Variability of Intraocular Pressure Measurements in Observation Participants in the Ocular Hypertension Treatment Study

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Purpose: To describe variability of intraocular pressure (IOP) measurements within the same eye and between right and left eyes over a 60-month period in participants in the Ocular Hypertension Treatment Study.

Design: Analysis of data from a prospective, randomized clinical trial.

Participants: Eight hundred ten participants randomized to the observation group.

Methods: Intraocular pressure measurements were obtained at the baseline visit and every 6 months thereafter. Pearson correlation coefficients were calculated for IOP measurements in the same eye between visits and for IOP measurements between right and left eyes of participants at each visit. Differences in IOP measurements between visits are reported in percent change (>15%, >20%, and >30%) and in millimeters of mercury (<3 mmHg, 3–5 mmHg, and >5 mmHg). The effects of regression to the mean, consistency in time of day, and sequence of IOP measurement of right and left eyes were examined.

Main Outcome Measures: Correlation of IOP measurements between consecutive 6-month visits.

Results: The correlation of IOP measurements within the same eye between consecutive visits was $r = 0.62$, whereas the correlation of IOP measurements between right and left eyes at the same visit was $r = 0.72$. Thirteen percent of eyes had >20% change in IOP between consecutive visits. Sixty-six percent of eyes had a change in IOP within 3 mmHg, and 10% of eyes had a change in IOP >5 mmHg between visits. Eyes with a higher baseline IOP had a lower IOP at 6 months. There was a stronger correlation of IOP measured within 2 hours of the time of day between visits ($r = 0.56$) than >2 hours apart ($r = 0.39$). IOP of the right eye, which was measured first, was 0.3±2.8 mmHg higher than the left eye.

Conclusions: The variability of IOP measurements in the same eye between consecutive visits is moderate and is greater than the variability of IOP measurements between right and left eyes at the same visit. Factors affecting the variability of IOP measurement include regression to the mean, time of day, and measurement order. Knowledge of variability in IOP and its measurements may help clinicians establish a more accurate baseline IOP, target IOP, and assessment of medication effect.

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Intraocular pressure (IOP) variability is a well-known phenomenon that may be the result of true variability (e.g., diurnal variation, progression of disease) or variability in IOP measurement (e.g., technician error, uncalibrated tonometer). Understanding variability in IOP and IOP measurement is important to diagnose and manage patients with glaucoma accurately. A clinician's understanding of a patient's IOP fluctuation may help to establish a more accurate baseline and target IOP as well as to determine IOP-lowering response to ocular hypotensive medications. In addition, knowledge regarding variability in IOP may help to clarify whether methods to determine response to a medication, such as the monocular trial, are valid in a clinical setting.

Most prior studies of IOP fluctuation have focused on diurnal curves and have reported conflicting results with regard to symmetry between eyes.[1–7] Only a few studies have examined long-term variability in diurnal curve patterns or IOP measurement either between eyes or within the same eye.[1,3,8] These studies, conducted over several months, also report disparate results on the amount of variability of IOP. Furthermore, factors that may affect the variability of IOP and IOP measurements over time have not been examined fully.

The Ocular Hypertension Treatment Study (OHTS) is a multicenter, randomized, clinical trial designed to evaluate whether lowering IOP by topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma (POAG) in participants with ocular hypertension.[9] Participants were randomized to either medication or observation. Intraocular pressure measurements were obtained every 6 months using a well-defined standardized protocol.[10] The purpose of this report was to describe variability of IOP measurements within the same eye and between right and left eyes of participants in the observation group in the OHTS over 60 months. The main focus of this report is descriptive. A careful, comprehensive analysis of factors affecting variability of IOP measurement is beyond the scope of this article.

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Patients and Methods

The Ocular Hypertension Treatment Study

The OHTS is a multicenter, randomized, clinical trial with 22 participating clinical centers. Each clinical center received approval for the study by its institutional review board. The OHTS is registered at www.clinicaltrials.gov (registration no. NCT00000125). The study protocol has been described in detail previously,[10] and the manual of procedures can be viewed online (https://vrcc.wustl.edu/mop/ohtsmop.pdf; accessed September 22, 2008).[11] Participants 40 to 80 years of age with no evidence of glaucoma by optic disc examination, review of optic disc photographs, or visual field testing were recruited for the study between February 1994 and October 1996. Eligibility criteria included IOP between 24 and 32 mmHg in one eye and between 21 and 32 mmHg in the fellow eye. Qualifying IOP was calculated from 2 consecutive measurements on separate visits. These visits occurred within 12 weeks of each other and were scheduled at the same time of day (±2 hours). Participants who met eligibility criteria returned for a baseline randomization visit in which they were randomized either to topical ocular hypotensive medication or to close observation without treatment. This report includes only data from participants randomized to close observation. There were no minimum or maximum IOP criteria required at the randomization visit. Participants completed follow-up visits every 6 months.

All IOP measurements were obtained by 2 OHTS-certified examiners using calibrated Goldmann applanation tonometers. One operator viewed the mires and rotated the tonometer dial while the second operator recorded the result. Two IOP measurements were obtained, but if the readings differed by more than 2 mmHg, a third measurement was obtained. The IOP in the right eye was measured first. The visit IOP was defined as the mean of 2 IOP measurements or the median of 3 measurements. The baseline IOP was defined as the mean of 2 or 3 IOP measurements recorded at the baseline randomization visit. Baseline IOP did not include IOP measurements used to determine eligibility to minimize potential regression to the mean. Diurnal IOPs were not performed in the OHTS. The protocol specified that follow-up visits to be scheduled within 2 hours of the time of day of the baseline visit.

After the June 2002 publication of the primary outcome article that demonstrated that treatment of participants with ocular hypertension delayed or prevented the onset of POAG, participants initially randomized to the observation group were offered ocular hypotensive medication.[9] Therefore, data from observation participants after June 2002 were excluded from this analysis. Before this date, there were participants in the observation group who were started on ocular medications in one or both eyes because of clinical concern by their physicians. Data from participants were censored after they were started on an ocular medication in one or both eyes or after a diagnosis of glaucoma was established in one or both eyes. More than 70% of the participants had completed their 60-month visit by June 2002; therefore, data through 60 months are reported.

Statistical Design and Methods

The primary outcomes of interest in this analysis were the association of IOP in the same eye between visits and the association of IOP between right and left eyes of participants at each visit. The effects on IOP from regression to the mean, time of day of IOP measurement, and sequence of IOP measurement (right eye measured first) also were examined.

Descriptive statistics (mean and standard deviation [SD]) are reported for IOP of both the right and left eyes at the baseline and follow-up visits. The variability of IOP measurements within the same eye between consecutive 6-month visits over 60 months are described in the following manner: (1) Pearson correlation coefficients of IOP in the same eye between consecutive visits (e.g., IOP at baseline correlated to IOP at 6 months, IOP at 6 months correlated to IOP at 12 months); (2) the proportion of eyes whose IOP measurement changed (increased or decreased) by more than 15%, more than 20%, and more than 30% between consecutive visits; (3) the proportion of eyes with an absolute difference in IOP measurement of less than 3 mmHg, 3 to 5 mmHg, or more than 5 mmHg between 2 consecutive visits. The proportion of eyes with an absolute difference in IOP change of more than 3 mmHg are reported because 3 mmHg has been reported to be within the errors of measurement of applanation tonometry between 2 examiners.[12]

Symmetry of IOP between eyes was defined as the association of IOP measurement in one eye to IOP measurement in the fellow eye at the same visit. Intraocular pressure symmetry between eyes is described as follows: (1) Pearson correlation coefficients of IOP measurements of right and left eyes at each 6-month follow-up visit from baseline to 60 months (e.g., IOP of right eye at 6 months correlated to IOP of left eye at 6 months), and (2) the proportion of participants with asymmetric fluctuation of IOP measurements between eyes across 2 visits. Asymmetric fluctuation between eyes was defined as the absolute difference in IOP change of 3 mmHg or more between visits [|(IOP change right eye) minus (IOP change left eye)|]. For example, if the IOPs measured at the 6-month visit were 21 mmHg in the right eye and 24 mmHg in the left eye and the IOPs measured at the 12-month visit were 25 mmHg in the right eye and 23 mmHg in the left eye, then the amount of fluctuation between the eyes between these 2 visits would be 5 mmHg: (25–21)–(23–24) = 5.

Regression to the mean was examined by comparing baseline IOP and 6-month IOP in the eye with the higher baseline IOP between the 2 eyes. When right and left eyes had the same IOP at baseline, 1 eye was selected randomly as the eye with the higher IOP. Descriptive statistics (mean and SD) for IOP are reported.

The effect of consistency of time of day of IOP measurements was assessed by dividing participants into 2 groups: those whose 6-month IOP was measured within 2 hours of the same time of day as the baseline IOP and those whose 6 month IOP was measured more than 2 hours beyond the same time of day as the baseline IOP. Descriptive statistics (mean and SD) of IOP for both groups are reported at the baseline visit and the 6-month visit. A Pearson correlation of IOP at baseline and 6 months was performed for both groups to determine whether the consistency of time of day of IOP measurement affected variability of IOP.

The association of measurement sequence and the IOP measured was examined by analyzing the IOP measurements in the order performed: IOP_1 right eye, IOP_2 right eye, IOP_1 left eye, and IOP_2 left eye. Descriptive statistics (mean and SD) are reported by the order of each IOP measurement at the baseline visit. All data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC).

Results

Of the 819 participants in the observation group, 810 participants had completed both a baseline visit and at least 1 follow-up visit over a 60-month period for inclusion in this report. Baseline characteristics of these participants are reported in Table 1. The mean follow-up time for participants included in the analysis was 53.2±13.7 months. Of the 810 initial participants, data were available for 574 participants (71%) at the 60-month visit.

Data from 116 participants were censored from this analysis. Data were censored after the date a participant was diagnosed with

Table 1. Baseline Characteristics

Characteristic	Mean±Standard Deviation or Percent (n = 810)
Age (yrs)	56.2±9.7
Gender	
Male	42.1%
Female	57.9%
Race	
African American	24.8%
Other	75.2%
Educational status	
High school or less	33.0%
College or more	67.0%
Marital status	
Married	65.1%
Not married or widowed	34.9%
Diabetes	
Yes	12.1%
No	87.9%
High blood pressure	
Yes	38.2%
No	61.8%
Heart disease	
Yes	6.7%
No	93.3%
Mean central corneal thickness of right and left eyes (μm)	574.5±37.7 (n = 719)

glaucoma in one or both eyes (n = 79) or if medication was initiated in one or both eyes (n = 80), with 43 participants meeting both criteria. The mean follow-up time for participants with data censored was 32.9±17.3 months. A downward trend in IOP measurement of 1.6 to 1.7 mmHg was observed over 60 months in the analysis sample. Whether censoring of data after the development of POAG and clinician-initiated medication affected the overall mean IOP in the analysis sample was assessed. The last precensored IOP measurement was used for participants with censored data, and it was carried forward through 60 months. Censoring of data from these participants accounted for 0.6 mmHg of the downward trend of IOP.

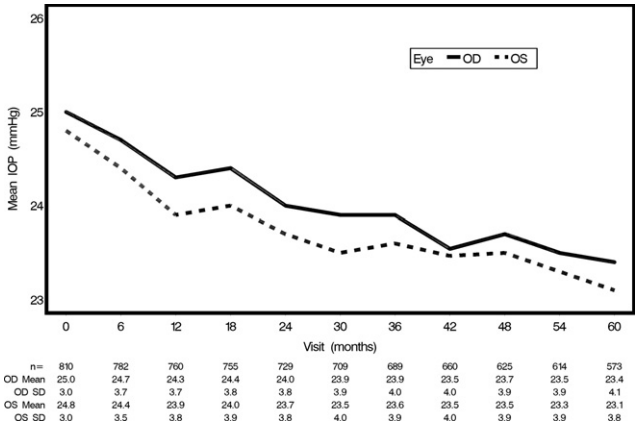

Figure 1. Graph showing the mean intraocular pressure (IOP; ±standard deviation [SD]) of right eyes (OD) and left eyes (OS) from baseline to 60 months.

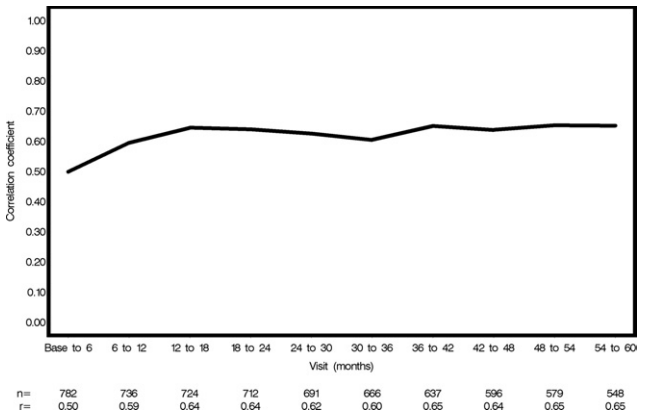

Figure 2. Graph showing the correlation of intraocular pressure measurements in the same randomly selected eye between consecutive visits at 6-month intervals through 60 months.

Variability of Intraocular Pressure Measurements of the Same Eye between Visits

The mean IOP (±SD) of right and left eyes over the 60-month period was 24.1±3.8 mmHg and 23.8±3.8 mmHg, respectively. Figure 1 displays the mean IOP of right and left eyes for each visit from baseline to 60 months. Across all visits for all patients, the Pearson correlation coefficient (r) of IOP measurements between consecutive visits (e.g., baseline to 6 months, 6 to 12 months) in the same randomly selected eye was $r = 0.62$ and ranged from $r = 0.50$ to 0.65 between visits (Fig 2). The correlation coefficient of a randomly selected eye is reported because of similar results for right and left eyes.

Over the 60-month follow-up period, 810 participants completed a total of 6671 consecutive visits. Of these 6671 consecutive visits, 13% of the eyes had a difference in IOP of more than 20% between any 2 consecutive visits. Of these, 5% of eyes had a decrease in IOP measurement of more than 20% at the second visit compared with the first visit and 8% of eyes had an increase in IOP measurement of more than 20% at the second visit compared with the first visit. Table 2 displays the percent of eyes with differences in IOP measurements of more than 15%, more than 20%, and more than 30% between consecutive visits within the same eye.

Between all consecutive visits, the mean absolute difference in IOP measured within the same eye was less than 3 mmHg in 66% of eyes, between 3 and 5 mmHg in 24% of eyes, and more than 5 mmHg in 10% of eyes. Figure 3 displays the distribution in the difference of IOP measured at the baseline and 6-month visits.

Table 2. Percent of Eyes with More Than 15%, 20%, and 30% Change in Intraocular Pressure Measurements between 2 Consecutive Visits (n = 6671) over 60 Months

Percent Change in IOP between Consecutive Visits	Increase	Decrease	Total
>15%	13% (n = 856)	11% (n = 746)	24% (n = 1602)
>20%	8% (n = 527)	5% (n = 352)	13% (n = 879)
>30%	3% (n = 221)	1% (n = 75)	4% (n = 296)

IOP = intraocular pressure.
One eye was selected randomly per participant.

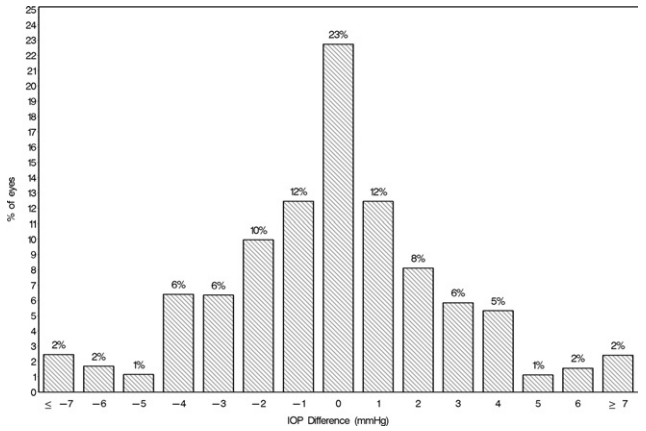

Figure 3. Bar graph showing the distribution of differences between baseline intraocular pressure (IOP) and 6-month IOP (6-month IOP minus baseline IOP) for a randomly selected eye of each participant (n = 782). Positive values indicate that IOP measured at 6 months was higher than at baseline and negative values indicate that IOP measured at 6 months was lower than at baseline.

Symmetry of Intraocular Pressure Measurements between Eyes at Each Visit

Across all visits for all patients, the Pearson correlation coefficient (r) of the IOP measurements between right and left eyes at each visit was $r = 0.72$ and ranged from $r = 0.65$ to 0.76 (Fig 4). Twenty-four percent of participants had asymmetric fluctuation of 3 mmHg or more between eyes between 2 consecutive visits over the 60-month period.

Regression to the Mean

Eyes with a higher baseline IOP had a mean decrease of IOP (±SD) of 0.6±3.5 mmHg between the baseline and 6-month visits ($P<0.0001$, matched-pair t test), whereas eyes with a lower baseline IOP had a mean change of 0.0±3.1 mmHg between the same visits ($P = 0.98$, matched-pair t test). Figure 5 displays the mean change in IOP between baseline and 6-month visits of all eyes. In general, eyes with IOP on the higher end at the baseline visit had a decrease in IOP at the 6-month visit and eyes with IOP on the lower end at the baseline visit had an increase in IOP at the 6-month visit.

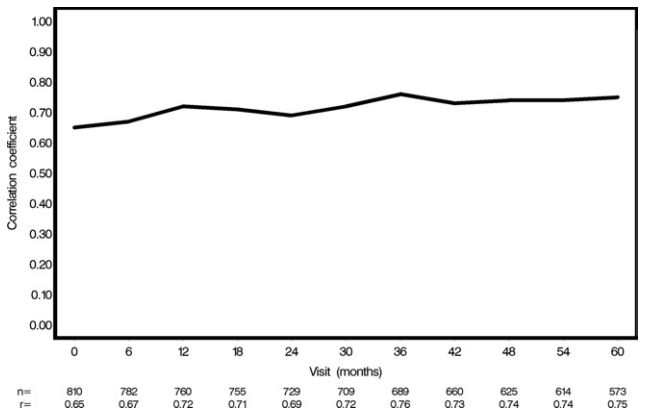

Figure 4. Graph showing the correlation of intraocular pressure measurement between right and left eyes at each visit over 60 months.

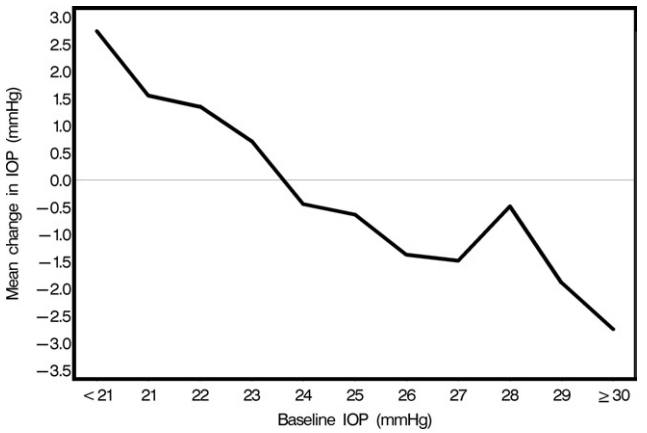

Figure 5. Graph showing the mean difference in intraocular pressure (IOP) from baseline to 6 months in eyes with a higher baseline IOP compared with their fellow eyes (n = 782). Positive values indicate that IOP measured at 6 months was higher than at baseline and negative values indicate that IOP measured at 6 months was lower than at baseline.

Consistency of Time of Day of Intraocular Pressure Measurement

There were 781 participants who had a baseline visit, a 6-month visit, and a recorded time of day for IOP measurements for both visits. Participants (n = 524) whose IOP at 6 months was measured within 2 hours (mean, 0.8 hours; range, 0–2 hours) of the time of day as baseline had a mean IOP in a randomly selected eye of 24.9±2.9 mmHg at baseline and 24.8±3.6 mmHg at 6 months (Pearson correlation coefficient, $r = 0.56$). Participants (n = 257) whose IOP at 6 months was measured more than 2 hours (mean, 4.0 hours; range, 2.1–8.2 hours) of the time of day as baseline had a mean IOP in a randomly selected eye of 24.9±3.3 mmHg at baseline and 24.3±3.5 mmHg at 6 months (Pearson correlation coefficient, $r = 0.39$). The difference between these correlations ($r = 0.56$ and $r = 0.39$) was statistically significant ($P<0.003$).

Sequence of Intraocular Pressure Measurement

Intraocular pressure measurement in the right eye was consistently higher than IOP measurement in the left eye at each visit over 60 months, with a mean IOP of 0.3±2.8 mmHg higher in right eyes than left eyes (Fig 1). To determine whether measurement order explains why IOP in the right eye was measured higher than the left eye, the mean IOP according to measurement sequence from the first to fourth IOP measurement in a given OHTS visit was examined. The mean IOP in order of sequence was: 25.1±3.0 mmHg (IOP_1 right eye), 25.0±3.0 mmHg (IOP_2 right eye), 24.9±3.0 mmHg (IOP_1 left eye), and 24.7±3.1 mmHg (IOP_2 left eye). A repeated-measures analysis of variance showed a significant difference among the 4 measurements ($P<0.0001$). There was also a significant difference between IOP_1 right eye and IOP_1 left eye ($P = 0.0028$) and between IOP_2 right eye and IOP_2 left eye ($P = 0.0023$).

Discussion

To the authors' knowledge, the OHTS provides the largest available database to date to investigate long-term variability of IOP within the same eye and between right and left

eyes of individuals with untreated ocular hypertension. The results suggest that the variability in IOP measurement in the same eye between visits is moderate and is greater than the variability in IOP measurement between right and left eyes at each visit.

Data from the OHTS were collected using a standardized protocol with strict quality assurance for IOP measurements. Measurement variability and observer bias were reduced by using a calibrated Goldmann applanation tonometer and a 2-operator system with a minimum of 2 IOP measurements and a third IOP measurement if needed per eye each visit. Diurnal variability was reduced by attempts to schedule visits within 2 hours of the same time of day as the baseline visit.

Intraocular Pressure Variability within the Same Eye

Prior studies regarding long-term IOP variability within the same eye report mainly on stability of diurnal curve patterns over time. Wilensky et al.[3] found that 28% of ocular hypertensive patients (n = 32) and 44% of open-angle glaucoma patients (n = 43) showed similar diurnal curve patterns of the same eye on a repeat test (1 to 45 months apart) using home tonometry. Langley et al[13] reported 66% of patients (n = 16) with a similar curve type between 2 visits separated by months. Both of these studies, however, analyze long-term IOP stability within the same eye through diurnal curve patterns as opposed to quantifying differences in IOP measurements, as in this analysis.

A moderate correlation of IOP measurements was found within the same eye between visits ($r = 0.62$) as well as a moderate amount of variability in IOP measurement within the same eye, with 13% of eyes having a difference in IOP of more than 20% between visits. Such a level of IOP variability may contribute to improper diagnosis and management of glaucoma. For example, a patient with glaucomatous progression may have a single baseline IOP measured at 1 visit. This single baseline IOP may be atypically high or low compared with their usual mean IOP, resulting in a calculated target IOP that may not be appropriate to prevent further glaucomatous progression. Intraocular pressure measurements obtained on multiple visits would provide a more accurate baseline and target IOP.[14] In addition, measuring IOP at more than 1 visit after a medication is initiated may reduce improper continuation or discontinuation of an ocular hypotensive medication.

Results from previous studies suggest that long-term variability in IOP may be a risk factor for glaucomatous progression.[15–19] These results, however, are controversial.[20] An analysis using data from the OHTS may help to elucidate whether long-term variability of IOP measurement in individuals with untreated ocular hypertension is a risk factor for development of POAG. If so, understanding an individual's long-term variability of IOP measurement from IOP measurements obtained on several different visits may help to assess the risk for glaucomatous progression.

Approximately one third of eyes in this sample had an absolute difference in IOP measurement of more than 3 mmHg between visits. The 3-mmHg minimum cutoff was chosen to exclude variability in IOP measurement that might have been the result of measurement error using Goldmann applanation tonometry.[12] The measurement error in OHTS, however, is likely even less than 3 mmHg given the strict protocol, multiple IOP measurements, and 2-operator system.

Interestingly, a downward slope of IOP measurement was observed in both right and left eyes over the 60-month period. This decrease in IOP measurement over time seemed to be attributable partially to censoring of POAG participants. Other possible causes, such as treatment for systemic hypertension, are under investigation.

Intraocular Pressure Symmetry between Eyes

Previous reports on the symmetry of IOP measurements between right and left eyes have focused on diurnal curves. Earlier studies report conflicting results with regard to the symmetry of diurnal curves between fellow eyes.[1–3] More recent studies, however, have found a strong correlation of IOP measurements between right and left eyes using Goldmann applanation tonometry over a 24-hour period in untreated ($r = 0.84$) and treated ($r = 0.84$) glaucoma patients, glaucoma suspects ($r = 0.78$), and normal-tension glaucoma patients ($r = 0.81$).[4,6] Similar correlations over a 24-hour period were found in older healthy individuals ($r =$ 0.77 to 0.86) and patients with untreated POAG ($r = 0.65$ to 0.79) using pneumotonometry.[5,7] In the sample of untreated ocular hypertension participants, the measured IOPs of right and left eyes also were well correlated ($r = 0.72$), regardless of the time of day that IOPs were measured.

The correlation of IOP between fellow eyes at the same visit was higher than the correlation of IOP within the same eye between visits, suggesting that factors that influence IOP measurement are more concordant at the same visit than at different visits. Therefore, when starting a patient on an ocular hypotensive medication in one eye, the fellow eye serves as a better control for IOP variability than the eye starting the medication. For example, a patient may have a baseline IOP of 22 mmHg in both eyes and start on a glaucoma medication in one eye, the trial eye. On the follow-up visit, the IOP measurements are 24 mmHg in the trial eye and 30 mmHg in the fellow eye. If the clinician uses only the trial eye to determine medication response, he may conclude that the trial eye did not have a response to the medication because it increased by 2 mmHg between visits. However, if the clinician uses the fellow eye as a control for IOP variability, it is apparent that the IOP between eyes was similar at the first visit but differed by 6 mmHg at the second visit, with the trial eye having a lower IOP than the fellow eye. Because the correlation of IOP between eyes at each visit should be strong, the clinician would conclude that the large difference in IOP between eyes at the second visit was likely the result of medication response in the trial eye as opposed to normal variability in IOP. Therefore, it is useful to use the fellow eye as a guide for IOP variability in addition to using IOP measurements from several visits to determine effectiveness of glaucoma medications.

Intraocular Pressure Variability between Eyes

Variability of IOP between eyes was determined by the proportion of eyes with asymmetric fluctuation of 3 mmHg or more between eyes between visits. The current data show 24% of participants with asymmetric fluctuation between any 2 visits over a 60-month follow-up. In a retrospective study, Realini et al[8] reported asymmetric IOP fluctuation between eyes (defined as more than 15% change from baseline and more than 3 mmHg IOP change between eyes) occurring at least once between consecutive visits in 50% of normals (n = 42) and 63.2% of treated glaucoma patients (n = 38). The follow-up visits in the study by Realini et al. spanned at least 1 year and had a mean number of 7.8±2.0 visits for normal participants and 8.4±1.9 visits for glaucoma participants. The proportion of participants with asymmetric fluctuation between eyes may be greater in Realini et al's study as compared with the current study because of a difference in sample populations, sample sizes, and study designs. The OHTS uses a strict protocol for IOP measurement that may decrease measurement error, resulting in less variability in IOP measurement compared with that seen in a retrospective study of patients in clinical practice.

Other studies have analyzed asymmetry of fluctuation between eyes over a 24-hour period. When IOP was measured at 6 time points over a 24-hour period, fellow eyes were found to fluctuate 3 mmHg or more between 2 time points in 5% to 22% of untreated patients, in 7% to 17% of treated glaucoma patients, in 6% to 13% of glaucoma suspects, and in 7% to 14% of normal-tension glaucoma patients.[4,6] In another study, 27.5% of patients in their habitual position (sitting during day, supine at night) had asymmetric variations of 3 mmHg or more between eyes between intervals throughout the day.[7] Results from these studies are fairly comparable with those of the current study.

Intraocular Pressure Variability That Masks or Mimics Medication Effect

In clinical practice, it is common to start an ocular hypotensive medication in 1 eye and aim for an IOP-lowering response between 20% and 30%. This study found that 13% of untreated eyes had either a more than 20% decrease (5% eyes) or a more than 20% increase (8% eyes) in IOP measurement between 2 consecutive visits. If these participants had initiated an ocular hypotensive medication aiming for a 20% IOP-lowering response, the 5% of participants with a lower IOP at the second visit would seem to show a good response to the medication when they really did not have such a response (IOP variability mimics medication effect), whereas the 8% of participants with a higher IOP at the second visit would seem not to show a good response to the medication when they really did have such a response (IOP variability masks medication effect). Therefore, variability in the IOP measurement may result in erroneous classification of medication response in 13% of patients. These results suggest that determining medication effect from only the treated eye on one return visit may lead to inappropriate continuation or discontinuation of medications.

Factors That Affect Intraocular Pressure Variability

Intraocular pressure variability may be the result of true changes in IOP, artifactual influences on IOP measurement, or both. Such variability may affect both eyes symmetrically or asymmetrically. This study analyzes a few factors that may contribute to variability in IOP measurement.

Regression to the Mean. Regression to the mean is a statistical phenomenon in which observations that are high relative to the mean regress toward the mean and have a lower value when measured the second time. Conversely, observations that are low relative to the mean regress toward the mean and have a higher value when measured the second time. Factors such as diurnal variability, measurement error, and patient-related factors (e.g., ocular squeezing, Valsalva maneuver, increased fluid intake) all may play a role in causing the IOP measurement to seem higher or lower than the true mean on any given visit. This study found that eyes with high baseline IOPs had lower IOPs at the 6-month visit and eyes with low baseline IOPs had higher IOPs at the 6-month visit. This occurred despite a strict protocol for measuring IOP, multiple IOP measurements per visit, and the use of the IOP at the randomization visit as opposed to the qualifying visit as the baseline IOP. Regression to the mean is likely even greater in the clinical setting. Therefore, clinicians should be wary that IOP of an eye started on medications may be lower at the subsequent visit partially because of effects from regression to the mean as opposed to medication effect alone.

Consistency of Time of Day. Diurnal variation may cause IOP measurements to differ when obtained on different days and at different times of the day. Wilensky et al.[3] reported similar diurnal patterns of the same eye on a repeat visit in only 28% of ocular hypertensive patients and in 44% of glaucoma patients. Other studies, however, have shown similar diurnal curves within the same eye on repeat visits.[1,13] Horie and Kitazawa[21] reported the diurnal peak of IOP occurring within 2 hours between subsequent visits in 94% of eyes. Although the current study did not calculate diurnal curves, the effect of consistency of time of day between 2 visits on the variability of IOP measurement was analyzed. The analysis revealed that the correlation between baseline IOP and 6-month IOP was stronger when the 6-month IOP was measured within 2 hours from the baseline IOP ($r = 0.56$) than when the IOPs were measured more than 2 hours apart ($r = 0.39$). These results suggest that variability of IOP within the same eye between visits may be reduced by measuring IOP at a similar time of day.

Measurement Order. On average over 60 months, the IOP of the right eye was 0.3 mmHg higher than the left eye. Although this difference is clinically insignificant, it is the mean difference and some patients have a greater difference in IOP between the 2 eyes. The mean IOP was measured as higher in the right eye than the left eye in a study of almost 6000 normal eyes using Goldmann tonometry as well as in a study using pneumotonometry in which right eyes were measured before left eyes.[5,22] However, other studies have

reported IOP to be higher in the left eye and no difference in IOP between the 2 eyes.[6,7,23–25]

Intraocular pressure measurement may be slightly higher in the right eye in this study because of either a real IOP difference between eyes or a measurement artifact. It was suspected to be the result of the order in which IOP measurements were obtained (right eye measured first), because there was a slight decrease in IOP associated with the progression of IOP measurements. Instillation of a topical anesthetic in an eye before IOP measurement may cause so-called quenching of the fluorescein in the tear film, resulting in hypofluorescence and an underestimation of IOP measurement.[26] This effect may be more prominent with subsequent IOP measurements because of the increased time of contact between the topical anesthetic and the fluorescein.[27] Another plausible explanation is that patients may be more anxious with earlier IOP measurements, causing an artificially elevated IOP measurement from ocular squeezing or the Valsalva maneuver. There has been no study to date that has addressed this question directly. If there is a true association of IOP measurement with sequence measured, then the order of right and left eye IOP measurement may play a role in variability of IOP measurement. Multiple IOP measurements at a single visit may help to decrease variability of IOP because of factors associated with the order of IOP measurement.

This report analyzes only a few factors that may affect variability of IOP measurement. A comprehensive analysis of demographic, clinical (e.g., central corneal thickness), and systemic (e.g., systemic medications) influences on variability of IOP measurement has yet to be conducted in the OHTS. In addition, variability of IOP measurement as a risk factor for glaucoma is an important question that needs further analysis.

The results from this study may not reflect clinical practice because of the strict protocol and multiple IOP measurements obtained. In addition, patients were asked to return for follow-up visits within 2 hours of the baseline visit when possible, which might have minimized the amount of IOP variability typically seen in clinical practice. Regression to the mean effects may have been lower in this study because of the multiple IOP measurements that might have reduced measurement error. Furthermore, the results reflect IOP fluctuation in ocular hypertensive patients and may be different in normal or glaucoma patients.

This report illustrates the variability of IOP and the complex factors involved. Multiple IOP measurements on several visits are required to assess IOP fluctuation accurately in any given patient. The findings also demonstrate how natural variation of IOP between visits may complicate the determination of IOP response to a medication. Factors that affect variability of IOP measurement include regression to the mean, consistency of time of day, sequence of IOP measurements, and likely many other factors that are yet to be elucidated.

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