Published in final edited form as:
Ophthalmology. 2010 September ; 117(9): 1700–1704. doi:10.1016/j.ophtha.2010.01.044.

Diurnal Intraocular Pressure Patterns are Not Repeatable in the Short Term in Healthy Individuals

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Abstract

Purpose—To evaluate the short-term repeatability of diurnal intraocular pressure (IOP) patterns in eyes of subjects without glaucoma.

Design—Observational cohort study.

Participants—40 healthy subjects without glaucoma.

Methods—Subjects underwent 12-hour diurnal IOP assessment sessions from 0800 to 2000 on two visits one week apart. IOP was assessed by Goldmann applanation tonometry. An analysis was performed to determine the strength of association of individual diurnal IOP patterns from the first visit to the second visit. The intraclass correlation coefficient (ICC) was utilized to analyze both agreement of IOP values at each time point between visits and IOP change over time periods between time points between visits.

Main Outcome Measure—Diurnal IOP patterns.

Results—Between-visit agreement of IOP values at each time point was generally fair to good, with ICCs ranging from 0.37 to 0.62 in right eyes and from 0.35 to 0.71 in left eyes. Between-visit agreement of IOP change over time periods between time points was uniformly poor and often below that expected by chance alone, with ICCs ranging from −0.25 to 0.15 in right eyes and from −0.40 to 0.22 in left eyes.

Conclusions—Eyes of healthy individuals do not manifest a sustained and reproducible diurnal IOP pattern when measured by Goldmann tonometry. A single-day assessment of IOP poorly characterizes the diurnal IOP pattern.

Introduction

Intraocular pressure (IOP) varies spontaneously over time, and it is generally accepted that this spontaneous variation follows a conserved circadian pattern in both glaucomatous and non-glaucomatous eyes. The presumed repeatability of this IOP pattern from day to day underlies

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several clinical and research practices. As an example, IOP is typically measured at the same time of day both before and after initiating therapy to minimize inter-day variation. This practice assumes that IOP is constant at any given time of day, regardless of the day on which it is measured. Thus, any changes observed after initiating therapy should be directly attributable to treatment efficacy.

There are few data describing the repeatability of diurnal IOP patterns in normal subjects. Daubs evaluated diurnal IOP patterns in seven international airline pilots using the Durham-Langham pneumatic-type electronic tonometer, reporting limited repeatability of IOP patterns within individual pilots over time.[1] Additionally, de Venecia and Davis collected 24-hour IOP data in 230 normal eyes for three consecutive days using Schiøtz tonometry and found poor reproducibility of 24-hour IOP range.[2]

We have conducted a prospective study to evaluate the short-term repeatability of diurnal IOP patterns in subjects without glaucoma measured using Goldmann tonometry, the clinical standard method of tonometry.

Methods

This prospective study was reviewed and approved by the West Virginia University institutional review board. The study was conducted in accordance with the tenets of the Declaration of Helsinki. All participating subjects provided written informed consent. Subjects were recruited between April 3, 2006 and April 16, 2007; the last subject exited the study on April 14, 2008. Participants were aged 18 years or older and were healthy subjects. Subjects were included only if they had IOP of 21mmHg or less, and no history of IOP above 21 mmHg. They also were required to have open angles and no family history of glaucoma. Subjects were excluded if their optic discs demonstrated excavation, diffuse or focal thinning or notching of the neuroretinal rim, visible nerve fiber layer defects, or asymmetry of the vertical cup-disc ratio of > 0.2 between eyes or confirmed visual field loss over at least two consecutive tests (pattern standard deviation (PSD) outside the 95% normal limits for Swedish Interactive Threshold Algorithm (SITA) fields, or a corrected PSD outside the 95% normal limits for Humphrey Full Threshold algorithm tests, or an abnormal glaucoma hemifield test using either test strategy). Subjects were excluded if they had any other ocular condition that might affect IOP, and all were free of corneal pathology that might limit the accuracy of tonometry readings.

All subjects underwent a complete ophthalmological examination including medical history, best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, standard automated perimetry using the Humphrey Field Analyzer II and the SITA-standard 30-2 algorithm, and a dilated fundus examination. Thereafter, consenting subjects attended two diurnal IOP assessment visits one week later. At each visit, following an interim medical history including any changes in systemic medications, visual acuity assessment and slit-lamp biomicroscopy, each subject underwent IOP assessment by Goldmann tonometry in the sitting position every two hours from 0800 to 2000. At each time point, both eyes were anesthetized with a solution of fluorescein sodium 0.25% and benoxinate HCl 0.4% (Fluress, Akorn Inc, Buffalo Grove, IL). Right eyes were always measured before left eyes. With the Goldmann tonometer set on 10 mmHg, the dial was adjusted until the inner edge of the fluorescein mires touched slightly. The technician then recorded the IOP value, reset the tonometer to 10 mmHg, and repeated the process. IOP values (rounded to the nearest whole number) at each time point were the mean of 2 measurements within 3 mmHg, or the mean of 3 measurements if the first two differed by 4 mmHg or more. All IOP measurements were performed by one of two certified ophthalmic technicians, and the same technician used the same tonometer on each patient at all visits. Study personnel obtaining IOP measurements

were masked to IOP measurements from prior visits but not to IOP measurements from the current visit. No attempt was made to control subjects' activity or diet during study visits.

The primary statistical objective of this report was to determine the short-term repeatability of IOP patterns of non-glaucomatous eyes between visits. The intraclass correlation coefficient (ICC) was used to assess the agreement of IOP at visits 1 and 2 occurring one week apart. Analyses included assessment of IOP at each time point (for instance, IOP at 0800 Visit 1 compared to IOP at 0800 Visit 2) and IOP change over time periods between time points (for instance, the change in IOP from 0800 to 1000 Visit 1 compared to the change in IOP from 0800 to 1000 Visit 2). The following interpretation scheme for ICC has been described: < 0.4 represents poor agreement beyond chance; 0.4–0.75 represents fair to good agreement beyond chance; and > 0.75 represents excellent agreement beyond chance.[3] Negative ICC values indicate greater within-subject variability than between-subject variability, which represents agreement that is even less than expected by chance alone. Data analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC). This study was powered to detect a minimum ICC of 0.4, the breakpoint between poor agreement and fair-to-good agreement in the Landis and Koch scheme. To achieve 80% power with a two-tailed Type I error rate of 0.05, a sample size of 36 subjects with two observations per subject was required.

Results

Overall, 44 subjects without glaucoma were enrolled in this study, of whom 40 subjects attended both Visits 1 and 2 and were included in this analysis. All included subjects were Caucasian, 65% (26/40) were female, and their mean age was 66.5 ± 12.9 years.

Mean IOP values by eye, time point and visit are given in table 1. IOP values were consistently lower at Visit 2 compared to Visit 1, although the difference was not statistically significant at any time point in either eye. Mean daily range of IOP (highest IOP minus lowest IOP) was 5.4 mmHg in right eyes and 4.9 mmHg in left eyes at both Visits 1 and 2.

IOP values at each time point on Visit 1 were compared to corresponding values at the same time point on Visit 2 (table 2). The ICCs ranged from 0.37 to 0.62 in right eyes and from 0.35 to 0.71 in left eyes. These values indicate generally fair to good agreement, with some values indicating poor agreement.

IOP changes over time periods between time points on Visit 1 were compared to corresponding IOP changes over time periods between the same time points on Visit 2 (Table 3). Dividing the diurnal period into six two-hour periods (0800 to 1000, 1000 to 1200, etc) enabled agreement analysis of IOP change over time. For these two-hour time periods, the ICCs ranged from −0.25 to 0.15 in right eyes and from −0.40 to 0.22 in left eyes. These values indicate uniformly poor agreement. If IOP followed a similar pattern on Visits 1 and 2 but was shifted temporally by two or more hours, agreement based on longer time periods should be higher than agreement based on shorter time periods. To evaluate this possibility, similar analyses were conducted on four-hour, six-hour, eight-hour, ten-hour and twelve-hour time periods (Table 3). The results of analyses on longer time periods did not support the hypothesis that IOP patterns between visits were conserved but offset in time. With the exception of ten- and twelve-hour data in the left eye only (two of forty-two time periods analyzed), the agreement of IOP change between visits at all of these time periods remained uniformly poor, with ICCs ranging from -0.16 to 0.35 in right eyes and from −0.4 to 0.49 in left eyes.

Discussion

These data show that individual eyes of healthy subjects do not follow a conserved IOP pattern from day to day. There was fair to good agreement for IOP at any given time on different days,

but essentially no agreement for IOP change over time periods between time points on different days.

There are few data in the literature regarding the repeatability of IOP patterns in normal eyes over time. Daubs' evaluation of a small group of airline pilots did not include a formal evaluation of IOP pattern reproducibility but included the following qualitative description: "Although [IOP] curve patterns were occasionally repeated for several consecutive days in some subjects, this was not always the case. A subject might have a 'falling curve' one day followed by a 'rising curve' the next day, or he might have almost any other combination of orders of curves." Similarly, de Venecia and Davis did not formally evaluate the repeatability of curve patterns, but did analyze repeatability of 24-hour range of IOP over three consecutive days. Range of IOP was calculated on each of the three days for each of their 230 eyes; the lowest of the three daily IOP ranges was subtracted from the highest of the three daily IOP ranges. From their report, "This difference varied from 0 to 14 mmHg with a mean of 3.5 mmHg." Notably, neither of these reports utilized Goldmann tonometry. We believe that ours is the first study to evaluate the reproducibility of diurnal IOP patterns in normal eyes using Goldmann tonometry.

The existence of a conserved circadian IOP rhythm in human eyes is dogmatic. In the evaluation and management of glaucoma, diurnal or circadian IOP assessment is commonly recommended to identify undetected IOP spikes which might explain the presence or progression of glaucoma in subjects whose randomly sampled IOP appears consistently normal or well-controlled, respectively. Diurnal IOP assessment can be costly, time-consuming, and inconvenient for patients. The information gleaned from diurnal testing would have greater value if IOP behavior remained stable among individuals over time (i.e., if measurement on one day provided reliable information about IOP behavior on subsequent days.) However, the current data suggest that such repeatability of IOP change over time is uniformly poor. During some time segments, agreement between visits was worse than that expected by chance alone. In essence, these data suggest that knowledge of the IOP behavior of a particular individual on a given day does not provide meaningful information regarding the IOP on other days.

These results in normal eyes do not diminish the value of assessing diurnal IOP patterns of individuals with suspected or established glaucoma. Rather, they suggest that fully characterizing diurnal IOP variability in such individuals may require more than a single diurnal IOP testing session.

There was a consistent trend toward lower IOP values on Visit 2 compared to Visit 1, although this inter-visit difference did not reach the level of statistical significance at any time points. The basis for this trend is not understood. All subjects were evaluated by the same study personnel using the same tonometers and techniques from visit to visit. Environmental factors such as diet were considered but do not seem to be involved. For example, although patients were fed at each of the visits, the meals varied from visit to visit and were not presented in any particular pattern. As an alternative, we suggest that the lower IOPs on the second visit may be related to a "white coat" phenomenon. As both the stress hormone cortisol and the sympathetic nervous system have been linked to regulation of IOP,[4] perhaps there is a "white coat" phenomenon for IOP just as there is for systemic blood pressure.[5] In this case, subjects could be more relaxed on subsequent visits than at the initial visit. Regardless of cause, a systematic bias toward slightly lower IOP at Visit 2 should not have significantly impacted the ICC analysis.

This study's strengths include its prospective design, the use of Goldmann tonometry for IOP measurements, and its trained study personnel who were masked to prior IOP measurements at each study visit. These features minimize the possibility of bias that might arise without

masking and optimize generalizability of the findings by virtue of the use of the most commonly-utilized clinical standard tonometer in studies of IOP. We did not utilize a two-person observer/recorder method of IOP measurement, solely due to resource limitations, but we did adhere to a strict IOP measurement protocol based on the Ocular Hypertension Treatment Study protocol[6] but modified for a single observer. A potential criticism of the current study is that the timing, amount and type of fluid and nutritional intake, light exposure, activity, and other conceivable environmental variables at both Visits 1 and 2 were not standardized. However, few, if any, individuals live such regimented lives that they eat and drink the same things at the same times every day, perform precisely the same daily physical activities at the same time of day, and so on. An additional potential environmental variable is overall systemic health status. These subjects were generally healthy, but as with any cohort of subjects in their 60s and 70s, many had concurrent chronic health issues such as diabetes, hypertension, and hypercholesterolemia. No subject experienced a significant change in systemic well-being between Visits 1 and 2. Further, regarding the use of systemic medications that might affect IOP, while several of the participants required the use of blood pressure medications, all were on a stable regimen at the time of study initiation and none underwent changes in therapy between the two visits.

That IOP patterns were assessed over 12 hours, and not 24 hours, also may limit the clinical relevance of these data, as recent reports have demonstrated that IOP tends to be highest in the nocturnal period in the supine position.[7–10] Our use of the ICC to analyze agreement, while effective in evaluating time point-by-time point associations between IOP at Visits 1 and 2, limited data analysis to a series of two-point comparisons without taking the entire diurnal IOP pattern into account in a single calculation. One potential criticism of the use of agreement analysis is that agreement can be artificially raised if variation is low. In normal eyes, diurnal IOP variation could be expected to be low or even flat. In our data, however, the average daily range of IOP was 5.4 mmHg in right eyes and 4.9 mmHg in left eyes. This represents sufficient variation to preclude artifactual inflation of the intraclass correlation coefficient. Alternate methods of data analysis were considered. Most of the early literature made use of classifications of IOP curve types based on general shape. This method was rejected as too subjective, as any such classifications chosen by the investigators would be arbitrary and indefensible, and such an analytic approach makes use of only a small portion of the complete data set. Curve-fitting by cosine rhythmometry requires at least one, and preferably two or more, full cycles (i.e., 24-hour curves) for valid results; its use was precluded by the 12-hour nature of our data. Finally, the study lacked racial diversity, which arises from the fact that West Virginia's population is 95% Caucasian.

In summary, non-glaucomatous eyes do not manifest a sustained and repeatable short-term diurnal IOP pattern when measured by Goldmann tonometry. While knowledge of diurnal IOP patterns has clinical value, these patterns are not fully characterized by single-day measurements.

Acknowledgments

Support for this study was provided by:

National Eye Institute grants K23EY018859 and R03EY015682 (TR)

Unrestricted grant to WVU from Research to Prevent Blindness

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Table 1

Mean intraocular pressure (IOP) values at each time point and for common diurnal IOP parameters among healthy individuals (n=40).

	Right Eye			Left Eye		
	Visit 1	**Visit 2**	**Difference**	**Visit 1**	**Visit 2**	**Difference**
0800	17.2 ± 3.3	16.1 ± 3.4	1.0	16.9 ± 3.4	16.0 ± 3.3	0.8
1000	16.7 ± 4.0	15.8 ± 3.1	0.9	15.9 ± 3.7	15.8 ± 3.4	0.1
1200	16.4 ± 2.9	15.9 ± 3.2	0.5	15.7 ± 2.9	15.6 ± 2.9	0.1
1400	15.6 ± 2.5	15.5 ± 3.0	0.1	15.3 ± 2.9	15.2 ± 2.8	0.1
1600	15.7 ± 2.6	15.2 ± 2.9	0.6	15.4 ± 2.7	15.0 ± 3.1	0.4
1800	15.5 ± 2.4	14.9 ± 2.8	0.5	15.3 ± 2.7	15.0 ± 2.8	0.3
2000	15.0 ± 2.5	14.1 ± 2.9	1.0	14.8 ± 2.9	13.8 ± 2.9	1.0

Table 2

Intraclass correlation coefficients for comparison of intraocular pressure values and for comparison of intraocular pressure changes over time periods between time points from Visit 1 to Visit 2 among healthy individuals (n=40).

	Right Eye	Left Eye
Time		
0800	0.58	0.67
1000	0.62	0.62
1200	0.62	0.71
1400	0.60	0.55
1600	0.49	0.35
1800	0.37	0.46
2000	0.58	0.60

Table 3

Intraclass correlation coefficients for comparison of intraocular pressure changes over time periods between time points from Visit 1 to Visit 2 among healthy individuals (n=40). Data for right eyes are given above the diagonal; data for left eyes are given below the diagonal.

Time	0800	1000	1200	1400	1600	1800	2000
0800	-----	−0.16	0.31	0.17	0.19	0.22	0.35
1000	0.09	-----	0.11	−0.16	0.06	0.06	0.13
1200	0.25	0.22	-----	0.12	0.01	0.14	0.08
1400	0.35	0.01	−0.13	-----	0.15	−0.03	0.04
1600	0.27	0.03	0.20	−0.10	-----	−0.25	0.01
1800	0.24	0.33	0.18	−0.07	−0.40	-----	−0.01
2000	0.48	0.49	0.21	−0.05	−0.22	−0.14	-----