Circadian Intraocular Pressure Fluctuation and Disease Progression in Primary Angle Closure Glaucoma

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**PURPOSE.** To document the continuous circadian intraocular pressure (IOP) fluctuation using a contact lens sensor during normal daily activities, and to study the relationship between IOP fluctuation and disease progression in primary angle closure glaucoma (PACG) eyes.

**METHODS.** Circadian IOP fluctuations were recorded by Sensimed Triggerfish sensors in 25 PACG eyes. The sensor output signals were smoothed using B-spline smoothing transform and described by functional data analysis. Glaucoma progression was documented with serial changes in mean deviation (MD) and visual field index (VFI) in Humphrey automated perimetry and retinal nerve fiber layer (RNFL) thickness. The signals were compared between the progressive and stable groups by permutation tests on functional t-statistic.

**RESULTS.** Statistically significant differences were found from 2200 to 2300 and from 0700 to 0800 in gradients of the IOP fluctuation curve, as well as from 2300 to 2400 and 0800 to 0900 in curvatures of the IOP fluctuation curves, between the progressive MD and stable MD groups (P < 0.05). Significant gradient differences were also found from 1500 to 1600 and 0600 to 0800 between the progressive VFI and stable VFI groups, and from 2400 to 0100 and 0200 to 0300 between the progressive RNFL and stable RNFL groups (P < 0.05).

**CONCLUSIONS.** Significant differences in circadian IOP fluctuation between progressive and stable PACG eyes were identified. Large IOP fluctuations may be associated with disease progression in PACG eyes.

Keywords: circadian, intraocular pressure, fluctuation, primary angle closure glaucoma, disease progression

Intraocular pressure (IOP) elevation is a major risk factor for the onset and progression of glaucoma. Intraocular pressure reduction is the only proven clinical therapy to slow down or stabilize glaucoma progression.1 The IOP fluctuates over the course of a day with metabolism, posture, and environmental factors.2 A single measurement in the clinic often underestimates the peak IOP value in the nonclinic environment, and does not represent the extent of IOP fluctuation. Intraocular pressure fluctuation may be more severe in primary angle closure glaucoma (PACG), where the IOP can be affected by the size of the pupil, which is in turn related to the ambient lighting and autonomic status of the subject. Recent evidence suggests that large short-term IOP fluctuation may be an independent risk factor for glaucoma progression, in addition to elevated mean IOP.3,4 To our knowledge, continuous circadian IOP fluctuation in PACG eyes and its relationship with PACG progression have not been documented in the published literature.

Previous documentation of short-term IOP fluctuation relied on traditional tonometry, including applanation tonometry (Goldmann or Perkins),5 electronic tonometry through a floating transducer (Tono-Pen; Reichert, Inc., Buffalo, NY, USA),6 noncontact air-puff tonometry (NCT),7 and rebound tonometry.8 Diurnal IOP measurements can be estimated at follow-up visits at different time points of different days or can be conducted at hourly intervals over the course of the same day, while 24-hour IOP measurements can be performed at hourly intervals during a hospital stay or in a sleep laboratory.9,10 None of these methods is able to document the continuous circadian IOP fluctuation during the patient’s normal activities of daily living. Moreover, IOP measurement by applanation tonometry or Tono-Pen requires topical anesthesia and even fluorescein staining, and needs to be conducted by ophthalmologists or trained health care professionals in a clinic setting. Although rebound tonometry could be used as self-measurement without topical anesthesia, patients would have to stop their activities when performing measurements. This may not accurately reflect the true IOP status of patients during normal living activities in their usual environments.

The Sensimed Triggerfish sensor device (Sensimed AG, Lausanne, Switzerland) is a contact lens-based device capable of recording continuous profiles over a 24-hour period. A strain gauge embedded in a soft silicone contact lens detects circumferential changes at the corneoscleral region. The relationship between these changes and the manometrically...
measured IOP in an anucleated pig eye model has been validated by Leonardi et al.\textsuperscript{11} This device allows continuous 24-hour monitoring while patients engage in their routine activities of daily living in their usual environments. The sensor records for 30 seconds at 5-minute intervals during the 24-hour period, which represents 288 readings over 24 hours.\textsuperscript{12-14}

The purposes of this study were (1) to document the 24-hour IOP fluctuation, as reflected by the ocular changes detected using the Sensimed Triggerfish contact lens sensor, in PACG eyes during activities of normal living in the patients’ usual environments, and (2) to demonstrate any significant differences in fluctuation profiles between progressive and stable PACG eyes.

**Materials and Methods**

**Patient Selection**

The study protocol was approved by the Ethics Committee for Human Research at the Chinese University of Hong Kong, and in accordance with the tenets of the Declaration of Helsinki and the International Conference on Harmonisation—Good Clinical Practice (ICH-GCP) guideline. Informed consent was obtained from all study subjects.

We prospectively recruited PACG patients at the eye clinics of the Chinese University of Hong Kong and the Hong Kong Eye Hospital between September 2009 and December 2013. All recruited patients were diagnosed with PACG using the following criteria: (1) on darkroom gonioscopy prior to any intraocular surgery, at least 180° of iridotrabecular contact (ITC) (whether synechial or appositional, segmented or continuous) identified, covering the posterior pigmented (functional) part of the trabecular meshwork in the presence of a patent peripheral iridotomy; (2) requiring IOP-lowering medications or IOP above 21 mm Hg without IOP-lowering medications; (3) characteristic glaucomatous optic nerve head morphology, including vertical cup-to-disc ratio > 0.5, discrepancy of vertical cup-to-disc ratios between the eyes > 0.2, thinned or notched neuroretinal rim, disc hemorrhage, and/or retinal nerve fiber layer wedge defect; and (4) functional glaucomatous optic neuropathy confirmed by Humphrey automated perimetry (Humphrey Field Analyzer II, Carl Zeiss Meditec AG, Jena, Germany; Central 24-2 threshold test, Swedish Interactive Thresholding Algorithm standard strategy, size III white stimulus, with the foveal threshold test turned on). The minimum criteria for diagnosing glaucomatous visual field defect included (1) glaucoma hemifield test (GHT) outside normal limits; (2) pattern standard deviation (PSD) with a P value < 5%; or (3) a cluster of ≥3 points in the pattern deviation plot in a single hemifield (superior or inferior) with P value < 5%, one of which had to have a P value < 1%.\textsuperscript{16} Any one of the above criteria, if repeatable, was considered sufficient evidence of a glaucomatous visual field defect. Patients with secondary causes of ocular hypertension or glaucoma or previous ocular surgery, except laser peripheral iridotomy (PI) and cataract extraction, were excluded from this study. If both eyes of a patient fulfilled the criteria, one eye would be randomly selected using a random number table.

**Ophthalmic Examinations**

All patients received complete ophthalmic examination at the time of recruitment, including best-corrected visual acuity (BCVA) (logMAR), refractive status, central corneal thickness (CCT), and axial length (AL) by ultrasonography. Darkroom gonioscopic examination of angle structures was graded by the gonioscopic examination of angle structures was graded by the Scharff system. Corneal endothelial cell density was measured by noncontact specular microscopy (Konan NonconRobo-CA SP-8000 specular microscope; Konan, Inc., Hyogo, Japan). Visual field (VF) was documented by static automated white-on-white threshold perimetry using the Humphrey automated perimetry (Humphrey Field Analyzer II). Retinal nerve fiber layer (RNFL) thickness was measured by spectral-domain optical coherence tomography (SD-OCT) imaging system (Spectralis HRA-OCT, software version 3.1; Heidelberg Engineering, Heidelberg, Germany). Serial visual field examinations and RNFL thickness scan were performed every 6 months.

**Glucoma Progression Analysis**

Functional PACG progression was based on mean deviation (MD) and visual field index (VFI) data from serial Humphrey automated perimetry, using linear regression. If a significant decrease with \( P \) value < 0.05 in MD and/or VFI was found, the eye would be classified as progressive in MD and/or VFI. Otherwise, the PACG eye would be classified as stable.

Similarly, RNFL thickness progression on OCT was based on linear regression of RNFL thickness data from serial visits, including global RNFL thickness, superior temporal thickness, superior nasal thickness, inferior nasal thickness, and inferior temporal thickness. If any significant decrease with \( P \) value < 0.05 in RNFL thickness was detected in any specific area, the PACG eyes would be classified as progressive in terms of RNFL thickness. When changes over all areas of RNFL thickness were not significant during the follow-up period, the eye was considered stable as to RNFL thickness.

**Documentation of Circadian IOP Fluctuation by Contact Lens Sensor**

The circadian IOP fluctuation profile was recorded by Sensimed Triggerfish contact lens sensor in PACG eyes over 24 hours. The contact lens sensor was placed on the recruited PACG eye on the study day at 1300, and recording of the sensor output signal was initiated as soon as there was satisfactory adaptation of the device on the subject’s eye. Patients were allowed to go home with the contact lens sensor and encouraged to engage in their normal activities of daily living in their usual environments. The output from the sensor is reported as a fluctuation profile with a unit of millivolt equivalents (mVeq). The patients returned to the clinic after 24 hours, at 1300 on the next day, for removal of the contact lens sensor. The IOP fluctuation data were downloaded from the signal recording device.

**Statistical Analyses**

Continuous variables are expressed as mean (± 1 standard deviation, SD).

The 24-hour signal curve data was smoothed using B-spline smoothing transform\textsuperscript{17,18} based on the least squares approach, to describe the overall shape characteristics of the 24-hour signal curve. The smoothed signal curve data were then analyzed by functional data analysis. Residual signal in terms of the difference between the observed signal data and the B-spline smoothed data was regarded as the fluctuation of signal against the overall shape. The frequency of fluctuation was quantified in terms of semivariogram (also known as semivariance)\textsuperscript{19} and analyzed by functional data analysis. The semivariogram of a signal curve is defined mathematically as

\[
\gamma(s(t) - s(t + \Delta t)) = \frac{1}{2} \text{var}[s(t + \Delta t) - s(t)],
\]

where \( s(t) \) represents the signal value at time \( t \), which describes the amplitude of fluctuation with frequency measured in terms of \( \Delta t \). The differences in signal patterns, gradients, and curvatures at any time point...
were compared between the progressive and stable groups by permutation tests on the functional \(t\)-statistic for the smoothed signal data.\(^{20}\) The functional \(t\)-statistic is defined mathematically by

\[
T(t) = \frac{\bar{s}_1(t) - \bar{s}_2(t)}{\sqrt{\text{var}[s_1(t)]/n_1 + \text{var}[s_2(t)]/n_2}}
\]

where \(\bar{s}_1(t)\) and \(\bar{s}_2(t)\) represent the mean signal values of the progressive and stable groups at time \(t\), \(\text{var}[s_1(t)]\) and \(\text{var}[s_2(t)]\) represent the variance of signal value of the progressive and stable groups at time \(t\), and \(n_1\) and \(n_2\) represent the sample size of the progressive and stable groups, respectively. Overall differences in signal patterns, gradients, and curvatures of the signal data in the whole 24-hour period, as well as specific periods within the bedtime hours (1800–0100) and the wake-up hours (0300–1100), were compared by permutation tests on the supremum \(t\)-statistic between the two groups, where the supremum \(t\)-statistic is defined as the least upper bound of the functional \(t\)-statistic across the specific time period.\(^{20}\)

A \(P\) value < 0.05 was considered statistically significant, and a \(P\) value < 0.10 was considered marginally statistically significant. All statistical analyses were performed using R (version 2.15.2; R Foundation, Vienna, Austria).

### RESULTS

#### Patient Demographics and Circadian IOP Fluctuation in PACG Eyes

Twenty-five PACG patients (6 male and 19 female) were recruited (Table 1). The mean age (± 1 SD) was 69.1 (±12.9) years (range, 36.3–89.2 years). The mean follow-up duration (± 1 SD) was 41.0 (±8.2) months (range, 24–54 months). There were 15 right eyes and 10 left eyes. The patients were classified into stable and progressive groups according to the progression analyses of their VF and RNFL thickness parameters as described above. The results of ophthalmic examinations in the stable and progressive groups are shown in Table 2.

Figure 1A shows an example of the circadian IOP profile in one eye documented by the contact lens sensor. Figure 1B shows the circadian IOP profiles from all study eyes.

#### B-Spline Basis Functions for Smoothing Transformation

B-spline basis functions transformation was performed for extracting information from the curves of the contact lens output signal (Fig. 2). To avoid underfitting or overfitting, 25 basis functions were deemed the most appropriate smoothing transformation. Figure 3 shows the spectrogram of signal profiles from the contact lens sensor from all study eyes.

The smoothed signal is the general pattern of all signals. Sixteen eyes showed increased signals at nighttime during sleep. Six eyes had decreased signals in the morning, while 10 eyes did not. The signals in 9 eyes were stable with less fluctuation during daytime. Four eyes had increasing signals in the morning (Fig. 3).

#### Comparison of Circadian IOP Fluctuation Between Progressive and Stable Groups

The signal patterns (Fig. 4A), gradients (first derivatives) (Fig. 4B), and curvatures (second derivatives) (Fig. 4C) were compared between the progressive and stable groups, as defined by MD, VFI, and RNFL thickness, using permutation test on the functional \(t\)-statistic (Figs. 4D, 4E). An example of comparisons of signal patterns, signal gradient patterns, and signal curvature patterns in clock-hours between the progressive MD and stable MD groups is shown in Figure 5. A summary of the statistical significance of clock-hour signals in the...
progressive and stable groups is shown in Figure 6A. Significant differences were found during 2200 to 2300 and from 0700 to 0800 in gradients, as well as from 2300 to 0100 and 0800 to 0900 in curvatures, between the progressive MD and stable MD groups. Gradient differences were also found from 1500 to 1600 and 0600 to 0800, between the progressive VFI and stable VFI groups, and from 2400 to 0100 and 0200 to 0300 between the progressive RNFL thickness and stable RNFL thickness groups.

The time when patients began to sleep ranged from 1800 to 0100 (median, 2200), and the time of awakening ranged from 0300 to 1100 (median, 0700). The signal patterns, gradients, and curvatures were compared between the progressive and stable groups at bedtime hours (1800-0100) and wake-up hours (0300-1100). A summary of statistical significance of bedtime and wake-up hours between the progressive and stable groups is shown in Figures 6B and 6C. Significant differences were noted during bedtime hours from 2100 to 2200 in gradients, and from 2000 to 2100 in curvatures, between the progressive MD and stable MD groups. Gradient differences were found from 2300 to 2400, and curvature differences from 2400 to 0100, between the progressive VFI and stable VFI groups. The differences in gradients from 1800 to 1900, and the differences in curvatures from 1800 to 2000, were statistically significant between the progressive RNFL thickness and stable RNFL thickness groups. During wake-up hours, the gradient difference from 0600 to 0800 was significant between the progressive MD and stable MD groups. Significant gradient and curvature differences were found from 0400 to 0700 between the progressive VFI and stable VFI groups, and from 0500 to 0600 and 0900 to 1100 in gradients and 0400 to 0600 in curvatures between the progressive RNFL thickness and stable RNFL thickness groups.

The residual signal variomags of the progressive and stable groups were compared over 24 hours (clock-hours) (Fig. 7), as well as during bedtime hours (1800-0100) and the wake-up hours (0300-1100). However, there was no statistically significant difference in these comparisons.

**DISCUSSION**

In this study, we report the first continuous circadian IOP fluctuation, measured by the contact lens sensor, in PACG eyes when patients engage in their normal living activities in their usual environments. To our knowledge, this is also the first study investigating the relationship between continuous circadian IOP fluctuation and disease progression in PACG.

Instead of producing IOP values in mm Hg, the contact lens sensor provides an output signal generated from the ocular dimensional changes in millivolt equivalents (mVeq). Direct transformation of the output signal in mVeq to actual IOP value in mm Hg is currently not possible. Nevertheless, the authors believe that this does not negate the value of such measurements. Just as the measurements made by Goldmann applanation and NCT are surrogates of the real IOP, the output signal fluctuation in this study is presented as a surrogate of IOP fluctuation. Factors that could influence the output signal from the contact lens sensor include corneal biomechanical properties, the change in corneal curvature caused by a unit change in IOP, and the sensitivity of the contact lens sensor in detecting the changes in corneal curvature. Even though the actual IOP level could not be obtained, the output signal can still reflect the IOP fluctuations because of its good correlation with IOP fluctuation, as demonstrated in enucleated porcine eyes. The contact lens sensor is currently the only device available to document a surrogate of IOP fluctuation continuously, without disturbing the activities of daily living in patients’ usual environments.

Other recent studies using the same contact lens sensor to record the circadian IOP defined the experimental output signal either by a modified cosine rhythmometry model or by a sine function model. However, these models presented...
FIGURE 1. A 24-hour intraocular pressure (IOP) fluctuation profile recorded in PACG eyes using the contact lens sensor. (A) An example of a 24-hour IOP profile of one PACG eye documented by the contact lens sensor. (B) 24-hour IOP profiles of all of the study eyes.
FIGURE 2. B-spline basis functions transformation was performed for extracting information from the curves of contact lens output signal. (A) There was underfitting if only 5 basis functions were used. By increasing to 25 basis functions, that is, one B-spline basis per hour, there was a reasonable number of basis functions with less root mean square error. If we increased to 49 basis functions, that is, 1 basis per half hour, there were too many basis functions, resulting in overfitting. (B) An example of fitting with 25 basis functions compared to overfitting with 49 basis functions.
In the current study, B-spline basis function and variogram transformation were used to analyze the two components of the output signal, the whole 24-hour signal profile and the fluctuation, which represent more detailed recognition of the curvature characteristics in the slopes and curvatures of the curves. These could be reflected in their derivatives, generating the acrophase or trough, the extent of increase or decrease during a phase, and the frequency of fluctuations. This study suggested that IOP fluctuation at certain time periods of the day may be associated with progression of PACG. Further studies are needed to confirm this finding.

Previous studies demonstrated the highest possibility of the highest IOP values occurring at night. However, the measurements by traditional devices may disturb sleep, which might cause postural and ocular hydrodynamic changes. Using the contact lens sensor, the nocturnal acrophase was observed in most healthy subjects and glaucoma patients. The current study revealed the continuous circadian IOP profile as well as the nocturnal acrophase in PACG patients (Figs. 1, 3). The circadian IOP profile showed that the signal decreased in the morning and decreased further during the daytime in most patients. Some patients may also have increasing signals in the morning. It seems probable that the nocturnal acrophase may be caused by body posture and positional change of the eye relative to the heart, inducing an apparent pressure increase when the patient lies down. When patients continuously remained in a supine position after waking up in the morning, the signal was not reduced as much as in patients in sitting or upright postures. The IOP level and fluctuation are both related to activities, and therefore the effects of ambient...
Figure 4. (A) Mean smoothed signal profile of the progressive and stable groups; (B) gradient profile of the progressive and stable groups; (C) curvature profile of the progressive and stable groups; (D) t-statistic on 24-hour signal comparison between progressive and stable groups; (E) P value on 24-hour signal comparison between progressive and stable groups.
environment and normal activities should be considered in the IOP fluctuation model.

The association of short-term IOP fluctuation with glaucoma progression has been reported in a prospective cross-sectional study comparing the IOP fluctuations among different types of angle closure and normal subjects, which found higher diurnal IOP fluctuation in PACG eyes. In that study, only a single visual field report was used to correlate with IOP fluctuation, without longitudinal data. In the current study, detailed six-monthly documentation of RNFL thickness by SD-OCT and VF by Humphrey automated perimetry for at least 24 months in all study subjects provides the possibility of progression analysis. Moreover, separate grouping by progression in MD, VFI, and RNFL thickness allows the identification of circadian IOP fluctuation patterns affecting the different measurements of progression. Comparing the progressive and stable groups, no statistically significant difference was observed in their overall signal patterns and residuals. Differences were found at specific time points within the bedtime hours (1800–0100) and the wake-up hours (0300–1100) in terms of gradients and curvatures. One possible explanation may be that IOP fluctuations within the bedtime and wake-up hours may be more likely to induce further glaucomatous nerve damage. When specific time points within the bedtime and wake-up hours were studied, more distinct differences were found in gradient and curvature signals. The variations in IOP fluctuation (extent of increase or decrease) were larger in the progressive group than in the stable group within the bedtime and wake-up hours. In contrast to the entire 24-hour IOP profile or the frequency of IOP changes, the IOP fluctuation within bedtime and wake-up periods appeared to be associated with disease progression in PACG eyes. Within bedtime and wake-up periods, PACG eyes in the progressive group experienced a larger IOP fluctuation after postural changes. This might imply a possible physiological mechanism involving blood pressure, ocular perfusion pressure, and IOP.

Some clock-hours were significant when the entire 24-hour period was evaluated en bloc, but became insignificant when only the waking or bedtime hours were analyzed. One possible explanation is that permutation test on the functional $t$-statistic was a resampling analysis to assess the differences between progressive and stable groups, with 500 bootstrap replicates. By increasing the number of bootstrap replicates, the output will become more consistent, but even then, the results may

**FIGURE 5.** Comparisons of signal patterns, gradients (first derivatives), and curvatures (second derivatives) of clock-hour signals between progressive and stable PACG eyes.
Figure 6. (A) Scattergram of statistical significance of clock-hour signals between progressive and stable PACG eyes. (B) Scattergram of statistical significance in bedtime signals (1800–0100) between progressive and stable PACG eyes. (C) Scattergram of statistical significance of wake-up hour signals (0300–1100) between progressive and stable PACG eyes. *p*: P value is by permutation tests on the supremum t-statistic; #: The differences in signal patterns, gradients, and curvatures at any time point were compared between the progressive and stable groups by permutation tests on the functional t-statistic for the smoothed signal data (red, P value < 0.05; yellow, P value < 0.10).
still not be completely consistent. We chose 500 bootstrap replicates as a reasonable and practical compromise. Our method should detect the most sensitive significant differences within the specific time periods.

There are inherent limitations in this study from the choice of the contact lens sensor for measurements, including the inability to produce actual IOP readings in mm Hg. Moreover, the signals from the contact lens could potentially be affected by other corneal properties, such as the corneal shape and thickness, particularly during sleep. After overnight wearing of the contact lens sensor, increases in CCT and irregularities in corneal curvature have been reported.26,27 The effects of corneal properties on IOP pattern should be investigated in further studies. Moreover, IOP-lowering drugs may also influence the IOP profile. The curve obtained represents only a medically treated IOP profile. Because of the small sample size in this study, it is difficult to investigate the independent association of IOP fluctuation with glaucomatous progression. Larger prospective studies should be conducted to identify the independent risk factors and to confirm the role of IOP fluctuation in PACG progression.

In summary, the contact lens sensor allows documentation of the circadian IOP fluctuation in PACG patients during their normal activities of daily living in their usual environments. Significant differences in IOP fluctuation profiles were found at specific time points within the bedtime hours (1800-0100) and the wake-up hours (0300-1100), in terms of gradients and curvatures, between the progressive and stable PACG eyes. Large IOP fluctuation within the bedtime and wake-up periods may be associated with PACG progression.

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