Repeatability of the Novel Intraocular Pressure Measurement From Corvis ST

Masato Matsuura¹,², Hiroshi Murata¹, Yuri Fujino¹, Mieko Yanagisawa¹, Yoshitaka Nakao³, Shunsuke Nakakura⁴, Yoshiaki Kiuchi¹, and Ryo Asaoka¹

¹ Department of Ophthalmology, The University of Tokyo, Tokyo, Japan
² Department of Ophthalmology, Graduate School of Medical Science, Kitasato University, Sagamihara, Kanagawa, Japan
³ Department of Ophthalmology and Visual Sciences, Hiroshima University, Hiroshima, Japan
⁴ Department of Ophthalmology, Saneikai Tsukazaki Hospital, Himeji, Japan

Correspondence: Ryo Asaoka, Department of Ophthalmology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan. e-mail: rasaoka-tky@umin.ac.jp

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Purpose: To assess the repeatability of intraocular pressure (IOP) measured with the Corvis ST (CST) and the Ocular Response Analyzer (ORA).

Methods: A total of 141 eyes from 141 subjects were studied, including 35 healthy eyes and 106 glaucomatous eyes. All subjects underwent IOP evaluations with Goldmann applanation tonometer, CST, and ORA. With CST, biomechanical corrected IOP (bIOP) was calculated; bIOP is purported to be less dependent on biomechanical properties. For ORA, corneal-compensated intraocular pressure (IOPcc) and Goldmann-correlated IOP (IOPg) were derived. The repeatability of the various IOP values was assessed using the coefficient of variance (CV) and the intraclass correlation coefficient (ICC).

Results: The CV with bIOP (5.5 ± 3.1): mean ± standard deviation) was significantly smaller than the CVs measured with IOPg (7.3 ± 4.3) and IOPcc (7.2 ± 4.4). ICC values were 0.90, 0.80, and 0.86 with IOPg, IOPcc, and bIOP, respectively.

Conclusions: The bIOP showed a better prevision and repeatability for IOP measurement.

Translational Relevance: The bIOP measurement from CST had a better reproducible than IOPcc measurement from ORA.

Introduction

Glaucoma can severely damage a patient’s visual function, including the visual field and visual acuity; it remains the second leading cause of blindness worldwide, affecting 60 million people.¹ It is widely acknowledged that the irreversible damage to visual fields, caused by progressive retinal ganglion cell loss, is intensified by elevated intraocular pressure (IOP), which is an established risk factor of glaucoma.²⁻¹⁰

The Goldmann applanation tonometer (GAT) is the most common method for measuring IOP, especially in the management of glaucoma. Importantly, the accuracy of GAT can be affected by many factors. Previous studies have shown that GAT IOP may be overestimated when central cornea thickness (CCT) is large, and underestimated when CCT is small.¹¹⁻¹³ However variations in CCT only account for up to 12% of the measured variation of GAT-IOP,¹⁴,¹⁵ and hence correction nomograms that adjust GAT IOP based solely on CCT are neither valid nor useful in individual patients.¹⁶ A recent study with a simulated cornea biomechanical model revealed that corneal biomechanics across individuals may have greater impact on IOP measurement errors than CCT.¹⁷ For instance, it has been reported that corneal hysteresis (CH) measured with the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY)¹⁸ influences the GAT IOP measurement,¹⁹ and reflecting this, ORA generates the following two IOP measurements: a corneal compensated IOP (IOPcc), which is corrected for CH, as well as the IOP Goldmann (IOPg).

In addition, there has recently been renewed interest in measuring IOP more accurately; in
particular, the Corneal Visualization Scheimpflug Technology instrument (Corvis ST tonometry; CST; Oculus, Wetzlar, Germany) is a new noncontact tonometer designed to measure IOP while correcting for the biomechanical properties of the cornea. Similar to ORA, a rapid air-puff is used in CST, but unlike ORA, an ultra-high speed Scheimpflug camera is used to directly visualize the associated corneal movement. CST generates a biomechanical corrected IOP (bIOP) measurement, which is corrected for CCT and other properties of the cornea. A previous study suggested that bIOP is not dependent on CCT in a normative population. Thus, bIOP may be useful in the management of glaucoma, however, the reproducibility and repeatability of the measurement have not been investigated. Thus, the purpose of the current study was to investigate the repeatability of these IOP values.

Materials and Methods

The study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at The University of Tokyo. Written informed consent was given by patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects

The current study investigated 141 eyes of 141 subjects (35 healthy eyes and 106 glaucoma eyes). Inclusion criteria for glaucomatous patients were as follows: no abnormal eye-related findings except for primary open-angle glaucoma (POAG) or normal-tension glaucoma (NTG) on biomicroscopy, gonioscopy, and funduscopy. Eyes with corneal pathologic features, such as Fuch’s endothelial dystrophy or keratoconus, were excluded. Eyes that had undergone any intraocular surgery, including cataract surgery, were also excluded. Only subjects aged more than 20 years were included. IOP was not used as an exclusion criterion so that a wide range of IOPs were considered in the analysis. As a result, ocular hypertensive eyes were included. Normative subjects were defined as having no abnormal findings except for clinically insignificant senile cataract on biomicroscopy, gonioscopy, and funduscopy, and no history of any ocular disease or surgery, including cataract surgery. Both glaucoma patients and normative subjects were recruited at the glaucoma clinic in the University of Tokyo hospital.

Corvis ST Tonometry Measurements

Measurements with CST were carried out three times per participant. An interval of approximately 1 minute was given between each measurement during which data storage and processing operations were carried out by the CST instrument. All CST measurements were considered reliable according to the “OK” quality index displayed on the device monitor.

The principles of the CST have been described in detail elsewhere. Briefly, a high-speed Scheimpflug camera records over 4000 frames/sec to monitor the corneal response to an air-puff pulse that forces the cornea inward until it reaches a concavity phase. A number of CST parameters are produced including bIOP, which is an IOP value corrected for CCT. The formula to calculate bIOP was initially suggested as:

\[
bIOP = (C_{CCST} \times C_{CST-IOP} + C_{CCT2}) \times C_{age} + C,
\]

where

\[
C_{CCT1} = 4.67 \times 10^{-7} \times CCT^2 - 7.8 \times 10^{-4} \times CCT + 0.63
\]

\[
C_{CCT2} = -1.73 \times 10^{-5} \times CCT^2 + 2.02 \times 10^{-3} \times CCT - 0.97
\]

\[
C_{CST-IOP} = 10 + (CST-IOP + 1.16)/0.389
\]

\[
C_{age} = -2.01 \times 10^{-5} \times age^2 + 1.3 \times 10^{-3} \times age + 1.00
\]

\[
C = 1.5 \text{ mmHg}
\]

However, an updated formula is used in the latest version of the software (personal communication with Oculus):

\[
bIOP = C_{CCT1} \times C_{AP1} \times C_{age1} + C_{CCT2} \times C_{age2} + C_{DCR} + a_{19}
\]

where

\[
C_{CCT1} = (a_1 \times CCT^3 + a_2 \times CCT^2 + a_3 \times CCT + a_4)
\]

\[
C_{AP1} = (a_5 \times AP1 + a_6)
\]

\[
C_{age1} = (a_7 \times [\ln(Beta)]^2 + a_8 \times [\ln(Beta)] + a_9)
\]

\[
C_{CCT2} = (a_{10} \times CCT^3 + a_{11} \times CCT^2 + a_{12} \times CCT + a_{13})
\]
The ORA measurement was carried out three times on the same day with the GAT measurement. An interval of approximately 1 minute was given between each repeated measurement. ORA records two applanation pressure measurements, during the inward and outward corneal movements, following application of a rapid air-puff. Due to its viscoelastic property, the cornea resists the air-puff, resulting in delays in the corneal movement, which cause a measurable difference in the applanation pressure values at the inward and outward corneal movements. The average of the inward and outward applanation pressure values defines the IOPg measurement, and the difference in the two values describes CH, which is primarily an indication of viscous damping in the corneal tissue. The corneal resistance factor (CRF) is also calculated from the two applanation pressure values, but places greater emphasis on the first applanation pressure because this gives more information about the elastic properties of the cornea.

IORPc is another IOP measurement generated by ORA that incorporates the CH metrics in its derivation. Only reliable data, as indicated by a waveform score more than 7.0, were used in the analyses.

The order of ORA and CST measurements was decided randomly.

Other Ocular Measurements

GAT measurements were carried out after the CST and ORA measurements, and after instillation of topical 0.5% tetracaine. The tonometer was set at 10 mm Hg before each reading. AL was measured three times using the IOL master (Carl Zeiss Meditec, Dublin, CA) and CCT was measured three times using the CST. Average values were used in analyses.

Statistical Analysis

The relationship between the different IOP measurements was analyzed using linear regression and the paired Wilcoxon test. The agreement between devices, (1) IOPcc and GAT IOP, and (2) biOPI and GAT IOP, measured using Bland-Altman plot. The coefficient of variation (CV) and the intraclass correlation coefficient (ICC) were calculated for biOPI, IOPg, and IOPcc. CV was calculated as follows:

$$CV = \frac{\text{standard deviation of three IOP readings}}{\text{average of three IOP readings}}.$$ 

CV values were compared using the paired Wilcoxon test.

All statistical analyses were performed using the statistical programming language R (R version 3.2.3; the Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study subjects are summarized in Table 1. The mean ± standard deviation (SD) (range) age of patients was 55.2 ± 16.5 (24–86). Seventy-one participants were male and seventy participants were female. Mean ± SD GAT IOP was 13.1 ± 2.7 (7.8–22) mm Hg. CCT was 537.7 ± 34.6 (458.7–644.0) μm. Corneal curvature was 7.7 ± 0.3 (7.2–8.3) mm. CH was 9.5 ± 1.2 (6.4–12.4) mm Hg. CRF was 8.8 ± 1.6 (4.2–15.2) mm Hg.

The ICC and CV values of IOPg, IOPcc, and biOPI are summarized in Table 2. The CV value of IOPg was 7.3 ± 4.3 (0.37–21.4)%). IOPcc was 7.2 ± 4.4 (0.41–24.2)%, and biOPI was 5.5 ± 3.1 (0.59–18.1)%.

The CV value of biOPI was significantly smaller than those with IOPg and IOPcc (P < 0.001, Wilcoxon test). ICC of IOPg, IOPcc, and biOPI were 0.90 (95% confidence interval [CI]: from 0.87–0.93), 0.80 (95% CI: from 0.75–0.85), and 0.86 (95% CI: from 0.82–0.89), respectively.

Mean ± SD values of IOPg, IOPcc, biOPI, and GAT IOP are shown in Table 3. IOPcc was significantly higher than GAT IOP (P < 0.001, paired Wilcoxon test), whereas biOPI was not significantly different from GAT IOP (P = 0.34, paired Wilcoxon test). Figure 1 shows the relationships between IOPcc and GAT IOP, and between biOPI and GAT IOP. There was a significant relationship between these values (r² = 0.39 and 0.38, respectively, P < 0.001, linear regression).

Figure 2 shows the agreement between IOPcc and GAT IOP, and between biOPI and GAT IOP, using the Bland-Altman plot. Mean difference between
IOPcc and GAT IOP was 1.4 mm Hg, whereas it was −0.2 mm Hg between bIOP and GAT IOP. There was no significant relationship between the difference between IOPcc and GAT IOP and the average of these values; however, the difference between bIOP and GAT IOP was significantly larger when the average of these values was small (P < 0.001); the bIOP value was smaller than the GAT IOP measurement when the average of these values was small.

### Discussion

In the current study, IOP measurements were carried out using GAT, CST, and ORA in glaucomatous patients and normative subjects. Among the IOP measurements, bIOP (CST) had a lower CV and a higher ICC compared with IOPg (ORA) and IOPcc (ORA), suggesting a high repeatability of bIOP. All IOP measurements were significantly related to one another as follows: IOPg tended to be lower than GAT IOP while IOPcc tended to be higher than GAT IOP; there was not a significant difference between bIOP and GAT IOP.

In a previous report, we investigated the repeatability of ORA IOP measurements in eyes with POAG. The CV and ICC values of IOPg were 6.5 ± 4.0% and 0.91, respectively.26 The CV and ICC values of IOPcc were 6.7 ± 4.0% and 0.84, respectively.26 Many others have also investigated the reproducibility of these measurements. Wang et al.27 reported that the CV and ICC of IOPg is 7.0% and 0.79, respectively, while these same values are 9.8% and 0.57 for IOPcc. Kopito et al.28 reported that the CV values of IOPg and IOPcc were 7.7 and 10.1%. Moreno-Montañés et al.29 reported that the ICC values of IOPg and IOPcc were 0.93 and 0.78. In the current study, the CV values of IOPg and IOPcc were 7.3 and 7.2, and the ICC values of IOPg and IOPcc were 0.90 and 0.80; these values align well with those published in previous reports. The results in the current study suggested lower CV (5.5 ± 3.1% with bIOP and 7.2 ± 4.4% with IOPcc) and higher ICC values (0.86 with bIOP and 0.80 with IOPcc) with bIOP compared with IOPcc, suggesting better repeatability of bIOP compared with IOPcc. The entire reason of this finding is not clear, but it may be because of the different calculations between these two IOP values. bIOP is calculated using age, CCT, and highest concavity radius. Age does not change between the CST measurements. We previously reported CST measured CCT was highly repeatable (CV = 0.9 ± 0.9% and ICC = 0.99) although highest concavity radius (formally named as highest concavity curvature) had a moderate repeatability (CV = 8.1 ± 8.7% and ICC = 0.68) in a previous study.30 The high repeatability of bIOP would be beneficial when used at the clinical settings.

Many earlier reports have suggested a difference between IOPcc and GAT IOP. Hager et al.31 compared IOPcc and GAT IOP in eyes with glaucoma, and reported that IOPcc was significantly higher than GAT IOP by 3.6 mm Hg (17.9 ± 5.9:

### Table 1. Subject Demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range), y</td>
<td>55.2 ± 16.5 (24–86)</td>
</tr>
<tr>
<td>Male/female</td>
<td>71/70</td>
</tr>
<tr>
<td>Right/left</td>
<td>113/28</td>
</tr>
<tr>
<td>AL, mean ± SD (range), mm</td>
<td>25.5 ± 1.6 (22.3–29.2)</td>
</tr>
<tr>
<td>GAT IOP, mean ± SD (range), mm Hg</td>
<td>13.1 ± 2.7 (7.8–22.0)</td>
</tr>
<tr>
<td>bIOP, mean ± SD (range), mm Hg</td>
<td>12.9 ± 2.2 (8.6–20.3)</td>
</tr>
<tr>
<td>Corneal curvature, mean ± SD (range), μm</td>
<td>7.7 ± 0.3 (7.2–8.3)</td>
</tr>
<tr>
<td>CCT, mean ± SD (range), μm</td>
<td>537.7 ± 34.6 (458.7–644.0)</td>
</tr>
<tr>
<td>CH, mean ± SD (range), mm Hg</td>
<td>9.5 ± 1.2 (6.4–12.4)</td>
</tr>
<tr>
<td>CRF, mean ± SD (range), mm Hg</td>
<td>8.8 ± 1.6 (4.2–15.2)</td>
</tr>
</tbody>
</table>

AL, axial length.

### Table 2. Repeatability of IOPg, IOPcc, and bIOP Measurements

<table>
<thead>
<tr>
<th></th>
<th>CV (%)</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOPg, mean ± SD (range), mm Hg</td>
<td>7.3 ± 4.3 (0.37–21.4)</td>
<td>0.90 (CI:0.87–0.93)</td>
</tr>
<tr>
<td>IOPcc, mean ± SD (range), mm Hg</td>
<td>7.2 ± 4.4 (0.41–24.2)</td>
<td>0.80 (0.75–0.85)</td>
</tr>
<tr>
<td>bIOP, mean ± SD (range), mm Hg</td>
<td>5.5 ± 3.1 (0.59–18.1)</td>
<td>0.86 (0.82–0.89)</td>
</tr>
</tbody>
</table>
mean $\pm$ SD and 14.3 $\pm$ 4.3 mm Hg). Martinez de la Casa et al.\textsuperscript{32} compared IOPcc and GAT IOP in POAG eyes and reported that IOPcc was significantly higher than GAT IOP by 8.3 mm Hg (25.1 $\pm$ 5.4 and 16.8 $\pm$ 3.4 mm Hg). Ehrlich et al.\textsuperscript{33} have reported that IOPcc was significantly higher than GAT IOP by 5.4 mm Hg (19.8 $\pm$ 3.4 and 14.4 $\pm$ 3.4 mm Hg) in NTG eyes. Oncel et al.\textsuperscript{34} reported that IOPcc was higher than GAT IOP by 1.0 mm Hg in healthy volunteers (15.8 $\pm$ 2.9 and 14.8 $\pm$ 3.1 mm Hg). Pepose et al.\textsuperscript{35} reported that IOPcc was higher than GAT IOP by 1.6 mm Hg (15.4 $\pm$ 3.2 and 13.8 $\pm$ 3.3 mm Hg) among eyes with myopia. In the current study, IOPcc was significantly higher than GAT IOP ($P < 0.001$); however, the difference was much smaller (by 1.4 mm Hg: 14.5 $\pm$ 2.6 and 13.1 $\pm$ 2.7 mm Hg) compared with these previous reports, but similar to that observed in our previous report where IOPcc was significantly higher than GAT IOP by 1.6 mm Hg.\textsuperscript{26} Thus, the reason for the small difference between IOPcc and GAT IOP observed in the current study is not clear, but may be attributable to the racial difference in study populations. Indeed, Morita et al.\textsuperscript{36} also compared IOPcc and GAT IOP in a Japanese population and likewise reported a much smaller difference between IOPcc and GAT IOP (by 2.1 mm Hg: 15.2 $\pm$ 2.0 and 13.1 $\pm$ 1.3 mm Hg) in NTG eyes, and no significant difference in healthy eyes (IOPcc: 13.6 $\pm$ 2.0 mm Hg and GAT IOP: 13.2 $\pm$ 1.4 mm Hg)\textsuperscript{36} In contrast to IOPcc, there was not a significant difference between biOP and GAT IOP in the current study. It would be of further interest to investigate whether similar results are obtained in other ethnicities.

A recent report from the United Kingdom Glaucoma Treatment Study suggested that, among IOPg, IOPcc, GAT IOP, and IOP with dynamic contour tonometry, IOPcc from ORA had the highest probability of being the best predictor of glaucoma progression (Lascaratos, et al. \textit{IOVS}. 2014;55:ARVO E-Abstract 128). Further, Hong et al.\textsuperscript{37} reported that rapid visual field (VF) progression was more likely to occur in patients with high IOPcc, low CH, and a large recorded difference between IOPcc and GAT IOP. CST is a relatively new noncontact tonometry, and we have shown glaucomatous VF progression\textsuperscript{38} and also severity\textsuperscript{39} can be even better analyzed using CST-derived parameters (biOP was not analyzed, because of the older software used). Albeit with the high repeatability suggested in the current study, biOP may be useful to assess the progression of glaucomatous visual field (VF) progression. Another aspect to be considered is the relationship between IOP reading with each device and corneal biomechanical properties, because IOP measurements, such as GAT, can be affected by CCT,$^{11,14,17,40–49}$ and also progression of glaucoma is associated with various corneal properties such as CCT,$^{4,50}$ ORA CH,$^{36,51}$

### Table 3. Summary of IOPg, IOPcc and biOP Measurements and Their Correlation With GAT IOP

<table>
<thead>
<tr>
<th>IOP Measurement</th>
<th>Mean $\pm$ SD (range)</th>
<th>Correlation to GAT IOP ($P$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOPg, mm Hg</td>
<td>12.6 $\pm$ 3.2 (6.2–26.3)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>IOPcc, mm Hg</td>
<td>14.5 $\pm$ 2.6 (8.7–23.2)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>biOP, mm Hg</td>
<td>12.9 $\pm$ 2.2 (8.6–20.3)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>GAT IOP, mm Hg</td>
<td>13.1 $\pm$ 2.7 (7.8–22.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1. The relationship between IOPcc and GAT IOP, and between biOP and GAT IOP. There was a significant relationship between both pairs of values ($R^2 = 0.39$ and 0.38, respectively, $P < 0.001$).
and also CST measured corneal biomechanical characteristics. In the current study, there was a significant difference between IOPcc and GAT IOP, whereas this was not the case between bIOP and GAT IOP. A future study would be of interest to investigate whether bIOP is a better predictor of glaucoma progression, preparing longitudinal data.

A limitation of the current study is that IOP data were obtained from a hospital clinic, hence true IOP could not be collected and compared against the various IOP readings, as in a previous study. Further, the effects of antiglaucomatous eye drops on corneal biomechanical properties was not considered. In addition, GAT IOP measurement was conducted either once, twice, or three times, and not in a masked fashion (i.e., the GAT dial was not set to a random number and then the final reading was recorded), as in a previous study, because the repeatability of GAT IOP has already been reported and it was not the purpose of the current study.

In conclusion, the CST-derived bIOP measurement has a good repeatability.

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