Central and peripheral intraocular pressure measured by a rebound tonometer

Tsutomu Yamashita 1
Atsushi Miki 1,2,3
Yoshiaki Ieki 2
Junichi Kiryu 2
Kiyoshi Yaoeda 3,4
Motohiro Shirakashi 1,5

1 Department of Sensory Science, Faculty of Health Science and Technology, Kawasaki University of Medical Welfare, 2 Department of Ophthalmology, Kawasaki Medical School, Kurashiki, Okayama, Japan; 3 Division of Ophthalmology and Visual Sciences, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; 4 Yaoeda Eye Clinic, Nagaoka, Japan; 5 Kido Eye Clinic, Niigata, Japan

Purpose: We investigated at which corneal region the intraocular pressure as measured by the Icare® rebound tonometer (Finland Oy, Espoo, Finland) (hereinafter referred to as IC) was closest to the intraocular pressure as measured by the Goldmann applanation tonometer (hereinafter referred to as GT). We also investigated which parameters would be best for preparing the most suitable model for predicting GT.

Methods: A total of 102 normal eyes in 102 subjects were enrolled. IC measurements were carried out at the central, superior, inferior, temporal, and nasal regions of the cornea (ICC,ICS,ICI,ICT, and ICN, respectively), followed by GT calculations. Differences between GT and IC were analyzed using the Bland–Altman method. Stepwise multiple regression analysis was performed using GT as the objective variable, and age, laterality of eye, spherical equivalent refractive error, corneal radius, axial length, central corneal thickness, GT, ICC, ICS, ICI, ICT, and ICN as the explanatory variables.

Results: IC was higher than GT at all of the corneal regions, but the region with the least bias was ICC, followed by ICT. In the multiple regression analysis, the following prediction formula was calculated: GT = (0.445 \times ICC) + (0.198 \times ICN) + 3.022. When ICC was excluded from the explanatory variables, ICT had the highest partial correlation coefficient with GT.

Conclusion: ICC was closest to GT, but GT could be explained better by adding ICN to the prediction model. Moreover, in instances where ICC cannot be calculated or where reliability is clearly poor due to abnormal ocular rigidity, ICT was the closest to GT measured in the central corneal region.

Keywords: IOP, Icare, Goldmann applanation tonometer, ocular rigidity

Introduction

Glaucoma is a disorder that causes serious visual impairment that leads to blindness if not treated appropriately.1 The greatest risk factor associated with the onset and progression of glaucoma is elevation in intraocular pressure (IOP).1 Therefore, the accurate measurement of IOP is extremely important for glaucoma management in patients.

The current gold standard for tonometers in ophthalmological practice is the Goldmann applanation tonometer (GAT).2 However, “IOP as measured by a GAT” (hereinafter referred to as GT) is affected by ocular rigidity.3 Ocular rigidity is defined as the distensibility or resistance to deformation in the ocular coat.4 If the ocular rigidity is abnormal due to abnormal corneal thickness, corneal disease, or ocular surgery, GT measurements will be inaccurate.5 For example, in cases where abnormal ocular rigidity occurs in association with disease or surgery, it is known that GT in the affected
area is higher than that in other corneal regions, following corneal calcareous degeneration such as band keratopathy. On the other hand, GT in the affected area is lower than that in other corneal regions in the case of keratoconus and laser in situ keratomileusis.

Obtaining accurate GT measurements in eyes with abnormal ocular rigidity is not an easy task. In cases where abnormal ocular rigidity of the central corneal region is encountered, IOP must sometimes be measured in the peripheral corneal regions. However, since the area that applanates cornea is large, 3.06 mm in the case of using a GAT, the measurement might be affected by the ocular rigidity in the central corneal region in no small way when measuring IOP in the peripheral corneal regions. Moreover, obtaining a measurement may be impossible in cases where the measured region contains corneal scarring or sclera.

Icare® (Finland Oy, Espoo, Finland), a recently developed rebound tonometer, makes it possible to measure IOP without anesthesia, and it is portable due to its small size and light weight. In addition, the diameter of the probe tip that comes into contact with the cornea is extremely small at 1.4 mm, making it easy to measure IOP in peripheral corneal regions.

In the present study, we investigated at which corneal regions “IOP measurements using the Icare rebound tonometer” (hereinafter referred to as IC) were closest to GT at the central corneal region. We also investigated which parameters would be best for preparing the most suitable model for predicting GT.

**Subjects and methods**

A total of 102 eyes in 102 subjects (male/female = 52/50) without any abnormality on ophthalmologic examination, other than refractive error, were studied. Informed consent was obtained from all subjects prior to the study. Niigata University Institutional Review Board approved all methodology. Study methods adhered to the provisions of the Declaration of Helsinki guidelines for research involving human participants.

Spherical equivalent refractive error (D) and corneal radius (mm) were calculated using the KR-8100P autorefractometer (Topcon Corporation, Tokyo, Japan).

IC was measured in the central corneal region (ICC) and four other regions (superior [ICS], inferior [ICI], temporal [ICT], and nasal [ICN]) located about 2 mm from the limbus. Subjects were instructed to look head-on (primary position) for measurement of ICC. For measurement of IC in the peripheral corneal regions on the other hand, subjects were instructed to look contralateral (secondary position) to the measured region. For example, subjects were instructed to look downward when measuring ICS. The peripheral corneal measurements were achieved by having the subjects fixate at the target on the wall. The order of the measurements was random. To investigate the reproducibility of Icare tonometry, an averaged IC (ICC) calculated from six consecutive measurements was obtained three times (from 18 measurements) in the central corneal region. In this study, median ICC was used for all analyses other than calculation of coefficients of variation and intraclass correlation coefficients. In the case of the superior, inferior, temporal and nasal corneal regions, IC was measured only once (from six consecutive measurements) to calculate ICS, ICI, ICT, and ICN, respectively.

GT was then measured in the central corneal region using a GAT (Haag-Streit, Koeniz, Switzerland). Finally, the central corneal thickness and axial length of each study eye were measured using an SP-2000 ultrasound pachymeter (Tomey, Nagoya, Japan) and a UD-6000 ultrasonic A/B scanner biomter (Tomey), respectively.

Coefficients of variation and intraclass correlation coefficients were calculated for the three consecutive measurements of ICC. ICC, ICS, ICI, ICT, and ICN were compared using a mixed model with IC as a fixed factor, and subjects and laterality of eye (right/left = 51/51) as random factors. The Bonferroni method was used for multiple comparison adjustments.

Pearson correlation coefficients were calculated, and a correlation matrix was prepared for the following parameters: age, spherical equivalent refractive error, corneal radius, axial length, central corneal thickness, GT, ICC, ICS, ICI, ICT, and ICN. Differences between GT and IC were analyzed using the Bland–Altman method.

To generate a model for predicting GT, multiple regression analysis was performed by the stepwise procedure, using GT as the objective variable, and age, laterality of eye, spherical equivalent refractive error, corneal radius, axial length, central corneal thickness, GT, ICC, ICS, ICI, ICT, and ICN as explanatory variables. In addition, assuming there will be instances where ICC cannot be calculated or where reliability is clearly poor due to abnormal ocular rigidity, multiple regression analysis was also performed without ICC as an explanatory variable. When an explanatory variable with a variance inflation factor exceeding 10 was present, another model was generated without the explanatory variable.

All statistical analyses were performed using SPSS 17.0 J (SPSS Japan Inc, Tokyo, Japan) and MedCalc version...
10.1 (MedCalc Software bvba, Mariakerke, Belgium). A significance level below 5% was considered to be statistically significant.

**Results**

A summary of the 102 eyes in 102 subjects in the present study is shown in Table 1. The average coefficient of variation of ICC was 8.8%. The intraclass correlation coefficient was 0.879.

ICS and ICN were significantly higher than ICC ($P < 0.001$ and $P = 0.003$, respectively), but there was no difference between any of the other regions. In terms of the correlation matrix of each parameter (Table 2), there was a strong positive correlation between GT and each IC. In addition, there was a significant correlation between the corneal radius and the central corneal thickness, and many ICs.

Differences of GT and IC using the Bland–Altman method are shown in Table 3. ICs were higher than GT in all of the corneal regions, but the IC with the least bias relative to GT was ICC (Figure 1), followed by ICT.

In multiple regression analysis using the stepwise procedure, GT was explained by the following formula:

$$GT = (0.445 \times ICC) + (0.198 \times ICN) + 3.022 \times (\text{coefficient of determination} = 0.636) \quad (1)$$

When approximated using only ICC, which had the highest coefficient of determination, GT was explained by the following formula:

$$GT = (0.530 \times ICC) + 5.196 \times (\text{coefficient of determination} = 0.599) \quad (2)$$

When ICC was excluded from the explanatory variables, GT was explained by the following formula:

$$GT = (0.203 \times ICT) + (0.159 \times ICS) + (0.215 \times ICN) + 3.166 \times (\text{coefficient of determination} = 0.447) \quad (3)$$

When approximated using only ICT, which had the highest coefficient of determination, GT was explained by the following formula:

$$GT = (0.451 \times ICT) + 5.695 \times (\text{coefficient of determination} = 0.360) \quad (4)$$

**Discussion**

In the present study, the average of the coefficients of variation of ICC was 8.8%, and the intraclass correlation coefficient was 0.879. These are comparable to the findings (coefficient of variation: 8.9%, intraclass correlation coefficient: 0.73–0.87) reported from a study by Martinez-de-la-Casa et al$^{11}$ carried out in subjects with glaucoma or ocular hypertension. Therefore, the IC measurements in this investigation have good reproducibility.

In the present study, ICS and ICN were significantly higher than ICC, but there were no differences between any of the other regions. There have been several reports in the past of IOP comparisons in the central and peripheral corneal regions. In a study using a GAT,$^{12}$ there was no difference in GT between the central corneal region and the peripheral corneal regions. In studies using the Tono-Pen tonometer, no difference in IOP was reported between the central corneal region and peripheral corneal regions in one study,$^{13}$ while IOP was slightly higher in the temporal corneal region as compared with the central corneal region in another study.$^{14}$ A past study using Icare reported no difference in IOP between the central

| Table 1 Summary of subjects (n = 102, male/female = 52/50, right eye/left eye = 51/51) |
|---------------------------------|---------|---------|---------|---------|
| Age (years)                    | Mean    | Standard deviation | Minimum | Maximum |
| Spherical equivalent refractive error (D) | 36.2    | 8.1       | 21      | 56      |
| Corneal radius (mm)            | 7.9     | 0.3       | 7.2     | 8.6     |
| Axial length (mm)              | 25.1    | 1.3       | 22.3    | 28.0    |
| Central corneal thickness (μm) | 554.4   | 39.8      | 456.0   | 651.0   |
| GT (mmHg)                      | 13.3    | 3.0       | 7       | 21      |
| ICC (mmHg)                     | 15.3    | 4.4       | 7       | 32      |
| ICS (mmHg)                     | 18.4    | 5.0       | 9       | 40      |
| ICT (mmHg)                     | 17.0    | 4.6       | 9       | 38      |
| ICN (mmHg)                     | 16.9    | 4.1       | 9       | 29      |

**Abbreviations:** GT, intraocular pressure measured by a Goldmann applanation tonometer; ICC, intraocular pressure in the central corneal region measured by Icare$^{6}$; ICS, intraocular pressure in the superior corneal region measured by Icare; ICI, intraocular pressure in the inferior corneal region measured by Icare; ICT, intraocular pressure in the temporal corneal region measured by Icare; ICN, intraocular pressure in the nasal corneal region measured by Icare.
Table 2 Correlation matrix for each parameter

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Spherical equivalent refractive error, D</th>
<th>Corneal radius, mm</th>
<th>Axial length, mm</th>
<th>Central corneal thickness, μm</th>
<th>GAT, mmHg</th>
<th>ICC, mmHg</th>
<th>ICS, mmHg</th>
<th>ICI, mmHg</th>
<th>ICT, mmHg</th>
<th>ICN, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.126 (0.209)</td>
<td>-0.147 (0.139) 0.163 (0.101)</td>
<td>-0.177 (0.075) -0.823 (0.000)</td>
<td>0.232 (0.019)</td>
<td></td>
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</tr>
</tbody>
</table>

Notes: *P < 0.01; †P < 0.05. Numbers in parentheses represent P values for each correlation coefficient.

Abbreviations: GT, intraocular pressure measured by a Goldmann applanation tonometer; ICC, intraocular pressure in the central corneal region measured by icare®; ICS, intraocular pressure in the superior corneal region measured by icare; ICI, intraocular pressure in the inferior corneal region measured by icare; ICT, intraocular pressure in the temporal corneal region measured by icare; ICN, intraocular pressure in the nasal corneal region measured by icare.
using subjects’ right and left eyes as random effects, thereby
taking into account the effects of the differences between the
right and left eyes on IC for comparison of IOP levels between
corneal regions in the same cornea.

In the present study, there was a strong positive correla-
tion between GT and IC, with the correlation between GT and
ICC being the highest ($r = 0.777$). In a past report involving
healthy subjects, the correlation coefficient between GT and
ICC was 0.82. In a report involving patients with glaucoma
or ocular hypertension, the correlation coefficient between
GT and ICC was 0.865. The results of the present study are
comparable to the results in these reports. In the present study,
differences between GT and IC were investigated using the
Bland–Altman method, which showed that the bias between
GT and ICC was –2.0 mmHg, while that between GT and
IC in the other corneal regions was –3.6 to –5.1 mmHg.
Overall, these data indicate that IC was higher than GT at
all corneal regions. These results are also comparable to a
past report of healthy persons (bias (GT – ICC) = –1.94) and
the results of a study involving patients with glaucoma
or ocular hypertension (bias (GT – ICC) = –1.8). Based on
these results, we concluded that IC correlates well with GT.
However, since some differences were seen, some correction
was needed to predict GT based on IC.

In the present study, generation of a model for predicting
GT using the stepwise procedure, with each IC as well as age,
laterality of eye, spherical equivalent refractive error,
corneal radius, axial length, and central corneal thickness as
explanatory variables, yielded Equation (1) above. ICC had
the highest coefficient of determination with GT (= 0.599) and
was selected as a significant explanatory variable. Moreover,
the coefficient of determination did not decrease much, even
when a model was generated with only ICC as an explanatory
variable. Although the partial correlation coefficient was low,
ICN was also selected as a significant explanatory variable,
likely because a GAT was affected more by ocular rigidity in
the peripheral cornea compared with Icare, due to the larger
corneal contact area during the measurement of IOP. Based
on these results, it may be useful to also measure ICN, as well
as the ICC, when predicting GT based on IC.

On the other hand, assuming there will be instances where
ICC cannot be calculated or where reliability is clearly poor
due to abnormal ocular rigidity, multiple regression analysis
was also performed without ICC as an explanatory variable.
The result was Equation (3). Here, ICT had the highest
coefficient of determination (= 0.360) and was selected as
a significant explanatory variable. Moreover, the coefficient
of determination did not decrease much even when a model
was generated with only ICT as an explanatory variable.
Additionally, when we consider the results of the investiga-
tion of the differences between GT and IC yielded by the
Bland–Altman method, IOP measurements using Icare in the
temporal corneal region might be most useful from the
standpoint of predicting GT, since bias was the smallest for
ICT among IC in the peripheral corneal regions. However,
the coefficient of determination is low compared with a GT
prediction model that includes ICC as an explanatory vari-
able, and the difference between GT and ICT according to the
Bland–Altman method is also larger than that between GT
and ICC. Therefore, it is likely inferior to ICC measurements
when trying to obtain consistency with GT measurements.

Parameters thought to be related to ocular rigidity such as
corneal curvature radius and central corneal thickness were
not selected as significant explanatory variables in these
prediction models. According to past reports, corneal
curvature radius and central corneal thickness were found to
have a significant correlation with GT and ICC, and corneal
curvature radius and central corneal thickness were found to
have a significant correlation with GT and many ICs in the
present study, as well. When generating a multiple regres-
sion model using the stepwise procedure, therefore, corneal
curvature radius and central corneal thickness were believed
to have acted as confounding factors with respect to the objec-
tive variable GT and the explanatory variable IC and been
removed from the prediction model. Moreover, this revealed
that corneal curvature radius and central corneal thickness data
are not necessarily required when predicting GT with IC.

IOP decreases when it is measured consecutively with
various tonometers, as in the case of IOP measurements by
GAT, a phenomenon that was first pointed out during the
development of the tonometer. Significant IOP-lowering
effects as a result of consecutive measurements are not seen
with Icare, or are less than those associated with consecutive
measurements using a GAT. In the present study, IOP was
measured with Icare before measurement with GAT, in order
to partially prevent the IOP-lowering effects associated with
consecutive measurements. However, it was reported that an
IOP-lowering effect was seen with consecutive measurement
of IOP with a rebound tonometer at the animal experiment
level. In the present study, IOP was measured randomly in
each of the corneal regions using Icare, but we cannot rule
out the effects of changes in IOP that may have been caused
by consecutive measurements.

In conclusion, of the ICs measured in the central or
peripheral corneal regions, ICC was the closest to GT.
In addition to ICC, GT could be explained better by generating
a prediction model using ICN. Moreover, in instances where ICC cannot be calculated or where reliability is clearly poor due to abnormal ocular rigidity, ICT was the closest to GT measured in the central corneal region.

Disclosure
The authors report no conflicts of interest in this work.

References