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# Asymmetry of Habitual 24-Hour Intraocular Pressure Rhythm in Glaucoma Patients

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**PURPOSE.** To examine the strength of association between 24-hour rhythms of habitual IOP in the paired eyes of healthy individuals and glaucoma patients.

**METHODS.** Laboratory records of 24-hour habitual IOP from 38 younger healthy individuals, 53 older healthy individuals, and 41 untreated older primary open-angle glaucoma patients were examined. Intraocular pressure was measured every 2 hours sitting during the day and supine at night using a pneumatonometer. Rhythms of 24-hour IOP in the right eye and in the left eye were estimated separately using cosinor rhythmometry. Estimated 24-hour IOP peak timing (acrophase) and estimated 24-hour IOP variation (amplitude) were compared between the paired eyes for each subject group. Strength of association was determined by the absolute time interval between paired 24-hour IOP peak timings and by the coefficient of determination ($r^2$) between paired 24-hour IOP variations.

**RESULTS.** Mean absolute time intervals between the paired IOP peak timings were 1 hour and 33 minutes in the younger healthy group and 1 hour and 37 minutes in the older healthy group. In the older glaucoma group, the mean absolute time interval was 2 hours and 30 minutes. Coefficient of determination for the paired 24-hour IOP variations in the older glaucoma group was 0.343, significantly lower than the coefficients of determination in the younger healthy group (0.571) and the older healthy group (0.646).

**CONCLUSIONS.** The strength of association between the paired 24-hour rhythms of habitual IOP is significantly weaker in glaucoma patients than in healthy individuals.

Keywords: 24-hour, asymmetry, glaucoma, intraocular pressure, rhythm

Levels of IOP in paired healthy eyes are usually close, and a significant IOP difference between paired eyes, commonly termed IOP asymmetry, has been suggested to be a clinical factor associated with glaucoma.[1] As paired IOP levels may be close in healthy eyes, the differences between IOP changes in the paired eyes as well as IOP peaks can show significant variation during various time periods within 24 hours.[2] Similar asymmetric IOP variations and IOP peaks also may occur in glaucoma patients.[3] These observations and others have prompted several groups to challenge the practice of the one-eye therapeutic trial in glaucoma management using single-pair IOP measurements.[4–8] In contrast to the use of single-pair IOP measurements, it was found that the use of IOP average from multiple measurements within 24 hours can reduce the deviation of IOP difference between the paired eyes and improve the correlation of IOP variations.[2,3,8]

Recently, a wireless contact lens sensor (CLS) intended for monitoring 24-hour IOP based on the change in corneal curvature, a proposed surrogate for IOP, has become available.[9–11] This device generates a large amount of data in ambulatory conditions and its use for glaucoma diagnosis and treatment is under investigation.[12,13] One proposed use strategy involves the analysis of 24-hour rhythm of CLS output signals based on all the data collected.[12,14] This use strategy raises a basic question of how similar the paired 24-hour rhythms of habitual IOP appear in glaucoma patients, specifically for the estimated 24-hour peak timing and

estimated 24-hour data variation. Although the paired habitual 24-hour IOP rhythms are probably symmetric in younger healthy individuals,[14] no information is available for glaucoma patients. In theory, an asymmetry in IOP levels between the paired eyes does not exclude a possible symmetry of the estimated 24-hour peak timings and/or a possible symmetry of the estimated 24-hour data variations. Simultaneous 24-hour CLS data from the contralateral eye has not been collected to date due to the precaution of fitting CLS in only one eye. However, the correlation of habitual 24-hour IOP rhythms in the paired eyes can be evaluated based on 24-hour data collected using a conventional tonometer.

## METHODS

Twenty-four-hour IOP data were collected using the pneumatonometer from healthy individuals and from glaucoma patients in our sleep laboratory. In two previous reports that examined all enrolled healthy individuals and untreated primary open-angle glaucoma patients from 1997 to the end of August 2004, the strength of association between IOP in the right eye and IOP in the left eye had been analyzed in younger healthy individuals, older healthy individuals, and older glaucoma patients using IOP averages from various time periods within 24 hours.[2,3] However, correlation analysis of 24-hour rhythms of habitual IOP between the paired eyes has not been examined in those two reports or in other studies of our laboratory

TABLE 1. Demographic Characteristics of Study Groups

| Subject Group | Younger Healthy | Older Healthy | Older Glaucoma |
|---|---|---|---|
| $n$ | 38 | 53 | 41 |
| Age (range) | $21.7 \pm 1.9$ (18–25) | $57.5 \pm 7.0$ (40–74) | $58.3 \pm 11.8$ (40–78) |
| Female sex (%) | 22 (58) | 36 (68) | 24 (59) |
| Race | 18 White | 42 White | 28 White |
| | 16 Asian | 4 Asian | 7 Black |
| | 2 Black | 3 Black | 5 Asian |
| | 2 Hispanic | 2 Hispanic | 1 Hispanic |
| | | 2 Native American | |

records. To provide comprehensive information of the 24-hour habitual IOP rhythm, including the potential influence of aging versus glaucoma, we examined IOP records from the same subjects in those two reports. For the present study, only habitual IOP data in the sitting body position during the day and in the supine body position at night were reviewed. Analyses included three subject groups of 38 younger healthy individuals, 53 older healthy individuals, and 41 older glaucoma patients. These subjects were recruited for various clinical investigations that followed the tenets of the Declaration of Helsinki and were approved by our institutional review board. Informed consent was obtained from each subject.

Healthy individuals were recruited from university students and local residents, and glaucoma patients were recruited from the university eye clinic.[2,3] Glaucoma patients were diagnosed with primary open-angle glaucoma based on abnormal optic discs and/or repeatable abnormal visual fields in the paired eyes. There was no case of pseudoexfoliation syndrome. Among the 41 glaucoma patients, 35 patients were newly diagnosed patients who had not received any glaucoma medication, three patients had received bilateral latanoprost treatments, and three patients had received bilateral timolol treatments. Treated glaucoma patients went through a washout period of 4 weeks before 24-hour laboratory IOP data were collected. Table 1 summarizes characteristics of the three subject groups.

Experimental procedure, including data collection in the sleep laboratory, has been described previously.[2,3] In brief, experimental subjects maintained the accustomed 8-hour sleep period for 7 days before the laboratory recording. They were asked to abstain from alcohol for 3 days and caffeine for 1 day. Subjects reported to the sleep laboratory at approximately 2 PM. Their normal activities in the laboratory were not restricted. Food and water were always available and meal times were not regulated. The 8-hour dark period in each sleep room was adjusted according to the individual's sleep cycle, which was verified by a wrist monitor of light exposure and physical activity. Clock times for the IOP measurements were individualized correspondingly. For data presentation, clock times were aligned as if each subject had a sleep period from 11 PM to 7 AM.

Measurements of IOP were taken in both eyes every 2 hours using a pneumatonometer (Model 30; Reichert, Depew, NY, USA). Measurements were first obtained from the right eye. The resolution of IOP reading was 0.5 mm Hg. A hard-copy record was evaluated for every IOP measurement.[15] Before the nocturnal/sleep period, sitting IOP measurements were obtained at 3:30 PM, 5:30 PM, 7:30 PM, and 9:30 PM after 5-minute supine and then 5-minute sitting rest. Room lights were turned off at 11 PM. Supine IOP measurements during the 8-hour nocturnal period were taken at 11:30 PM, 1:30 AM, 3:30 AM, and 5:30 AM. Subjects were awakened, if necessary, and the measurements were taken in dim red light (<10 lux). The

assigned nocturnal period ended at 7 AM. Room lights were turned on and subjects were awakened. Sitting measurements continued at 7:30 AM, 9:30 AM, 11:30 AM, and 1:30 PM.

Using least-squares cosinor rhythmometry,[12,16,17] the 24-hour IOP rhythm in each eye was estimated with the parameters of mesor, acrophase, and amplitude. The model assumes that the 24-hour rhythm resembles a cosine profile and can be written as follows:

$$y(t) = b_0 + b_1 \times \cos[(2\pi/24) \times t] + b_2 \times \sin[(2\pi/24) \times t],$$

where $y$ is the estimated IOP value at time $t$ and $b_0$, $b_1$, and $b_2$ are regression coefficients, estimated from the IOP data. The principle underlying the least-squares procedure is the minimization of the residual sum of squared differences between the observed values and the values estimated from the model at corresponding time points. The periodicity of the 24-hour IOP pattern is represented by the constant $(2\pi/24)$. Unbiased estimates and confidence limits of mesor ($b_0$; rhythm-adjusted mean), acrophase (time of peak value), and amplitude were obtained from the individual IOP waveforms. The clock time of the acrophase represented the peak timing of the rhythm. The amplitude was defined as half the distance between the cosinor-fit maximum and minimum (square root$[b_1{}^2 + b_2{}^2]$). It represented the estimate of the 24-hour data variation. To estimate the goodness of fit between the IOP values predicted by the cosinor fitting and the observed IOP values for each subject, the method of Spearman rank correlation was used.[12]

A null hypothesis that peak timings were randomly distributed around 24 hours for each group of younger healthy individuals, older healthy individuals, and older glaucoma patients was tested using the Rayleigh test for the right eye and for the left eye.[18] A rejection of the null hypothesis would indicate a synchronized 24-hour IOP rhythm for each subject group. If a synchronized 24-hour IOP rhythm was present for both the right eye and the left eye, a paired $t$-test was used to compare the cosinor parameters (mesor, acrophase, and amplitude) between the paired eyes in each subject group. In addition, one-way ANOVA and post hoc Bonferroni $t$-test was used to compare the study parameters among the three subject groups for the right eye and for the left eye separately. $P < 0.05$ was considered as statistically significant.

The absolute differences in mesor, acrophase, and amplitude, regardless of the order of right and left eyes, were calculated for the paired eyes in each subject and grouped. These absolute differences were compared among the three subject groups using the nonparametric Kruskal-Wallis test. In addition, the strength of association in the paired peak timings of 24-hour IOP rhythm was examined using the cutoff time of 2 hours. An absolute time interval larger than this cutoff time indicated a significant clinical difference because the IOP data were collected every 2 hours.

**TABLE 2.** Percentage Distributions of 24-Hour IOP Peak and the Peak Duration

| | | % IOP Peaks Occurred at | | | | | | | | | | | | Peaks Lasted for | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 7:30 AM | 9:30 AM | 11:30 AM | 1:30 PM | 3:30 PM | 5:30 PM | 7:30 PM | 9:30 PM | 11:30 PM | 1:30 AM | 3:30 AM | 5:30 AM | Single Time Point | Two Time Points | Three Time Points |
| Younger healthy, | Right eye | | 5.3 | | | 2.6 | 2.6 | | | 16.7 | 24.6 | 28.5 | 19.7 | 92.1 | 5.3 | 2.6 |
| n = 38 | Left eye | 5.3 | | 2.6 | | | | | | 9.2 | 21.1 | 27.6 | 34.2 | 92.1 | 7.9 | |
| Older healthy, | Right eye | | | 1.9 | | | 1.9 | | | 19.8 | 11.9 | 13.8 | 50.6 | 92.5 | 5.7 | 1.9 |
| n = 53 | Left eye | | | 5.7 | | 3.8 | 1.9 | | | 18.9 | 21.7 | 12.3 | 35.8 | 94.3 | 5.7 | |
| Older glaucoma, | Right eye | 6.1 | 2.4 | 3.7 | 4.9 | 4.9 | 7.3 | | | 9.8 | 14.6 | 13.4 | 32.9 | 97.6 | 2.4 | |
| n = 41 | Left eye | 11.0 | 6.1 | 7.3 | 4.9 | 5.5 | 4.9 | 2.4 | 2.4 | 9.1 | 15.2 | 20.1 | 11.0 | 97.6 | | 2.4 |

Diurnal sitting IOP measurements obtained 7 AM to 11 PM and nocturnal supine IOP measurements obtained 11 PM to 7 AM. For subjects having IOP peak that occurred more than once, the percentage was divided evenly between or among clock time points.

Linear regression and coefficient of determination ($r^2$) were used to examine the strength of association between the estimated 24-hour IOP averages (mesors) and between the estimated 24-hour IOP variations (amplitudes) in the paired eyes. A coefficient of determination with the maximal possible value of 1.0 indicates a perfect predictability of values between the right and left eyes. A coefficient of determination with a value of 0.5 suggests that half of the magnitude in one eye (either the right eye or the left eye) can be explained by the magnitude in the fellow eye, which represents a moderate strength of association. A coefficient of determination with a value significantly below 0.5 suggests a weak strength of association. Linear regression and coefficient of determination were not performed on the estimated 24-hour IOP peak timings (acrophases), because the distribution of this parameter is circular, not linear, in nature.

## RESULTS

Table 2 summarizes the percentage distribution of IOP peaks among the 12 time points and the percentage distribution of IOP peak durations lasting for a single time point, two time points, and three time points of each subject group in the raw dataset. After the least-squares cosinor fitting, the Spearman rank correlation between the IOP values predicted by the cosinor fitting and the observed IOP values were statistically significant for the younger healthy individuals, older healthy individuals, and older glaucoma patients with the overall coefficient $r_s$ values of 0.60/0.65 (right/left), 0.66/0.64, and 0.61/0.63, respectively ($P < 0.05$).

The Rayleigh test rejected the null hypothesis that peak timings of the estimated 24-hour IOP rhythms in the right eye and in the left eye were randomly distributed around the 24 hours for all three subject groups. Table 3 summarizes the paired values of mesor, acrophase, and amplitude for all subject groups. Mesor and acrophase for the older glaucoma group were statistically larger than the values for both the younger healthy group and the older healthy group in the right eye and in the left eye (one-way ANOVA and Bonferroni $t$-test). For the older glaucoma group, the estimated 24-hour IOP variation (amplitude) in the right eye was significantly less than the estimated 24-hour variation in the older healthy group.

Paired $t$-test showed that the mesor in the left eye was significantly less than the mesor in the right eye for the two healthy subject groups, but not for the older glaucoma group. The absolute difference in the study parameters of mesor, acrophase, and amplitude between the right eye and the left eye were calculated. The Kruskal-Wallis test showed no significant difference in each study parameter among the three subject groups. However, the absolute time interval between the paired estimated 24-hour IOP peak timings was less than 2 hours for the two healthy subject groups (1 hour and 33 minutes and 1 hour and 37 minutes) and the absolute time interval was 2 hours and 30 minutes for the older glaucoma group.

**TABLE 3.** Strength of Association Between the Paired 24-Hour Habitual IOP Rhythms

| Subject Group | n | Right Eye | Left Eye | Difference, Right − Left | Absolute Difference | Correlation, $r^2$ |
|---|---|---|---|---|---|---|
| Mesor/IOP average, mm Hg | | | | | | |
| Younger healthy | 38 | 18.52 ± 1.93 | 17.99 ± 2.20 | 0.53 ± 0.95* | 0.84 ± 0.69 | 0.814 |
| Older healthy | 53 | 18.30 ± 2.13 | 17.92 ± 2.24 | 0.38 ± 0.72* | 0.67 ± 0.46 | 0.886 |
| Older glaucoma | 41 | 21.13 ± 3.17† | 21.19 ± 3.57† | −0.07 ± 2.35 | 1.49 ± 1.81 | 0.582 |
| Acrophase/IOP peak timing, h | | | | | | |
| Younger healthy | 38 | 3.46 ± 2.12 | 3.51 ± 1.39 | −0.05 ± 2.54 | 1.55 ± 1.99 | |
| Older healthy | 53 | 3.83 ± 2.79 | 4.21 ± 2.93 | −0.37 ± 2.49 | 1.62 ± 1.90 | |
| Older glaucoma | 41 | 6.11 ± 3.91† | 6.10 ± 4.48‡ | 0.01 ± 3.75 | 2.50 ± 2.76 | |
| Amplitude/IOP variation, mm Hg | | | | | | |
| Younger healthy | 38 | 2.95 ± 1.57 | 3.21 ± 1.41 | −0.26 ± 1.05 | 0.84 ± 0.67 | 0.571 |
| Older healthy | 53 | 3.12 ± 1.47 | 2.98 ± 1.54 | 0.13 ± 0.94 | 0.80 ± 0.51 | 0.646 |
| Older glaucoma | 41 | 2.29 ± 1.22§ | 2.43 ± 1.43 | −0.14 ± 1.22 | 0.97 ± 0.74 | 0.343 |

Values are mean ± SD.
* $P < 0.01$ paired $t$-test between the right eye and the left eye.
† $P < 0.01$ compared with each healthy subject group (ANOVA and post hoc Bonferroni $t$-test).
‡ $P < 0.01$ compared with younger healthy group and $P < 0.05$ compared with older healthy group.
§ $P < 0.05$ compared with older healthy group.

The coefficient of determination ($r^2$) between the paired 24-hour IOP averages for the older glaucoma group, 0.582, was significantly less than the coefficients of determination for the younger and the older healthy groups, 0.814 and 0.886, respectively. The decreases of $r^2$ from the two healthy subject groups to the older glaucoma group were 0.232 and 0.304. The coefficient of determination between the paired 24-hour IOP variations for the older glaucoma group was 0.343, significantly less than the coefficient of determination for the younger healthy group, 0.571, and for the older healthy group, 0.646. The decreases of $r^2$ from the two healthy subject groups to the older glaucoma group were 0.228 and 0.303.

## DISCUSSION

The 24-hour rhythms of habitual IOP showed good strengths of association between the right and the left eyes in the younger healthy group and in the older healthy group. A moderate to high $r^2$ appeared for the estimated 24-hour IOP averages (0.814 and 0.886) and the estimated 24-hour IOP variations (0.571 and 0.646). The absolute time intervals between the estimated 24-hour IOP peak timings were less than the time interval of 2 hours used for IOP data collections. These results support a presumed symmetry between the paired habitual 24-hour IOP rhythms in younger healthy individuals.[14] For the two healthy subject groups, the observed strengths of association in the estimated 24-hour IOP averages, estimated 24-hour peak timings, and estimated 24-hour IOP variations between the paired eyes were comparable. Aging seems to have limited impact on the symmetry of habitual 24-hour IOP rhythms in the paired healthy eyes; presumably the symmetry exists. These observations also may be used to evaluate possible asymmetry in the habitual 24-hour IOP rhythm.

The observed rhythm of 24-hour habitual IOP in the older glaucoma group confirmed several already known IOP characteristics, including a well-known IOP elevation associated with glaucoma. The paired 24-hour IOP averages had a moderate $r^2$ of 0.581, a decrease of 0.232 to 0.304 from the healthy subject groups that reflected the IOP asymmetry in some glaucoma patients.[1] A systematic IOP difference of approximately 0.5 mm Hg between the paired eyes, probably due to the measurement order, did not appear in this group of older glaucoma patients as it did in the two healthy subject groups.[2,19] The estimated 24-hour IOP peak timing in the glaucoma patients occurred a few hours later than that in the healthy individuals. A delay of IOP peak timing in older glaucoma patients compared with older healthy individuals was previously observed in a smaller dataset of 24 patients showing early glaucomatous signs.[20] Results also showed that the estimated 24-hour IOP variation in the older glaucoma group was less than the IOP variation in the older healthy group for the right eye. A reduction of 24-hour IOP variation also was previously observed in those 24 patients showing early glaucomatous signs when the average IOP values from the right and left eyes were used for the estimation.[20]

The present study identifies two additional new findings: a weak strength of association between the estimated 24-hour IOP peak timings in the older glaucoma patients and a weak strength of association between the estimated 24-hour IOP variations in these patients. First, the paired 24-hour IOP peak timings differ in average by more than the time interval of 2 hours used for data collections. For most of these glaucoma subjects under ideal experimental conditions, 24-hour IOP peaks in the paired eyes should not appear at the same time points when using a pneumatonometer every 2 hours. If one extends this observation clinically, bilateral IOP measurements every 2 hours would detect different 24-hour IOP peak timings

in most, but not all, older glaucoma patients. In contrast, a similar measurement procedure may not detect such a peak timing difference in most healthy individuals. Second, an $r^2$ value of 0.343 for the older glaucoma group, a decrease of 0.228 to 0.303 from the values observed in the healthy subject groups, indicates that approximately two-thirds of the estimated 24-hour IOP variation in one eye cannot be explained by the estimated 24-hour IOP variation in the other eye. The observed magnitude of $r^2$ reduction associated with the paired estimated 24-hour IOP variations is substantial, similar to the magnitude of reduction in the estimated 24-hour IOP averages. The latter $r^2$ reduction reflects the IOP asymmetry (significant IOP difference between the paired eyes) associated with glaucoma.

Cosinor rhythmometry has been used to study 24-hour IOP patterns obtained using CLS.[12,14] With this use strategy, undesirable impact from data outliers of spontaneous artifacts would be minimized. After applying the cosinor rhythmometry, 24-hour CLS output signals from individual eyes frequently presented an estimated 24-hour peak timing during the nocturnal/sleep period for glaucoma patients and for younger healthy individuals.[12,14] As for a whole study group, the estimated 24-hour peak timing was consistent for repeated CLS recordings on the same eye in glaucoma patients or in younger healthy individuals.[12,14] The corresponding estimated 24-hour data variation between repeated CLS recordings also was consistent in the group of glaucoma patients and in the group of younger healthy individuals. Considering a potential use of the paired eyes for IOP management in glaucoma,[4] one may estimate the 24-hour peak timings and data variations using the paired 24-hour CLS recordings from the same day or from different days.

For the present study, use of cosinor rhythmometry to determine the asymmetry in 24-hour IOP rhythm between the paired eyes has several limitations. There are assumptions underlying the use of cosinor: normality of residuals, independency of residuals, homogeneity of variance, stationarity, and model adequacy.[21] We have verified the normality and independency of residuals as well as the homogeneity of variance when applying the least-squares procedure. However, our raw dataset is composed of a single IOP record every 2 hours within a 24-hour cycle. The assumption of stationarity related to the cosinor parameter changes as a function of time cannot be verified because of the absence of multiple data cycles. In addition, goodness of fit for the model adequacy commonly verified using either multiple 24-hour data cycles or multiple measurements at the same clock times cannot be performed. Instead, we verified the goodness of fit using the Spearman rank correlation as previously used for the analysis of 24-hour CLS data.[12] Although the estimated 24-hour peak timing and data variation are consistent for the same eye between repeated CLS recordings,[12,14] the present study does not determine whether or not 24-hour IOP peak timing and variation are consistent for the same eye between repeated 24-hour data collections by the pneumatonometer. Therefore, results from the present study are not useful for the evaluation of a strategy that involves collecting IOP data from different days to compare the paired 24-hour IOP rhythms.

The 24-hour rhythms of habitual IOP in the paired eyes seem to be reasonably symmetric in healthy individuals. Whether or not one can evaluate changes in the 24-hour habitual IOP rhythm in a healthy eye using the contralateral healthy eye as a reference needs more investigation. Compared with healthy individuals, there is a significant weakening in the strength of association for the paired 24-hour rhythms of habitual IOP in untreated older glaucoma patients. Therefore, caution is needed when using the habitual 24-hour IOP rhythm in the contralateral eye as a reference to evaluate changes in the habitual 24-hour IOP rhythm in older glaucoma patients.

This caution is due to the asymmetry of habitual 24-hour IOP rhythm, and the caution should apply to data collected with the newly developed CLS monitoring device, as well as with a more conventional tonometer.

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