Title
Asymmetry of habitual 24-hour intraocular pressure rhythm in glaucoma patients.

Permalink
https://escholarship.org/uc/item/33v4p5cr

Journal
Investigative ophthalmology & visual science, 55(11)

ISSN
0146-0404

Authors
Liu, John HK
Weinreb, Robert N

Publication Date
2014-10-16

DOI
10.1167/iovs.14-14464

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

John H. K. Liu and Robert N. Weinreb

Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, La Jolla, California, United States

The strength of association between the paired 24-hour rhythms of habitual IOP in healthy individuals, older healthy individuals, and older glaucoma patients was determined. In the younger healthy group, the mean absolute time interval was 1 hour and 37 minutes in the older healthy group and 1 hour and 37 minutes in the older healthy group. In the older healthy 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 healthy 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).

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. 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. Similar asymmetric IOP variations and IOP peaks also may occur in glaucoma patients. 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. In contrast to the use of single-pair IOP eye therapeutic trial in glaucoma management using single-pair IOP measurements, the paired eyes of healthy individuals and glaucoma patients can be evaluated based on 24-hour data collected using a conventional tonometer.

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. However, correlation analysis of 24-hour rhythms of habitual IOP in the paired eyes has not been examined in those two reports or in other studies of our laboratory.

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. However, correlation analysis of 24-hour rhythms of habitual IOP in the paired eyes has not been examined in those two reports or in other studies of our laboratory.
Asymmetry of Habitual 24-Hour IOP Rhythm

TABLE 1. Demographic Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Younger Healthy</th>
<th>Older Healthy</th>
<th>Older Glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Age (range)</td>
<td>21.7 ± 1.9 (18–25)</td>
<td>57.5 ± 7.0 (40–74)</td>
<td>58.3 ± 11.8 (40–78)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>22 (58)</td>
<td>36 (68)</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Race</td>
<td>18 White</td>
<td>42 White</td>
<td>28 White</td>
</tr>
<tr>
<td></td>
<td>16 Asian</td>
<td>4 Asian</td>
<td>7 Black</td>
</tr>
<tr>
<td></td>
<td>2 Black</td>
<td>3 Black</td>
<td>5 Asian</td>
</tr>
<tr>
<td></td>
<td>2 Hispanic</td>
<td>2 Hispanic</td>
<td>1 Hispanic</td>
</tr>
<tr>
<td></td>
<td>2 Native American</td>
<td>3 Hispanic</td>
<td></td>
</tr>
</tbody>
</table>

subject 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 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 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 pneumotonometer (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.¹ 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).
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 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 $t$-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 57 minutes) and the absolute time interval was 2 hours and 30 minutes for the older glaucoma group.

### Table 2. Percentage Distributions of 24-Hour IOP Peak and the Peak Duration

<table>
<thead>
<tr>
<th>% IOP Peaks Occurred at</th>
<th>Single Peaks</th>
<th>Two Peaks</th>
<th>Three Peaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>7:30</td>
<td>9:30</td>
<td>11:30</td>
<td>1:30</td>
</tr>
<tr>
<td>Younger healthy, Right eye</td>
<td>5.3</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Older healthy, Right eye</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Older glaucoma, Right eye</td>
<td>5.7</td>
<td>3.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

### Table 3. Strength of Association Between the Paired 24-Hour Habitual IOP Rhythms

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

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.
Asymmetry of Habitual 24-Hour IOP Rhythm

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 0.503.

**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. 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 0.252 to 0.304 from the healthy subject groups that reflected the IOP asymmetry in some glaucoma patients. 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. 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. 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.

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 pneumotonometer 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. 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. 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. 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, 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, independence of residuals, homogeneity of variance, stationarity, and model adequacy. We have verified the normality and independence 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. Although the estimated 24-hour peak timing and data variation are consistent for the same eye between repeated CLS recordings, 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 pneumotonometer. 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.

Acknowledgments

Disclosure: J.H.K. Liu, None; R.N. Weinreb, None

References