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Journal

Translational Vision Science & Technology, 4(1)

ISSN

2164-2591

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Publication Date

2015

DOI

10.1167/tvst.4.1.4

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DOI: 10.1167/tvst.4.1.4

Article

Automated Detection and Quantification of Circadian Eye Blinks Using a Contact Lens Sensor

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Received: 18 August 2014
Accepted: 28 November 2014
Published: 22 January 2015

Keywords: glaucoma; eye blinks; contact lens sensor; circadian; 24-hour

Citation: Gisler C, Ridi A, Hennebert J, Weinreb RN, Mansouri K. Automated detection and quantification of circadian eye blinks using a contact lens sensor. Trans Vis Tech Sci. 2015;4(1):4, http//tvstjournal.org/doi/full/10.1167/tvst.4.1.4, doi: 10.1167/tvst.4.1.4

Purpose: To detect and quantify eye blinks during 24-hour intraocular pressure (IOP) monitoring with a contact lens sensor (CLS).

Methods: A total of 249 recordings of 24-hour IOP patterns from 202 participants using a CLS were included. Software was developed to automatically detect eye blinks, and wake and sleep periods. The blink detection method was based on detection of CLS signal peaks greater than a threshold proportional to the signal amplitude. Three methods for automated detection of the sleep and wake periods were evaluated. These relied on blink detection and subsequent comparison of the local signal amplitude with a threshold proportional to the mean signal amplitude. These methods were compared to manual sleep/wake verification. In a pilot, simultaneous video recording of 10 subjects was performed to compare the software to observer-measured blink rates.

Results: Mean (SD) age of participants was 57.4 ± 16.5 years (males, 49.5%). There was excellent agreement between software-detected number of blinks and visually measured blinks for both observers (intraclass correlation coefficient [ICC], 0.97 for observer 1; ICC, 0.98 for observer 2). The CLS measured a mean blink frequency of 29.8 ± 15.4 blinks/min, a blink duration of 0.26 ± 0.21 seconds and an interblink interval of 1.91 ± 2.03 seconds. The best method for identifying sleep periods had an accuracy of 95.2 ± 0.5%.

Conclusions: Automated analysis of CLS 24-hour IOP recordings can accurately quantify eye blinks, and identify sleep and wake periods.

Translational Relevance: This study sheds new light on the potential importance of eye blinks in glaucoma and may contribute to improved understanding of circadian IOP characteristics.

Introduction

The number of eye blinks performed over a certain period of time constitutes the so-called spontaneous blink rate (SBR). The ability to measure the SBR objectively may be of value in the study of different systemic conditions as well as conditions of the eye.[1] Alterations in SBR have been observed in a variety of neurological and psychiatric conditions.[2–4] Reported values of SBR in adults vary widely in the literature, ranging from 11.9 to 31.3 blinks/min.[5,6] The variability may be due to different definitions, populations, experimental conditions, and sampling. Most recent studies use video analysis whose times of observation usually are in the range of 3 to 5 minutes. This provides a small sample given a healthy subject's average blink rate of over 1000 times per hour. In addition, at present to our knowledge there is no literature on the 24-hour characteristics of the SBR.

Recently a contact lens sensor (CLS) for near-continuous 24-hour ambulatory monitoring of intraocular pressure (IOP) patterns has been introduced with the potential to improve the understanding of circadian blinking activity.[7,8] The CLS measures

circumferential changes of the globe at the corneoscleral junction that have been shown to correspond to changes in IOP and volume.[9] Eye blinks produce a transient IOP rise of 10 mm Hg and higher,[10,11] which the CLS registers as characteristic short-duration, high-amplitude spikes.[9,12] Transient IOP elevations during blinking have been hypothesized to have an important role in the pulsatile flow of aqueous into aqueous and episcleral veins.[13] Blinks have been hypothesized to cause an IOP transient (difference between baseline IOP-episcleral venous pressure and IOP after blinking) of approximately 125%, which drives a bolus of aqueous through the outflow pathway. Therefore, the ability to measure blink parameters may be of value in investigating mechanisms of glaucoma damage.

The purpose of this study was to evaluate the ability of the CLS to detect automatically and quantify 24-hour blinking characteristics. We further hypothesized that this information can be used for the identification of sleep and wake periods.

Methods

Participants

The study was approved by relevant institutional review boards and written informed consent was obtained from all participants. From a database of 572 eyes that underwent 24-hour CLS monitoring at 17 clinical centers, 249 profiles (134 left and 115 right eyes) were qualified as good quality and were included for this study. Good quality was defined as meeting all criteria of: (1) a minimum effective acquisition duration of 22 hours, (2) the maximal time interval between two consecutive bursts being less than 2.5 hours, (3) the maximal time interval between the acquisition start and first burst less than 1 hour, (4) the maximal time interval between the acquisition and last burst less than 1 hour, (5) the maximal number of outliers less than 6, and (6) the maximal number of artifactual signal "jumps" equal to 0. In addition, the availability of complete clinical data on participants was required for study inclusion.

Instrumentation

The CLS (Triggerfish; Sensimed AG, Lausanne, Switzerland) measures changes in ocular circumference and corneal curvature at the corneoscleral junction secondary to changes in IOP. Measurements from the CLS are obtained in electronic units of voltage (mV) via dilatation of the strain gauge. The output is provided in arbitrary units (a.u.). A correlation between IOP changes and CLS-obtained mV has been shown previously.[9,12] The current generation CLS records these changes during continuous periods of 30 seconds every 5 minutes, corresponding to a "burst." The sampling frequency is 10 Hz, yielding 300 points per burst.[14]

Data Analysis

A blink can be characterized as a sequence of three successive and continuous local extrema: first a local minimum (the start point), then a local maximum (the peak), and finally a local minimum again (the end point). To be qualified as a blink, the difference between the peak and the start as well as the end points must be greater than a threshold (T). The value of T is proportional to the mean amplitude of all bursts (MA_{Bursts}) in a given profile. Hence $T = k * MA_{Bursts}$, with $0 < k < 1$, because the mean amplitude of a blink (MA_{Blink}) is smaller than MA_{Bursts}. Empirical tests gave the best results with $k = 1/8$. All burst points are parsed chronologically. Each point potentially may be the peak of a new blink. A given candidate point can be the peak of a blink only if the sequences of nearby points toward the left and right are strictly monotonically decreasing until reaching a local minimum, namely the blink start and end points. When such points have been found, the difference between the peak and the start as well as the end point is computed. If it is greater than the previous computed threshold, then a new blink has been found.

As soon as we detect blinks with this algorithm, we can perform various measures and statistics over the recorded patient profiles. The blink rate is measured in blink/min and corresponds to the number of blinks occurring during a certain period. The blink duration is measured in seconds and corresponds to time difference between the start and end points of a blink. The interblink interval, also measured in seconds, corresponds to the time difference between the end point of a blink and the start point of the following blink. Finally, the blink amplitude is defined as the extent of signal rise from the mean of the start and end points of the blink to the peak blink signal. Figure 1 shows the results of the blink detection method. Each detected blink is marked with a vertical dashed line drawn on its peak.

Blinks can be considered as noise on the IOP pattern signal variation during the wake time. Being able to detect them, and particularly their start and end points, enables deletion of these from the signal of

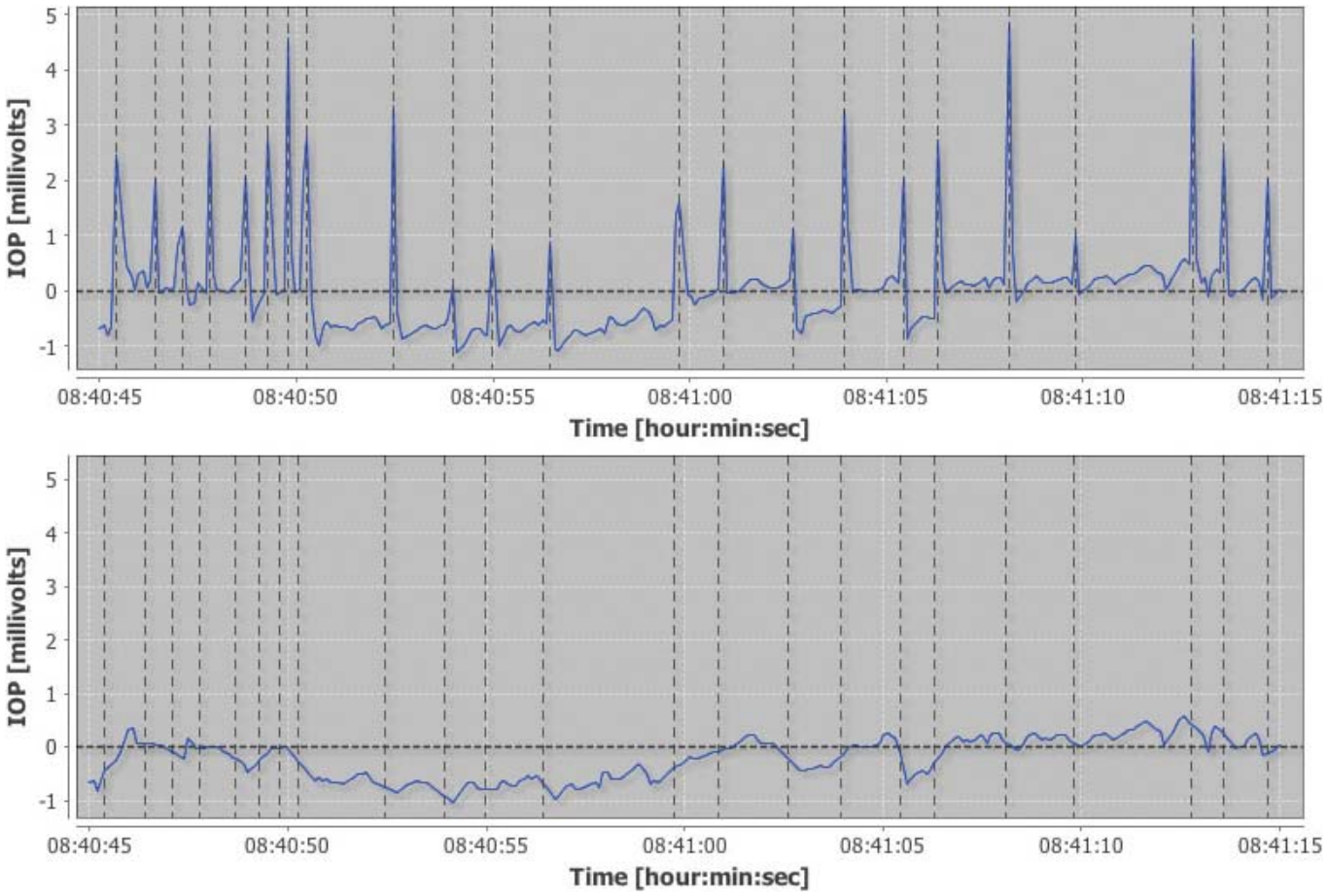

Figure 1. Example of result obtained with the blink suppression method. Blink detection method is able to detect the presence of a blink, as well as its start and end points, and uses this information to remove all blinks from the IOP signal of a burst. Example of a raw burst with blinks (*top*) and the same one without blinks (*bottom*), after blink suppression.

the profile bursts. A simple linear interpolation then is applied to fill in the resulting gaps. Figure 2 shows an example of the blink suppression method.

In 10 subjects, video recording for the duration of 5 minutes was performed to compare the software detected blink rate with measurements by two observers.

Wake and Sleep Period Identification

Blinks occur mostly during the wake time and can be used to estimate sleep and wake times. Figures 3 and 4 show examples of bursts captured during wake and sleep periods. Three sleep period identification methods were developed and tested:

1. Method 1: 0BIB (Zero Blink In Bursts). As part of the proposed blink detection algorithm, efforts were made to detect bursts with an absence of blinks in a given profile. It was estimated that the probability of these periods corresponding to a subject's sleep would be high. However, there are potential drawbacks to this method. The absence of blinks in bursts doesn't ensure that a subject is sleeping or that his eyes are closed. For instance, prolonged fixation at an object for the entire burst duration can take place in the absence of blinking. Moreover, the blink detection algorithm itself can be subject to errors, especially type II errors, when highly varying IOP patterns are detected as blinks. Such patterns can occur during the rapid eye movement (REM) stage of sleep, when eye movements occur with closed eyelids. A single false-positive signal in a burst during sleep would label that period as "awake," causing a gap to appear in the surrounding sleep period.
2. Method 2: BMLT1 (Blink Mean Less Than One). This method was developed to avoid some shortcomings of the 0BIB method. Herein, all

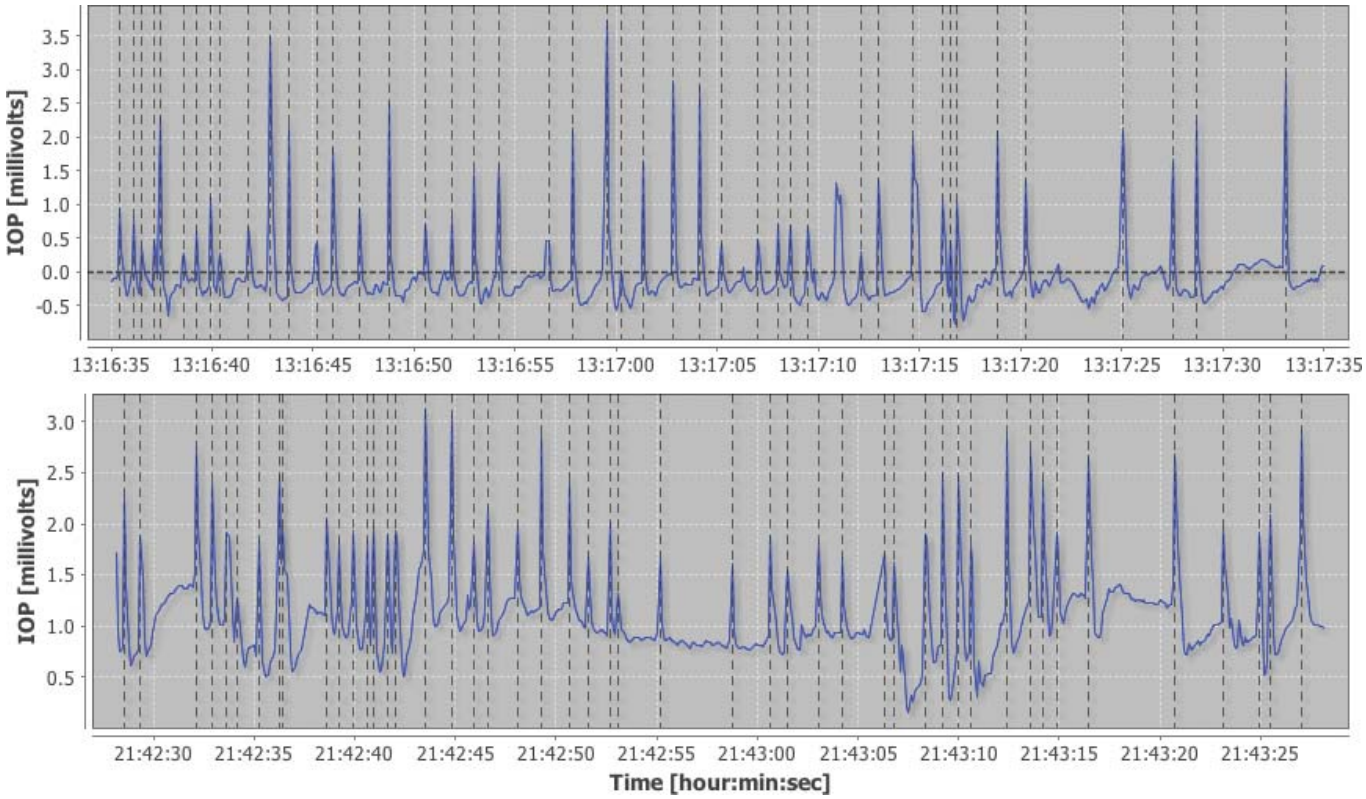

Figure 2. Example of result obtained with the blink detection method. Peaks of all detected blinks are marked with a *dashed vertical line*. The blink rate is high in this burst.

bursts in a profile are scanned and the mean numbers of blinks over N consecutive bursts are computed. If an obtained mean value over N bursts is less than 1, the subject is assumed to be asleep for the duration of those bursts. By taking the blink mean, the context of the nearby bursts is taken into consideration, which avoids detecting a short wake period (type II error) of 1 or 2 bursts during a known sleep period. This method is assumed to produce more consistent results and more homogenous detected wake and sleep periods. However, this second method still has the

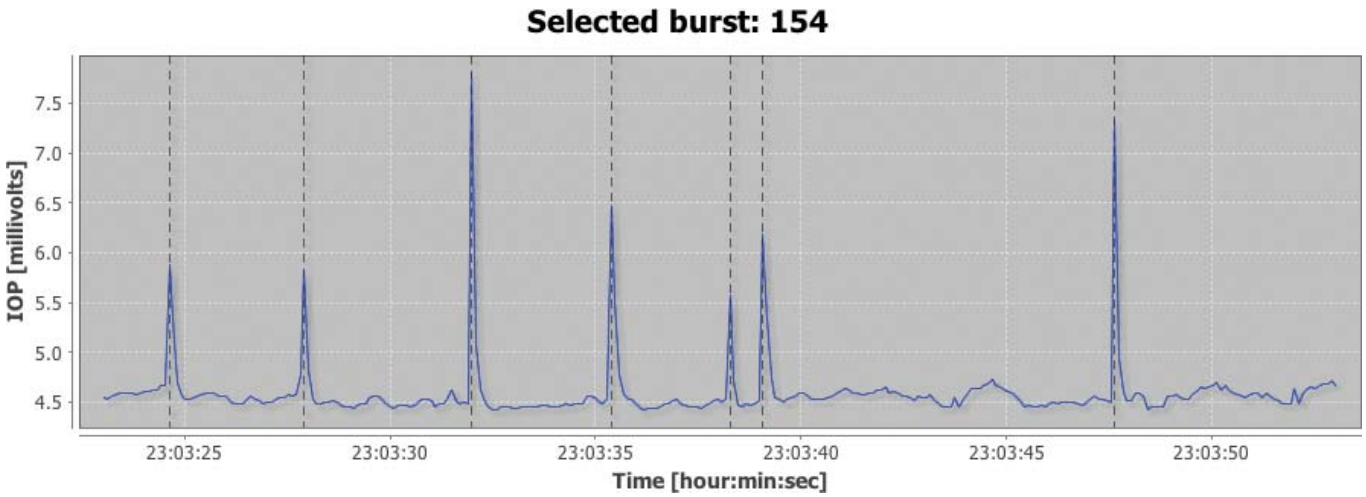

Figure 3. Examples of bursts captured during the wake period, that is while a patient was awake (afternoon, *top* and evening, *bottom*). The high number of present blinks suggest that the monitored patient was awake at that time (confirmed with subject diary).

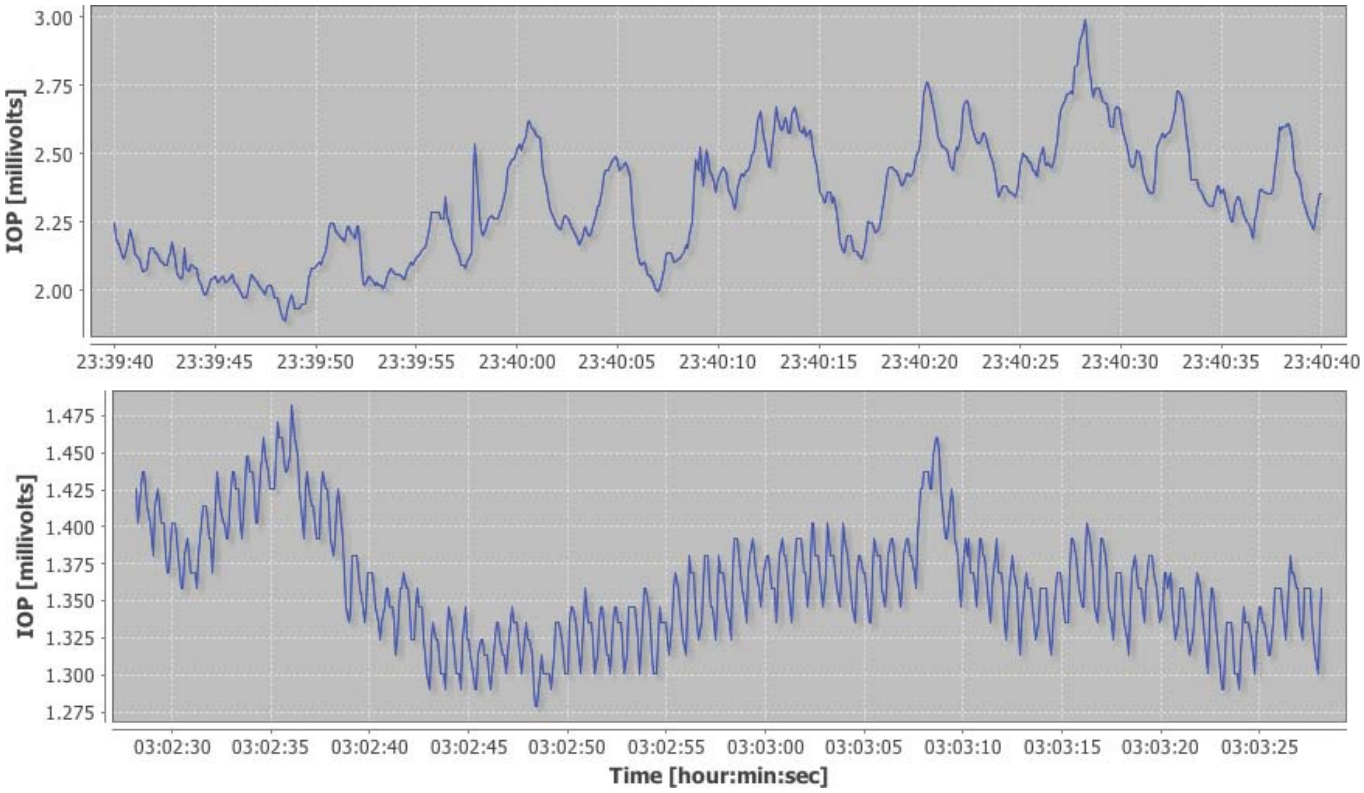

Figure 4. Examples of bursts captured during a sleep period, that is while a patient was asleep (early sleep, *top* and late sleep, *bottom*). The absence of blinks ensures that the monitored patient was asleep at that time (confirmed with subject diary). Differences in patterns correspond to different sleep stages.

drawback of depending on blinks, whose absence does not ensure a sleep state.

3. Method 3: BLAM (Burst Local Amplitude Medians). This method is based on the shape of the burst and does not depend on blink detection. First, in every burst of a given profile, a fixed-size sliding window (i.e., a considered portion of the burst) is shifted. At each step of the shift, the amplitude of the signal is computed inside the sliding window. Experiments conducted previously have shown that a length of 30 burst points with an overlap of 10 points between two consecutive windows provides the best results. Hence, for each burst, a vector of "local amplitudes" is yielded. Then, the median of the computed vector is compared to a dynamical threshold, which has been set empirically to the mean of the global amplitudes of all bursts in the profile divided by 8. This value comes from the fact that this global mean burst amplitude strongly depends on the eye activity during the wake time (e.g., the blinking) and, hence, is largely bigger than local amplitudes computed on portions of the signal containing most of the time no eye activity. Looking at the IOP signal in bursts, it appears that the amplitude at a blink peak is approximately 8 times bigger than the one at an interblink. Finally, a constraint ensuring that a sleep period contains at least 5 bursts stated as "asleep" was added to the algorithm.

To evaluate the elaborated sleep period detection methods, an accurate comparison with the obtained results was obtained. Therefore, wake and sleep periods of the 249 selected profiles were parsed visually and manually annotated by an experienced examiner. The resulting annotations were compared to the patient-reported sleep times from the diary when available. The accuracy of the methods subsequently was computed by comparing each burst result with its corresponding burst annotation. Intraclass correlation coefficients (ICC) were used to assess agreement between software detected blinks and observer-measured blinks on video recordings. All hypothesis testing was 2-sided, at 2-sided $\alpha = 0.05$. All analyses were conducted using Mathematica 9.0 (Wolfram, Inc., Oxfordshire, UK).

Table 1. Mean Blink Frequencies (Blinks/min), Durations, and Intervals

Blink Statistics	All	Males	Females	Healthy	Glaucomatous
Blink frequency, b/m	29.8 ± 15.4	27.3 ± 15.4	32.3 ± 15.6	28.3 ± 14.8	30.2 ± 15.5
Blink duration, s	0.26 ± 0.21	0.26 ± 0.21	0.26 ± 0.21	0.26 ± 0.22	0.26 ± 0.21
Blink interval, s	1.91 ± 2.03	2.01 ± 2.20	1.80 ± 1.85	1.99 ± 2.18	1.89 ± 1.99

Blinks were measured during wake periods of patient IOP profiles. Differences between groups were not statistically significant. s, seconds.

Results

A total of 249 CLS recordings was obtained from 202 participants with a mean (SD) age of 57.4 ± 16.5 (range, 18–87). They were diagnosed as established glaucoma ($n = 126$), suspected glaucoma ($n = 27$), and healthy ($n = 49$). There were 102 (50.5%) women and 100 (49.5%) men. Participants reported their ancestry as white/Caucasian ($n = 171$), Asian ($n = 8$), African American ($n = 8$), and other ($n = 15$). Among the 10 eyes with simultaneous video recording, there was excellent agreement between software-detected number of blinks and visually-measured blink rate for both observers (ICC, 0.97 for observer 1; ICC, 0.98 for observer 2).

Using the most accurate sleep period detection method, which combines BMLT1 and BLAM methods, the mean blink rate obtained for the entire group was 29.8 ± 1.9 blinks/min during wake times of the entire 24-hour period. Mean blink duration was 0.26 ± 0.21 seconds with an interblink interval of 1.91 ± 2.03 seconds (Table 1). On average, blink amplitude was 116.0 ± 69.0 a.u.

Wake periods were determined with the help of the best sleep period detection method combination. Table 2 shows the sleep period detection accuracies in percent obtained using the 3-presented methods and their combinations. The best result was obtained by combining BMLT1 and BLAM with an accuracy of 95.2 ± 0.5%. Figure 5 shows an example of results obtained with the sleep period identification method (left) and the corresponding manual sleep period annotation (right) for comparison.

Discussion

In this study, a method was developed to detect eye blinks derived from 24-hour IOP monitoring data using a CLS. We showed that the CLS signal can be used to estimate blink rates throughout the 24-hour period, which in turn can be used to estimate sleep and wake times. Previous studies used different methods to measure blink movements. The most frequently used ones (videographic monitoring electromyography) generally measure the blink rate for periods of 5 to 30 minutes during daytime. The CLS, however, provided 288 measurement points for a continuous period of 30 seconds, repeated every 5 minutes and for the duration of 24 hours.

With an average blink rate of 29.8 ± 15.4, our results are within the range of previous reports that reported rates between 10 and 31 blinks/min.[5,6,15] Sun et al.[6] studied the effect of aging on healthy adults. They found a modest, but nonsignificant increase of spontaneous blink rates from 23.5 ± 3.8 (mean ± SE) blinks/min (40–60 years of age group) to 31.3 ± 5.7

Table 2. Sleep Period Detection Method Accuracies (%)

	Min. Required Number of Consecutive Bursts for a Sleep Period						
Methods	2	3	4	5	6	7	8
0BIB	91.9	91.9	91.9	91.9	91.9	91.9	91.9
BMLT1	91.6	93.1	94.1	94.5[a]	94.5	94.4	94.0
BLAM	92.6	92.8[a]	92.7	92.4	91.7	91.1	90.3
0BIB + BMLT1	93.5	94.3	94.9	95.1[a]	95.0	94.8	94.3
0BIB + BLAM	93.2	93.8	94.1	94.3[a]	94.3	94.3	94.2
BMLT1 + BLAM	93.6	94.5	95.0	95.2[a]	95.1	94.8	94.4
0BIB + BMLT1 + BLAM	93.5	94.3	94.9	95.1[a]	95.0	94.8	94.3

[a] Best obtained results for each method or method combination.

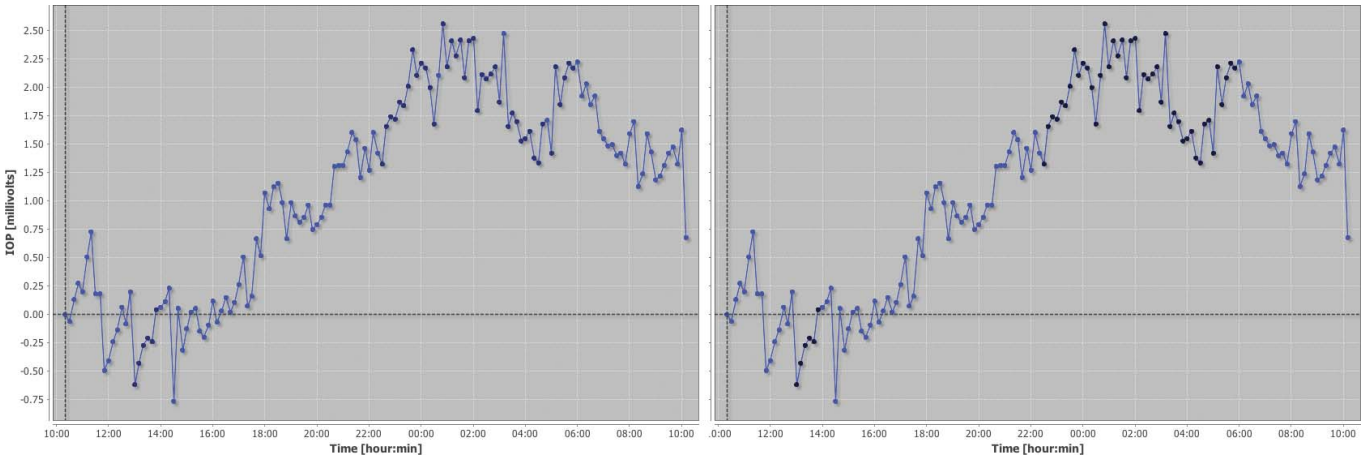

Figure 5. Example of sleep period annotations obtained with the sleep period identification method (*left*) and the corresponding manual sleep period annotation (*right*) for comparison. The automatic method has an accuracy mean of 95.2%.

blinks/min (80–89 years). Patients on topical therapy for glaucoma generally have more ocular surface disturbances than healthy subjects, which may increase spontaneous blink rates. We did not find a statistically significant difference ($P = 0.4028$) between healthy patients and treated glaucoma patients in terms of blink frequency. The blink rate in our study was composed of all three types of blinking and we were not able to calculate the different blink types individually. The interblink interval of 1.91 ± 2.03 seconds found in our study was similar to 2.33 ± 1.10 seconds recently measured in healthy subjects.[16] Zaman et al.[5] videotaped 45 elderly patients over a period of 5 minutes and measured their blink characteristics. They found a mean interblink interval of 10.4 ± 8.9 seconds. Differences in methodology and population may explain this discrepancy: (1) Due to the short observation period, the sample of blinks obtained in 5 minutes is extremely small compared to our sample obtained over 24-hours. (2) The act of fixating a target may reduce blink frequency.[17] (3) There may be an age-related reduction of blink frequency.[6] The literature on the distribution and range of amplitude of spontaneous blinks is scant. Previous studies have calculated the blink amplitude in degrees (which can be converted to millimeters through a trigonometric function) and reported a range of 10° to 60°.[6,17] The CLS used in the present study provides the amplitude of IOP changes secondary to blinks in electronic voltage units. Therefore, the mean blink amplitude of 116 ± 69 a.u. cannot be compared directly to previous reports.

The ability to measure 24-hour blink characteristics in an ambulatory setting may have practical applications in different fields of medicine. Johnstone et al.[13] postulated that blink-related IOP elevations can increase aqueous humor outflow. Using an 80-power magnification microscope for real-time observation of human eyes during the blinking process, they observed a propulsive aqueous wave after each blink and were able to trace it forward from Schlemm's canal to the scleral emissaries. This wave initially entered the aqueous veins followed by discharge into the episcleral veins. Based on these observations, they confirmed earlier theories of the existence of a pulsatile aqueous outflow mechanism with a pulse wave source originating from Schlemm's canal. They opined that a blink would function as a source of force, Schlemm's canal as a reservoir, trabecular meshwork as a compressible tissue, and collapsible tubes or pores at the level of Schlemm's canal acting as one-way valves. The same group expanded on this hypothesis by showing that the optic nerve head undergoes motion in response to cardiac pulse induced transients.[18] These findings would suggest that excursions of the optic nerve head could to be considerably larger with blinks and eye movements, which cause larger amplitude pulse transients. If confirmed, the role of transients could take on increased significance.

The present study further showed how the absence of blinks can be used to automatically estimate sleep and wake times. The ability to obtain objective wake/sleep times (versus patient reports) may be of practical use in the assessment of 24-hour IOP patterns. Different investigators have demonstrated that, in healthy subjects and glaucoma patients, IOP rises during sleep in the habitual body position.[19,20] Their

findings were confirmed recently using the CLS.[8,21] Lee et al.[22] found that all sleeping positions of head and body result in an elevation of IOP and an increase in ocular perfusion pressure compared to the sitting position in healthy, young subjects. The postural change from supine to lateral decubitus or prone with head turn position led to an additional IOP increase in the dependent eyes. Currently, it is unknown how nighttime IOP elevations affect long-term glaucoma prognosis.[23]

In the field of ocular surface disease, knowing blinking characteristics can be of diagnostic and therapeutic value.[16] The tear film, which maintains a healthy ocular surface, is dynamically regulated by blinking activity. Consequently, the rate of blinking has been shown to be associated with the presence and severity of ocular surface disease.[24–26] For instance, patients with dry eyes were found to have a higher SBR than healthy subjects,[27] possibly as a secondary mechanism to increase tear production. Neurologic disorders are associated with abnormal blinking. The central dopaminergic system has been shown to control spontaneous blinking.[28] In parkinsonism, blinking is reduced due to dopamine depletion from the substantia negra, whereas patients with schizophrenia have increased blink rates due to dopamine hyperactivity.[29,30] Some investigators have hypothesized that the spontaneous blink rate could be used as a clinical marker of central dopaminergic activity.[31,32]

This study has several limitations. One drawback of the evaluation procedure was the difficulty to evaluate the accuracy of the blink detection method. A manual annotation of all blinks in all bursts of all selected profiles would have been required to have an accurate comparator (as was done with sleep periods). In this case, the method accuracy would be able to be computed by comparing blinks automatically detected by the computer to those visually detected by the grader. However, the large amount of data and the difficulty to perform truly reliable annotations make this task hard to realize. The recorded IOP signal can be too noisy and preclude the differentiation of a blink from an artifact. Nevertheless, after having visually checked the bursts in selected profiles, the accuracy of the blink detection method over the selected profiles was over 90% (data not shown). Signal noise led to false positives in blink detection. However, video recording of 10 eyes found excellent agreement (ICC, 0.97–0.98) between software and observer measurements of eye blinks (Supplementary Video). Furthermore, saccades and other eye movements may produce transient changes in IOP that can resemble the effect of blinks. However, as we found on video recordings, the effect of saccadic eye movements on the CLS signal is fundamentally different. While blinks produced short-duration high-amplitude spikes, saccades produce smaller changes in the CLS signal that are of longer duration (Supplementary Video). Finally, it is possible that the presence of the CLS itself may have altered the physiological blinking behavior of study participants. Thai et al.[33] showed that alterations in the tear film secondary to contact lens wear can produce a stimulus to blinking. However, as the wireless CLS technology is relatively new, other uncharacterized parameters may lead to more data variations. These may include signal drift over the 24-hour period, effect of external manipulation on the signal output, and sudden rise and fall in electronic transmissions. Future studies should address potential CLS-related issues.

In conclusion, we demonstrated that 24-hour IOP monitoring data can be used to study circadian blinking characteristics. The proposed software has the ability to automatically quantify blink rates as well as detect sleep and wake times with excellent accuracy. These data have the potential to improve our understanding of the effect of eye blinks on aqueous outflow dynamics. The ability to quantify blink parameters continuously and in an ambulatory setting may be of value in ophthalmology and in other fields of medicine.

Acknowledgments

Supported in part by grant P30EY022589 from the National Eye Institute and an unrestricted grant from Research to Prevent Blindness (New York, NY).

Disclosure: **K. Mansouri**, Research and financial support from Sensimed AG (Switzerland); **R.N. Weinreb**, Research and financial support from Carl Zeiss Meditec, Inc., Dublin, CA; Heidelberg Engineering, GmbH, Heidelberg, Germany; Optovue, Inc., Fremont, CA; Topcon Medical Systems, Inc., Livermore, CA; Nidek, Aichi, Japan; Sensimed AG (Switzerland); **C. Gisler**, None; **A. Ridi**, None; **J. Henneberrt**, None

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