Effect of Measurement Order Between Right and Left Eyes on Intraocular Pressure Measurement

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Objective: To determine whether the order of intraocular pressure (IOP) measurement between right and left eyes affects IOP measurement.

Methods: A total of 105 healthy volunteers from the eye clinics and staff at Washington University were randomized into 2 groups. Group 1 underwent 3 sets of 2 IOP measurements per eye, starting with the right eye (right eye twice, left eye twice, right eye twice). Group 2 underwent similar measurements starting with the left eye. After 2 weeks the order of IOP measurements were reversed between groups. A mixed-model repeated-measures analysis of variance analyzed the association of IOP measurement with the order measured (1) between first and second eyes, (2) between first and second visits, (3) between right and left eyes, and (4) with ocular squeezing.

Results: Intraocular pressure measured higher in first eyes compared with fellow eyes regardless of whether right or left eyes were measured first (P=.002). Intraocular pressure measurements decreased between the first and second visits (P<.001). No difference was found in IOP measurements between right and left eyes (P=.41). Moderate and severe ocular squeezing were associated with higher IOP measurements (P<.001) and occurred more during earlier than later IOP measurements within a set (P<.001) and between sets (P<.001 to P=.03).

Conclusions: Intraocular pressure measured in the first eye, whether right or left, is higher than IOP measured in the fellow eye; this may be partially because of ocular squeezing. Measurements of IOP decrease between first and second visits. Multiple IOP measurements at multiple visits are necessary to accurately diagnose and treat patients with glaucoma and ocular hypertension.

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first IOP measurement, traditionally in the right eye, causing an erroneously higher IOP measurement in the right eye compared with the left. In addition, ocular dominance has been associated with higher IOP. If ocular dominance affects IOP, the presence of more right eye–dominant participants may explain the higher IOP measurement of right eyes. To date, there are no studies that have analyzed whether the order of IOP measurement between right and left eyes, ocular squeezing, or ocular dominance contribute to previously reported differences in IOP measurement between right and left eyes.

METHODS

STUDY POPULATION

The study was approved by the institutional review board at Washington University in St Louis, Missouri. Healthy participants aged 18 to 70 years with no major ocular disease were recruited from ophthalmology and optometry clinics and volunteer employees at Washington University School of Medicine. All participants underwent a routine ophthalmic examination or a review of their most recent ophthalmic examination for inclusion in the study. Patients excluded from the study were those with a history of glaucoma or glaucoma suspect status, a first-degree relative with glaucoma, proliferative or severe nonproliferative diabetic retinopathy, age-related macular degeneration requiring treatment, corneal pathology, severe dry eye syndrome, uveitis, visually significant cataracts, history of cerebrovascular accident, or history of intraocular injections or intraocular or laser surgery. Demographic and clinical data of participants were recorded.

IOP MEASUREMENTS

Following informed consent, participants were randomized to 1 of 2 groups by a randomized permuted block design with equal allocation to both groups in the study. All participants underwent 2 visits. At each visit, a set of 2 IOP measurements was taken in the first eye, repeated in the fellow eye, and repeated again in the first eye. At the first visit, participants in group 1 underwent IOP measurements starting with the right eye while participants in group 2 underwent IOP measurements starting with the left eye.

All attempts were made to schedule the second visit within 2 weeks of the first and within 2 hours of the time of day as the first visit to reduce effects of diurnal variation on IOP. At the second visit, participants underwent the same sets of IOP measurements as the first visit but starting with the opposite eye.

All IOP measurements were conducted in a similar manner for both visits. One drop of a combined solution of fluorescein sodium, 0.23%, and benoxinate hydrochloride, 0.4%, was instilled in both eyes prior to the first set of IOP measurements. The drop was instilled in each eye in the same sequence as the order of the IOP measurement (eg, if the right eye was measured first, the fluorescein was applied to the right eye first). If the participant wore contact lenses, they were asked to remove them 10 to 15 minutes prior to the IOP measurements. All IOP measurements were performed using a calibrated Goldmann applanation tonometer, with one examiner measuring the IOP and rotating the tonometer dial and a second examiner reading and recording the IOP measurement from the tonometer dial. The tonometer dial was rotated to 10 mm Hg prior to all measurements. All measurements were performed by a single examiner (M.P.) who was right-handed, while all IOP readings were performed by 1 of 3 examiners. Participants were reminded to breathe naturally and maintain fixation at a distance before each measurement. After all IOP measurements were obtained, the central corneal thickness of each eye was measured using a System Corneo-Gauge III ultrasound pachymeter (Chiron IntraOptics Inc, Irvine, California) with the lowest of 3 consecutive measurements recorded as the central corneal thickness for each eye.

OCULAR SQUEEZING

The degree of ocular squeezing during each IOP measurement was graded by the same examiner who measured IOP (M.P.) using the following scale: none, IOP measured on the first attempt with no difficulty and no ocular squeezing; mild, IOP measured on the first attempt with no difficulty but mild ocular squeezing; moderate, IOP measured on the first or second attempt with some difficulty due to ocular squeezing; severe, IOP measured on the second or third attempt with great difficulty due to ocular squeezing; and unable, unable to measure IOP because of extreme ocular squeezing and/or discomfort reported by the participant.

OCULAR DOMINANCE TESTS

The pointing-a-finger, hole-in-card, and hole-in-card at face tests were performed to determine the dominant eye of each participant. The overall dominant eye was the eye deemed dominant by at least 2 of the 3 ocular dominance tests. If the tests were inconclusive then the dominant status was recorded as undetermined.

STATISTICAL ANALYSIS

Descriptive statistics (means and standard deviations) are reported for all IOP measurements obtained at both visits and the proportion of moderate or severe ocular squeezing recorded during IOP measurements by each set, within a set, and by each visit. Mixed-models, repeated-measures analysis of variance (Proc Mixed in SAS version 9.2; SAS Inc, Cary, North Carolina) were designed to test for differences in IOP measurement between: (1) sets of IOP measurements (first set vs second set vs third set), (2) IOP measurements within each set (first IOP measurement vs second IOP measurement), (3) first and second visits, (4) right and left eyes, (5) no or mild vs moderate or severe ocular squeezing, and (6) dominant vs nondominant eyes. Generalized estimating equations for repeated categorical data (Proc Genmod; SAS Inc) were designed to test for differences in moderate or severe ocular squeezing due to the order it was measured between (1) sets of IOP measurements, (2) IOP measurements within each set, and (3) first and second visits. Because of the relatively low incidence of ocular squeezing, the effects of ocular laterality and dominance were not included in this model.

RESULTS

Between January 2, 2008, and June 30, 2008, 148 of 194 screened patients met eligibility criteria for the study. Of the eligible participants, 108 agreed to participate in the study; however, 3 were later excluded because of difficulty measuring IOP (2 participants) and erratic IOP measurements (1 participant). Of the 105 participants included in the analysis, 50 (48%) were randomized to group 1 and 55 (52%) to group 2.
There were no statistically significant differences in baseline characteristics between the 2 groups (Table 1). Both visits were completed for 47 participants (94%) in group 1 and 48 (87%) in group 2. The second visits occurred within 2 weeks of the first visit in 42 participants (89%) in group 1 and 34 (71%) in group 2. Furthermore, the second visits were scheduled within 2 hours of the first visit in 36 participants (77%) in group 1 and 37 (77%) in group 2.

### RELATIONSHIP OF IOP TO MEASUREMENT ORDER

All 12 IOP measurements (means [standard deviations]) obtained for each group on both visits are displayed in Figure 1. There was no overall difference in IOP measurement between the 2 groups (P = .41); thus, the following results reflect the combined IOP measurements from both groups.

At both visits, the initial IOP measurement obtained in each eye was higher in the first eye than in the second. For example, when the right eye was measured first, its initial IOP measurement (mean [SD], 14.1 [2.3] mm Hg) was higher than the initial IOP measurement of the left eye (14.0 [2.3] mm Hg). Regardless of which eye was measured first, there was a significant difference in IOP measurement between the first and second eyes (first set vs second set P = .002). There was also a significant decrease in IOP measurement between the first and second measurements within a set (obtained from the same eye) and between the first and second visits (Table 2).

There was no statistically significant difference in mean IOP measurements obtained from both visits between right and left eyes (P = .41).

### RELATIONSHIP OF IOP TO OCULAR SQUEEZING

There was no statistically significant difference in moderate or severe ocular squeezing between group 1 (mean 8.5%) and group 2 (mean, 4.0%) for all IOP measurements obtained at both visits (P = .17). Therefore, the results for ocular squeezing reflect the combined results from groups 1 and 2.

Moderate or severe ocular squeezing occurred in 75 of 1200 measurements obtained (6.3%) and was associated with higher IOPs compared with measurements with no or mild ocular squeezing (Table 2). There was a significant decrease in moderate or severe ocular squeezing between the first and second IOP measurements within a set, the first and second sets, and the second and third sets (Figure 2). No significant difference in moderate or severe ocular squeezing was found between the first and second visits or right and left eyes.

### RELATIONSHIP OF IOP TO OCULAR DOMINANCE

The overall dominant eye was the right eye in 55 participants (52.4%), the left eye in 46 participants (43.8%), and undetermined in 4 participants (3.8%). There was no significant difference in IOP (P = .39) between dominant and nondominant eyes (Table 2).
To our knowledge, this is the first study that investigates whether the order of IOP measurement between right and left eyes plays a role in previously reported IOP asymmetry between right and left eyes. We found that the IOP measured in the first eye, whether the right or left, was higher than the IOP measured in the fellow eye. Thus, prior reports of higher IOP measurements in right than left eyes are likely because of the right eyes being measured first and not a physiologic difference in IOP between eyes.

We also report a decrease in IOP measurements with repeated applanation tonometry both within a visit and between visits. Previous studies demonstrated this same phenomenon and at values comparable with our 0.3-mm Hg decrease in IOP measurement in the same eye (ie, between the first and third sets of IOP measurements). Other studies, however, did not specifically test whether the order of IOP measurement between right and left eyes explains the asymmetry between IOP measurement of right and left eyes.

Why is IOP measured higher in initial as opposed to fellow eyes and why does IOP decrease with repeated applanation tonometry? One plausible explanation is that patients have more anxiety and unfamiliarity with tonometry during earlier IOP measurements, causing artificially higher IOPs than those measured later. Patients who receive sham tonometry prior to real tonometry measured IOP 2 mm Hg lower than patients without sham tonometry, suggesting that familiarity with applanation tonometry may result in a lower measured IOP. Ocular squeezing, Valsalva maneuver, or other unknown phenomena associated with anxiety or unfamiliarity with tonometry may play a role in the higher initial IOP measurements.

Figure 2. Percentage of eyes with moderate/severe ocular squeezing during intraocular pressure measurements. *P<.001.

To our participants were reminded to breathe naturally and maintain fixation at distance, it is possible that participants with anxiety or unfamiliarity with tonometry may exhibit more of these behaviors with earlier IOP measurements.

Another factor that may explain why IOP measurement decreases with repeated applanation tonometry is the changing status of the tear film, with a smaller tear meniscus associated with IOP underestimation. Previous studies performing tonography in one eye report a decrease in IOP measurement in the fellow eye, likely because of evaporation of the tear film. Evaporation of the tear film over time may occur naturally or because of increased contact time with a topical anesthetic. In addition, prolonged contact of the topical anesthetic with fluorescein may cause fluorescein "quenching," resulting in hypofluorescence and an underestimation of IOP measurement. Therefore, both increased tear film evaporation and fluorescein quenching have a greater effect over time and may be related to the decrease in IOP measurement with repeated applanation tonometry.

Table 2. Intraocular Pressure Measurements by Subclassification for All Participants

<table>
<thead>
<tr>
<th>Subclassification</th>
<th>IOP, Mean (SD), mm Hg</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP by set</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First set (n=400)</td>
<td>14.5 (2.3)</td>
<td>.002</td>
</tr>
<tr>
<td>Second set (n=400)</td>
<td>14.2 (2.3)</td>
<td>.088</td>
</tr>
<tr>
<td>Third set (n=400)</td>
<td>14.2 (2.3)</td>
<td>.0002</td>
</tr>
<tr>
<td>IOP within a set</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First measurement (n=600)</td>
<td>14.4 (2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Second measurement (n=600)</td>
<td>14.2 (2.3)</td>
<td></td>
</tr>
<tr>
<td>IOP by visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit (n=630)</td>
<td>14.7 (2.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Second visit (n=570)</td>
<td>13.9 (2.1)</td>
<td></td>
</tr>
<tr>
<td>IOP by eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right eye (n=596)</td>
<td>14.3 (2.3)</td>
<td>.41</td>
</tr>
<tr>
<td>Left eye (n=604)</td>
<td>14.2 (2.3)</td>
<td></td>
</tr>
<tr>
<td>IOP by ocular squeezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/mild (n=1125)</td>
<td>14.2 (2.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Moderate/severe (n=75)</td>
<td>14.9 (2.4)</td>
<td></td>
</tr>
<tr>
<td>IOP by ocular dominance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondominant eye (n=582)</td>
<td>14.3 (2.4)</td>
<td>.39</td>
</tr>
<tr>
<td>Dominant eye (n=582)</td>
<td>14.2 (2.2)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.

*Mixed-model, repeated-measures analysis of variance.
An interesting finding in our study was the 0.8–mm Hg mean decrease in IOP measurement between the first and second visits. This decrease is comparable with the 0.6–mm Hg mean decrease in IOP measurement reported between the baseline and first follow-up visit in untreated participants in the Ocular Hypertension Treatment Study. These differences are likely not due to evaporation of the corneal tear film or fluorescein quenching, and we did not find a significant difference in ocular squeezing between visits. Effects of diurnal variation or changes in ocular or physical health affecting IOP measurements are unlikely in our study given that most visits were scheduled within 2 weeks and within 2 hours of the same time of day. Other factors affecting tonometry not examined in our study (eg, Valsalva, eccentric gaze) may differ between visits resulting in the lower IOP measurements at the second visit.

In a study by Dane et al, right eye–dominant patients had a mean IOP that was 0.76 mm Hg higher in right than left eyes. Because dominant eyes perform most of the near work, the greater accommodative effort required in dominant eyes may result in a higher IOP. We analyzed whether ocular dominance may account for higher IOPs in right than left eyes but we did not find a significant difference in IOP measurement between dominant and nondominant eyes.

The results of this study emphasize that the order of IOP measurement between right and left eyes may affect IOP measurement, with the first eye measuring higher than the second eye. In addition, IOP measured on the first visit may be higher than IOP measured on the second visit. Therefore, a single IOP measurement taken on a single visit may not reflect the true IOP of that eye. Artifactual influences may cause earlier IOP measurements to appear higher (eg, more squeezing on earlier measurements) or later IOP measurements to appear lower (eg, evaporation of corneal tear film over time) than true IOP. Such information is important since many clinicians establish a baseline or target IOP or assess medication efficacy based on a single IOP measurement at a single visit. During a medication trial, a decrease in IOP at a second visit may be interpreted as a successful medication trial as opposed to normal regression to the mean. Because of the multiple known and unknown factors that affect IOP measurement, we recommend multiple IOP measurements be recorded at each visit. Factors that affect IOP measurement such as the amount of ocular squeezing should be routinely recorded to alert for possible inaccurate measurements. In addition, baseline and target IOPs as well as medication assessment should be evaluated over multiple visits.

The mean differences in IOP measurements in our study were small but may have clinical significance. Results from the Early Manifest Glaucoma Trial suggest that even a 1–mm Hg increase in IOP was associated with an 11% increase in the hazard ratio for the progression of glaucoma. Thus, measuring IOP accurately is critical in the management of glaucoma. The values we report are mean values, with some patients having larger differences between IOP measurements that may be clinically significant. In addition, our study analyzed the effect of measurement order on IOP of participants with healthy eyes; this effect may be even greater in patients with glaucoma.

The strengths of this study include the randomization scheme with repeated measures, crossover design, and standardized method of IOP measurement using a 2-operator system to minimize measurement bias. The use of 1 examiner to measure IOP reduced the effect of varying technique but may have introduced a bias (eg, handedness) that affected the IOP measurements. Future studies may use several masked examiners to further reduce the potential bias and possibly reflect a more clinical setting. In addition, the assessment of ocular squeezing in our study was subjective. Our results imply that IOP measurement decreases with repeated application tonometry within a visit and between 2 visits; however, factors affecting this phenomenon need to be further elucidated.

In conclusion, we found that IOP measured in the first eye, whether the right or left, was higher than IOP measured in the fellow eye and IOP measurement in both eyes decreased with repeated application tonometry. Clinicians should be aware of this phenomenon and obtain multiple IOP measurements on multiple visits to establish accurate baseline and treated IOPs to determine medication efficacy in patients with glaucoma.

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