public release may account for this discrepancy.

Comparison of the IOP Estimates

The slight overestimation of GAT by both ORA IOP estimates is consistent with studies in normal and glaucomatous eyes that found that ORAg and ORAcc are higher than GAT by up to 3.2 and 3.7 mm Hg, respectively.31–35 although some studies find no mean difference between GAT and both ORA IOP measurements.6,29,36

<table>
<thead>
<tr>
<th>Predictor</th>
<th>CH</th>
<th>CRF</th>
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<tbody>
<tr>
<td>CCR, mm</td>
<td>-0.70 [0.44]</td>
<td>-0.41 [0.54]</td>
</tr>
<tr>
<td>CCT, 10 (\mu)m</td>
<td>0.20 [0.04]</td>
<td>0.27 [0.04]</td>
</tr>
<tr>
<td>Constant</td>
<td>4.9 [3.8]</td>
<td>-1.4 [4.5]</td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.252</td>
<td>0.290</td>
</tr>
</tbody>
</table>

Data are expressed as the coefficient [SE]. Bold type denotes statistically significant \((P < 0.05)\) predictor coefficients.
Both ORAg and ORAcc agreed poorly with GAT, with the latter performing slightly worse. Most other studies on normal\textsuperscript{6,29-32} and glaucoma subjects\textsuperscript{33,35,36} also found the 95\% limits of agreement between the ORA IOP estimates and GAT to span a range of approximately 10 mm Hg or greater. A much lower 95\% range of 6.6 mm Hg was observed in healthy subjects by Oncel et al.\textsuperscript{34}; however, the reasons for these narrower limits are not evident.

Calculation of the ORA Parameters

Equations 1 and 2 confirm that ORAg and CH are calculated as the mean and difference of the ORA applications, respectively.\textsuperscript{14} The equations determining ORAcc and CRF are also linear; however, calibration coefficients that have not been reported are used in their calculation.\textsuperscript{13} These values were determined and presented in equations 3 and 4.

The almost perfect $R^2$ for these equations indicates that each determinant of the calculated ORA parameters, such as IOP, corneal geometry, corneal biomechanical behavior, and possibly other unknown factors must be represented through P1, P2, and constants alone. Luce\textsuperscript{14} claimed that two applications are necessary to separate the IOP and corneal effects. However, this claim is questionable, given that the information contained within P1 and P2 is extremely similar ($R^2 = 0.867$, $P < 0.001$). In fact, the suitability of the NCT process for determining corneal biomechanics and the true IOP has not been demonstrated with reference to traditional biomechanical testing and manometry. Studies inducing pharmacologic changes in IOP\textsuperscript{37} and using finite element analysis\textsuperscript{38} suggest that the calculation of ORAcc, CH, and CRF could at least be improved.

At best, CH and CRF can be only partially valid. CH is a scalar quantity based only on the difference between P1 and P2, whereas the area of the hysteresis loop represents the mechanical energy dissipated as heat in viscoelastic materials during cyclic loading. It is also uncertain how a time-dependent quantity (i.e., hysteresis) could be accurately measured using the near-instantaneous NCT process. CRF is intended to be a measure of overall corneal rigidity; however, it was designed to be strongly related with only CCT, ignoring biomechanical properties such as Young’s modulus.\textsuperscript{15}

Corneal Effect on Tonometry

Under physiological conditions, the true IOP and corneal thickness are uncorrelated.\textsuperscript{2,59} The accepted interpretation of the positive association between applanation tonometry and CCT measurements is that an increased corneal thickness provides greater resistance to applanation tonometry, causing overestimation and vice versa.\textsuperscript{2,5} The current results indicate that a 0.19 [0.10] mm Hg GAT overestimation would be expected if CCT was thicker than average by 10 mm, which is toward the lower end of the range of 0.13 to 0.34 mm Hg/10 mm CCT reported in recent work.\textsuperscript{2,40-45}

ORAg had a stronger relationship with CCT compared with GAT, which is consistent with the accuracy of NCT being more affected by the cornea.\textsuperscript{44,45} The cornea may behave as a comparatively more rigid structure during the NCT process because of its viscoelastic properties; the resistance of a viscoelastic material to deformation is greater if the stress is applied at a faster rate.\textsuperscript{44} The applanation process is performed over the order of milliseconds during NCT/ORAg,\textsuperscript{14,15} in comparison to seconds for GAT. Another possible explanation is that overall corneal resistance to CCT is greater due to its larger nominal applanation area.\textsuperscript{15,46} In contrast, ORAcc and CCT were unrelated, as previously observed.\textsuperscript{15,29,32} This finding is consistent with the claim that ORAcc is an IOP estimate with reduced corneal dependence.\textsuperscript{13,16}

CH was not a statistically significant predictor of GAT or ORAg. The lack of association between CH and both GAT\textsuperscript{32,47,48} and ORAg\textsuperscript{28,32} agrees with work done on normal eyes. These findings suggest that under physiological conditions, CH is independent to the IOP and does not describe a corneal-related GAT error. To our knowledge, the effects of corneal hysteretic behavior or viscoelasticity on GAT accuracy have not been studied. It is thus difficult to infer whether this null result supports or refutes the validity of CH.

In contrast, CRF was associated with both GAT and ORAg. Moderate to strong correlations between CRF with GAT\textsuperscript{32,47} and ORAg\textsuperscript{28,32} also appear in the literature. These co-variations support the description of CRF as a response related to corneal resistance, since its inclusion in the model caused CCT to lose its statistical significance when GAT or ORAg was the outcome variable. The effect of CCT causing tonometric overestimation is therefore encompassed by CRF.

However, the variance of GAT related to CRF ($R^2 = 0.266$) was much higher than the combined influence of CCR and CCT ($R^2 = 0.068$). Two potentially inclusive interpretations are proposed. First, because corneal biomechanics affect the accuracy of GAT,\textsuperscript{8,12} CRF may have a stronger relationship with GAT because it is an overall composite response related to both corneal biomechanics and geometry. Second, the implication that at least 26.6\% of the variation in GAT occurs because of corneal errors appears fallaciously high. Since it is highly improbable that the equation derived to calculate CRF is entirely specific in separating the corneal and IOP contributions to P1 and P2, CRF is likely to be IOP dependent and hence only partially valid. This theory is supported by the much stronger relationship between ORAg and CRF. It is inconceivable that corneal interference could be responsible for over half of the variation in NCT measurements ($R^2 = 0.552$). A portion of this shared variance probably occurs due to the IOP affecting both parameters.

The statistically significant associations of both CH and CRF with ORAcc also suggest a lack of internal consistency between these the ORA parameters. Three potentially inclusive possibilities are that ORAcc may not have complete corneal independence, CH and/or CRF may be IOP dependent, or a third, unknown factor affecting P1 and P2 may influence both the ORA IOP estimates and corneal parameters. Another unusual result was that CCT gained the ability to predict ORAcc when CH was included in the regression model. Other than questionable validity of the ORA parameters, there does not appear to be another obvious explanation for these significant co-variations.

Corneal Geometry, CH, and CRF

CCT is known to be moderately to strongly correlated with both CH and CRF, with slightly higher effect sizes observed for the latter.\textsuperscript{28,30-50} The findings in Table 3 are thus consistent with those in previous work. However, other factors such as corneal hysteresis and possibly IOP may contribute to CH and/or CRF given that most of their variation was not explained by CCT ($R^2 = 0.252$ and 0.290, respectively).

CH was empirically developed without reference to corneal properties, and hence the association between CH and CCT supports the description of the former as a corneal measurement. Although a thicker cornea should have an increased capacity for viscous damping and hence a higher CH, it is nevertheless unclear whether CH truly is a measure of viscoelasticity. It is possible that CH represents one or more other corneal attributes.

CRF is intended to quantify the corneal viscoelastic resistance to the NCT air pulse. A thicker cornea provides more opposition to applanation, as evidenced by the overestimation
of GAT in such eyes. CRF was thus developed to correlate strongly with CCT, as also observed in the present study. However, it is still unclear how strongly CRF is related to corneal rigidity.

Study Limitations and Future Work
Only a small number of healthy subjects within a narrow, young age range were studied. However, the ability of the ORA to produce clinically useful information in young, normal participants must be demonstrated before its use can be justified in eyes with disease or age-related changes.

The ORA parameters discussed in this article have been based only on corneal applanation. Each ORA measurement is also accompanied by an applanation signal waveform. Quantitative analysis of the waveform may also be of interest and is now possible with version 2.04 of the ORA software. The waveform morphology can potentially describe the corneal and IOP response to the air pulse more completely; however, the relationship of the varying aspects of the ORA signal to their underlying ocular determinants is unknown. Conversely, it is more ideal to quantify ORA results in terms of their waveform morphology rather than the calculated ORA parameters, because the latter makes unvalidated assumptions on the underlying quantity and quantities being measured.

Conclusions
The normative data for CH and CRF were consistent with other reports based on healthy eyes. The poor agreement of ORAg and ORAcc with GAT was also as previously observed. The intercorrelations between the ORA parameters suggest a lack of internal consistency; the equations used to calculate the ORA parameters may not separate the corneal, IOP, and possibly other unknown determinants of P1 and P2 appropriately. The effect of CCT on GAT was encompassed by CRF, which indicates that the latter is at least a partial representation of corneal rigidity. However, CRF may be still be IOP dependent to some extent, as indicated by its relatively high correlation with GAT. In contrast, the corneal and potentially other properties determining CH are unclear, but may be unimportant in the tonometric process.

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References


