Correlation of Serial Scleral and Corneal Pneumatonometry

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Purpose: To evaluate the usefulness of scleral pneumatonometry as an alternative for corneal measurements of intraocular pressure (IOP) over a broad range of IOPs.

Design: Prospective, observational cohort study.

Participants: The study was conducted in the University of California, San Francisco, Retina Clinic between August and November 2013 in 33 adult patients (age range, 34–94 years; mean ± standard deviation, 74.1±13.4 years) receiving anti–vascular endothelial growth factor intravitreal injections, which transiently increase IOP.

Methods: Corneal pachymetry and serial corneal and temporal scleral pneumatonometry (baseline, immediately after, and 10, 20, and 30 minutes after injection) were collected. One-time baseline corneal and scleral pneumatonometry readings were obtained in the noninjected eye.

Main Outcome Measures: Correlation analysis and a Bland-Altman plot were used to evaluate reliability and agreement between scleral and corneal measurements of IOP. A linear mixed model was used to determine the relationship between measurements and to perform covariate analyses.

Results: Scleral and corneal pneumatonometry showed nearly 1:1 linear correlation, although scleral pneumatonometry was biased toward higher values (r = 0.94; P < 0.001). Scleral pneumatonometry averaged 9.0 mmHg higher than corneal pneumatonometry (95% limits of agreement, −1.5 to 19.5 mmHg). A linear mixed model resulted in the following equation: corneal IOP = 1.04 × scleral IOP − 10.37. Age, central corneal thickness, laterality, and glaucoma and lens status did not impact this relationship. The difference between corneal and scleral pneumotonometry was correlated between the two eyes of individual patients (r = 0.75; P < 0.001).

Conclusions: Differences between serial scleral measurements reflect differences between serial corneal measurements. Scleral pneumotonometry should be considered as an alternative to corneal pneumotonometry for following patients in whom corneal measurements are unreliable or unobtainable. Ophthalmology 2015;122:1771-1776 © 2015 by the American Academy of Ophthalmology.

Intraocular pressure (IOP) normally is measured over the cornea. However, for patients with significant corneal pathology, such as scarring, thinning, and edema, or for those who have keratoprosthesis implants, corneal tonometry can be inaccurate or impossible to obtain. However, these corneal diseases are associated commonly with either primary or secondary glaucoma. For example, in the case of keratoprosthesis, difficulty with IOP measurement is a significant problem. Glaucoma has been reported to be a preoperative comorbidity in more than two-thirds of patients and to be newly diagnosed in an additional 13% to 25% of patients after keratoprosthesis implantation.1-3 Furthermore, keratoprostheses are associated with postoperative elevation in IOP and progression of glaucoma, which can become vision limiting.1-5

Scleral pneumotonometry has been proposed as an alternative method for IOP measurement in patients for whom corneal measurements are not possible. In a study performed in cadaveric eyes, we previously showed that serial measurements of scleral pneumotonometry correlate strongly and linearly to IOP when IOP was set from 20 to 50 mmHg by infusion cannula.4 Importantly, this relationship was unchanged after the eyes underwent keratoprosthesis implantation. In patients, a cross-sectional study by Kapamajian et al5 found a positive correlation between one-time corneal and scleral pneumotonometry in healthy adult patients. However, the IOP range was limited by the physiologic pressures of this population (10.5–27 mmHg), and the relationship between changes in corneal and scleral pneumotonometry in patients was not studied. Furthermore, scleral pneumotonometry generally resulted in higher measurements than corneal pneumotonometry, but this difference was highly variable across individuals (mean ± standard deviation, 8.4±5.7 mmHg).5

For scleral pneumotonometry to be a useful clinical tool, scleral measurements should correlate to corneal measurements over a wide range of both physiologic and pathological pressures and have a predictable relationship over multiple measurements when used to follow patients clinically. Therefore, in the current study, we measured serial scleral and corneal pneumotonometry in patients receiving intravitreal injections, which transiently increase IOP, to evaluate the relationship between these 2 measurements over a broad range of IOPs. Since the baseline difference between scleral and corneal pneumotonometry in an eye with corneal disease may be unknown, in the case of
unilateral or asymmetric disease, we hypothesized that one could use the contralateral eye as a surrogate for the baseline difference in the eye of interest. Thus, we also evaluated whether the difference between corneal and scleral measurements was correlated between the 2 eyes of individual patients.

Methods

Study Design

The Institutional Review Board/Ethics Committee at University of California, San Francisco, approved this prospective observational study. This study complied with Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki.

Adult patients receiving anti—vascular endothelial growth factor intravitreal injections in the Retina Clinic of the University of California, San Francisco, were recruited between August and November 2013. We had a minimum target enrollment of 28 patients, which was predicted to have a 90% power to detect a correlation coefficient of 0.57 (based on the results from Kapamajian et al.) with an α of 0.05 in an a priori sample size calculation. Patients with previous incisional glaucoma surgery, scleral buckle, strabismus surgery, refractive cornea surgery, scleral pathology such as thinning or scarring, or significant corneal pathology such as scarring or edema that would prevent accurate measurement of IOP over the cornea were excluded. The risks and benefits of participation were discussed with each participant and informed consent was obtained. We collected patient information on demographics, diagnosis of glaucoma, and lens status (phakia or pseudophakia) by chart review.

Measurements

A single observer (D.S.K.) obtained all measurements. Eyes were anesthetized with 1% proparacaine. At each time point, IOP measurements were obtained from the central cornea and temporal sclera with the edge of the pneumatonometer probe (Model 30 Classic; Reichert Ophthalmic Instruments, Depew, NY) placed directly temporal 1 mm from the limbus with the patient in primary gaze, which centered the probe approximately 3.5 mm posterior to the limbus. Corneal and temporal scleral pneumatonometry measurements (abbreviated as corneal IOP and scleral IOP, respectively) were obtained at baseline in both eyes before injection, and then serial measurement were obtained in the treated eye immediately after injection and 10, 20, and 30 minutes after injection. All measurements were obtained with patients sitting up. For each pair of measurements, we checked the corneal IOP before the scleral IOP. All corneal measurements had a standard deviation of less than 1 mmHg and all scleral measurements had a standard deviation of less than 1 mmHg for IOPs between 0 and 40 mmHg and a standard deviation of less than 1.5 mmHg for IOPs of more than 40 mmHg. The waveform was examined for good quality in all measurements with IOPs of less than 40 mmHg, where it was within the limits of the paper printout. We measured central corneal thickness by pachymetry (DGH-550 Pachette 2; DGH Technology, Inc. Exton, PA), averaging 5 measurements, at the time of the baseline measurements.

Statistical Analysis

The Pearson correlation coefficient is reported herein. For paired data with more than 1 time point for each study subject, an ordinary correlation coefficient is not appropriate because it does not take into account the lack of independence between repeated measurements for the same subject. Instead, we calculated a within-subjects correlation coefficient, which removes the variation between subjects to examine whether an increase in a variable within the same subject is associated with an increase in another variable. Similarly, agreement between scleral and corneal IOP was analyzed using a Bland-Altman plot with correction for multiple measurements per subject using MedCalc Statistical Software (MedCalc Software, Ostend, Belgium). The data were fit with a linear mixed model with random slope and intercept using R (R Foundation for Statistical Computing, Vienna, Austria). Confidence intervals were derived from bootstrap analysis, an iterative resampling of the data. Covariate analysis was performed using the linear mixed model and likelihood ratio test with P < 0.05 considered statistically significant.

Results

Thirty-three patients ranging in age from 34 to 94 years were included in the study. Baseline characteristics are shown in Table 1. Pseudophakia was present in 52% of patients and glaucoma was present in 15% of patients. A total of 164 serial paired measurements of corneal and scleral IOP were obtained in the treated eye (1 subject missed 1 time point). Corneal IOPs ranged from 9 to 61.5 mmHg and scleral IOPs ranged from 13.5 to 74 mmHg. Thirty-two patients had baseline measurements of scleral and corneal pneumotonometry in the contralateral untreated eye. At baseline, the difference between scleral and corneal pneumotonometry measurements in the 2 eyes of individual patients was correlated significantly (r = 0.75; P < 0.001; Fig 1).

We used correlation to analyze the linear association between serial scleral and corneal IOP by pneumotonometry and found that they were significantly correlated (r = 0.94; P < 0.001) for the injected eyes (Fig 2). The data were fit using a linear mixed model, which takes into account longitudinal measurements over time. This analysis resulted in the following equation: scleral IOP = 0.97 x corneal IOP + 10.0. The standard deviation of the residuals, an error measurement for the entire model, was 2.78 mmHg. The slope (mean ± standard deviation, 0.97±0.21 mmHg) was statistically significant (P < 0.001) and showed a nearly 1:1 relationship between changes in scleral and corneal IOP on average with some variability between individual patients (Fig 3A). Similarly, the intercept (mean ± standard deviation, 10.0±5.83 mmHg) was statistically significant (P < 0.001), but demonstrated greater variability among patients (Fig 3B).

A Bland-Altman plot was created to examine the agreement of scleral IOP and corneal IOP over a range of IOP using data from

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>No. of patients enrolled</td>
</tr>
<tr>
<td>Mean age ± SD (yrs)</td>
</tr>
<tr>
<td>Eye (no.)</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Mean CCT ± SD (μm)</td>
</tr>
<tr>
<td>Lens status (no.)</td>
</tr>
<tr>
<td>Phakic</td>
</tr>
<tr>
<td>Pseudophakic</td>
</tr>
<tr>
<td>Glaucoma (no.)</td>
</tr>
</tbody>
</table>

CCT = central corneal thickness; NOS = not otherwise specified; POAG = primary open angle glaucoma; SD = standard deviation.
serial IOP measurements (Fig 4). Scleral IOP averaged 9.0 mmHg higher than corneal IOP (95% limits of agreement, −1.5 to 19.5 mmHg). Importantly, there was not a trend toward larger differences at higher IOPs, but there were fewer data points and more outliers at higher values. For measurements with a mean of scleral and corneal IOP less than 40 mmHg, which are potentially more clinically relevant, 81.7% of the measurements were within 5 mmHg of the mean difference between scleral and corneal IOP.

To test the impact of age, eye laterality, central corneal thickness, lens status (phakia versus pseudophakia), and glaucoma on the relationship between scleral and corneal pneumotonometry, we added these covariates to the linear mixed model and evaluated them with a likelihood ratio test. None of these factors was statistically significant (Table 2).

Discussion

This study was designed to evaluate the relationship between serial corneal and scleral pneumotonometry over a wide range of physiologic and pathologic levels of IOP. We found that scleral pneumotonometry was significantly correlated to corneal pneumotonometry, but was biased toward higher values. Although we did not compare scleral pneumotonometry directly with Goldmann applanation, the relationship between Goldmann applanation and corneal pneumotonometry has been well described (\[T_{\text{applanation}} = T_{\text{pneumotonometry}} / 1.2\]), and corneal pneumotonometry has been reported to be age-independent and to correlate best with manometric IOP measurements compared with applanation and Tono-Pen (Reichert Ophthalmic Instruments, Depew, NY) IOP measurements in patients.8

Scleral pneumotonometry previously was found to be increased compared with both corneal measurements and assigned IOP, and our results are consistent with prior reports (Table 3).4,5 The difference measured between scleral and corneal IOP likely reflects differences in the biomechanical properties between cornea and sclera, which can vary by quadrant and anterior–posterior location within an individual.9,10 We chose to obtain measurements over the sclera temporally in primary gaze because eccentric eye position can change IOP measurement and the temporal region is the most accessible and would be preserved even after glaucoma surgery.11,12 However, more studies are required to determine the optimal location for scleral pneumotonometry in patients.

Our results showed a significant correlation \((r = 0.94)\) between scleral and corneal pneumotonometry in patients using a different approach from Kapamajian et al3 \((r = 0.57)\). Kapamajian et al obtained one-time measurements of scleral and corneal pneumotonometry in patients, which can give variable results for the relationship between corneal and scleral measurements because of the individual differences in scleral rigidity. In our study using patients from the retina clinic receiving intraocular injections, we were able to obtain multiple measurements per patient over a short period, spanning a large range of IOPs in each subject. This strategy allowed us to remove the variation among subjects and evaluate whether an increase in scleral pneumotonometry was associated with an increase in corneal pneumotonometry within an individual using a within-subjects Pearson correlation coefficient.
In serial IOP measurements, we found close to a 1:1 linear relationship between changes in scleral and corneal pneumatonometry. This finding supports that following scleral pneumatonometry measurements would be useful clinically, because differences in scleral tonometry measurements reflect differences in corneal tonometry even at pathologically elevated levels of IOP. To calculate the predicted corneal IOP from a scleral IOP measurement, our data yielded the following equation: corneal IOP = 1.04 \times \text{scleral IOP} - 10.37. This formula is remarkably similar to the one we found in our study of cadaveric eyes (Table 3). The standard deviation of the residuals, which is a measure of the accuracy of predictions made with our model, is 2.8 mmHg. Therefore, measured differences greater than this value are likely to represent true changes in scleral pneumatonometry. This value is similar to the 95% measurement accuracy published for corneal pneumatonometry (1.5 mmHg between 0 and 40 mmHg and 3.5 mmHg between 40 and 80 mmHg). On average, we found that scleral pneumatonometry was approximately 10 mmHg higher than corneal pneumatonometry in our model. This value was close to that obtained
by analyzing the raw data using a Bland-Altman plot. The Bland-Altman plot also showed that the average difference between scleral and corneal pneumatonometry measurements appeared consistent over the range of IOPs that we tested. Furthermore, at more clinically relevant levels of IOP, such as mean scleral and corneal IOPs of less than 40 mmHg, more than 80% of measurements were within 5 mmHg of the average difference between scleral and corneal IOP (Fig 4).

Ideally, to estimate best the corneal IOP from a scleral IOP measurement, a baseline measurement of corneal and scleral pneumatonometry should be obtained in the eye of interest before the development of significant corneal pathology to know the exact relationship between these measurements. In practice, this may not be feasible, and our data support the use of the contralateral eye to estimate the baseline difference between scleral and corneal IOP in the eye of interest, because the 2 eyes are significantly correlated within an individual (Fig 1). Using this calculated relationship between scleral and corneal pressure in the contralateral eye of an individual would be more accurate than using an estimate from a population-based equation. Because the relationship between Goldmann applanation tonometry and pneumotonometry is linear, one could use the baseline difference between Goldmann applanation of the cornea and scleral pneumotonometry in the contralateral eye to estimate the predicted Goldmann applanation value for the eye of interest using scleral pneumotonometry.

In our patient population, the relationship between scleral and corneal pneumotonometry was not impacted by age, eye laterality, central corneal thickness, glaucoma, or lens status. Age has been shown to affect scleral rigidity and was reported to affect the relationship between scleral and corneal pneumotonometry significantly in the study of Kapamajian et al.5,14 One possibility for age not affecting our model significantly is that we had an older population of patients. The mean age of our population was 74.1 ± 13.4 years compared with 54.4 ± 17.7 years in the study by Kapamajian et al. Although the range of ages in our patient population did span 34 to 94 years, we may not have been powered adequately to detect a difference in age on scleral IOP. Furthermore, there may be changes to the sclera related to intravitreal injections or underlying disease that were not assessed. Additionally, we evaluated only adult patients in our study, which limits the generalizability of our results. Additional studies are needed to understand the relationship of scleral IOP to corneal IOP for children because there are significant differences in scleral rigidity between adult and pediatric populations.

Table 2. Covariates Do Not Impact Relationship between Scleral and Corneal Pneumotonometry

<table>
<thead>
<tr>
<th>Factor</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.36</td>
</tr>
<tr>
<td>Eye</td>
<td>0.41</td>
</tr>
<tr>
<td>Central corneal thickness</td>
<td>0.48</td>
</tr>
<tr>
<td>Lens status</td>
<td>0.60</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0.92</td>
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</tbody>
</table>

Table 3. Studies of Scleral Pneumotonometry

<table>
<thead>
<tr>
<th>Study</th>
<th>Correlation (r)</th>
<th>Mean Difference</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuo et al</td>
<td>0.94</td>
<td>9.0 mmHg compared with corneal IOP</td>
<td>corneal IOP = 1.04 × scleral IOP – 10.37</td>
</tr>
<tr>
<td>Lin et al5</td>
<td>—</td>
<td>13.2 mmHg compared with assigned IOP*</td>
<td>assigned IOP = 1.01 × scleral IOP – 14.14</td>
</tr>
<tr>
<td>Kapamajian et al5</td>
<td>0.57</td>
<td>8.08 mmHg compared with corneal IOP</td>
<td>corneal IOP = 0.32 × scleral IOP – 0.05 × age + 11.90</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure; — = no data.
*Assigned IOP > corneal IOP by 3.78.
relationship between scleral and corneal pneumatonometry across the range of physiologic and pathologic IOPs for individual patients and show that changes in scleral pneumatonometry reflect changes in corneal pneumatonometry.

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References


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Analysis and interpretation: Kuo, Han
Data collection: Kuo, Han
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Overall responsibility: Kuo, Ou, Jeng, Bhisitkul, Stewart, Duncan, Han
Abbreviations and Acronyms:
Corneal IOP = corneal pneumatonometry; IOP = intraocular pressure;
Scleral IOP = scleral pneumatonometry.
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