Spontaneous Interblink Time Distributions in Patients with Graves’ Orbitopathy and Normal Subjects

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PURPOSE. To determine the shape of spontaneous interblink time interval distributions obtained in a long observation period in normal subjects and patients with Graves’ orbitopathy.

METHODS. The magnetic search coil technique was used to register the spontaneous blinking activity during 1 hour of video observation of two groups of 10 subjects each (normal controls aged 27–61 years, mean ± SD = 46.0 ± 13.6; patients with Graves’ orbitopathy aged 33–61 years, mean ± SD = 46.7 ± 8.9). The spontaneous blink rate of each subject was calculated for the entire period of observation and for 5 six-minute bins. Histograms of the interblink time interval were plotted for each measurement of blink rate.

RESULTS. Neither the overall mean blink rate (controls, 19.8 ± 4.9; Graves’, 17.6 ± 5.4) nor the interblink time (controls, 5.2 ± 3.1, Graves’, 7.9 ± 3.5) differed between the two groups. There was a large variation of both measurements when the 5-minute bins were considered. The interblink time distribution of all subjects was highly positively skewed when the 1-hour period was measured. A significant number of the 5-minute bin distributions deviated from the overall pattern and became symmetric.

CONCLUSIONS. The normal blinking process is characterized by highly positively skewed interblink time distributions. This result means that most blinks have a short time interval, and occasionally a small number of blinks have long time intervals. The different patterns of distribution described in the early literature probably represent artifacts because of the small samples analyzed. (Invest Ophthalmol Vis Sci. 2011;52:3419–3424) DOI:10.1167/iovs.10-7060

The concept that subjects with identical spontaneous blink rate (SBR) may display different distributions of the time interval between consecutive blinks (interblink time interval or IBI) was first introduced by Ponder and Kennedy.1 In their seminal paper published at the beginning of the past century, the authors recorded the spontaneous blink activity (SBA) of 50 normal subjects during a reading task. Four classes of distribution were found when IBI histograms were plotted: J-shaped, irregular plateau, bimodal, and symmetrical. These different distributions were considered to be an invariant individual characteristic and thus to reflect an intrinsic property of the blinking process. The results of Ponder and Kennedy were replicated, with some variations, by other investigators.2–6

It is well known that upper eyelid retraction (Dalrymple’s sign) is a prominent finding in patients with Graves’ orbitopathy (GO). In the ophthalmology literature, there are eponyms suggesting that spontaneous blinking activity is not normal in GO. For instance, the name of Stellwag is associated with infrequent blinking and Pochin’s sign refers to reduced blinking amplitude.7,8 We have recently confirmed that spontaneous blink metrics are not normal in patients with GO.9

Interblink time interval distributions have never been carefully studied in patients with GO. It is not known whether a peripheral abnormality, such as lid retraction has any influence on interblink time interval distributions.

In the present study, we report an analysis of SBR over a long period in controls and patients with GO. Our results indicate that the IBI distributions of patients and controls have the same pattern, and the distinct types of IBI distributions described earlier are an artifact resulting from the small size of the sample analyzed.

METHODS

This research adhered to the tenets of the Declaration of Helsinki.

Subjects

Twenty subjects, divided into two groups of 10 (normal controls and patients with GO), had their SBAs measured when watching a commercial movie during a period of 1 hour.

The control group consisted of five men and five women aged 27 to 61 years (46.0 ± 13.6; mean ± SD). None of the subjects had any history of eye disease or ocular symptoms. The mean of the upper eyelid margin distance was 3.5 ± 0.49 mm (SD). The Graves’ group consisted of three men and seven women aged 33 to 61 years (46.7 ± 8.9; mean ± SD). At the time of testing, nine patients were euthyroid and just one patient was still using antithyroid drugs. All had upper eyelid retraction. The mean upper eyelid margin distance was 6.1 ± 1.25 mm (SD).

Blink Measurement

A magnetic search coil was used to continuously register the upper eyelid movements during the experiment.10 The subjects were comfortably seated with the head stabilized on a chin rest in a weak magnetic field. A small coil (3.8 mm diameter, 30 turns, 30 mg, copper wire 0.102 mm in diameter) was taped to the center of the pretarsal area of the upper eyelid. The coil did not impair lid movement, and subjects became unaware of the coil shortly after application. During blinking, as the eyelid slid over the curved surface of the eye, the coil produced a current proportional to the angle between the coil and the magnetic field and consequently proportional to lid angular position. The recordings were low-pass

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filtered at 10 kHz, amplified 20,000 times, digitized with 12-bit precision, and sampled at 200 Hz by a computed system (Remel Laboratories, San Antonio, TX), providing detection of lid rotations with a spatial resolution of 0.1° (equivalent to a linear lid motion of 0.02 mm) at a temporal resolution of 5 ms. The magnetic search coil output current and lid angular position were calibrated by measuring the angle of lid rotation with a protractor, while a fine wire was placed perpendicular to the eyelid margin at the site of the coil. The experimenter centered the protractor over the point that would be the projected center of rotation of the wire.

Data Analysis
Spontaneous blinks were then continuously recorded for 1 hour while the subjects watched the same video (a Brazilian commercial movie). A program developed in Python 2.6 was used to analyze the data (provided by the Python Software Foundation, Wolfeboro Falls, NH, and available at http://www.python.org). An algorithm based on the blink signal’s derivatives was used to detect the blinks automatically. In addition, the data retrieved were checked manually to avoid mistakes. Histograms of IBI were plotted for the whole time of observation and for the maximum number of contiguous different bins of 5 minutes (1–6, 2–7, 3–8, and so on). This way we obtained 56 bins. The degree of symmetry of all distributions was determined by the calculation of the skewness coefficient, according to Joanes and Gill.11

RESULTS
Neither the overall mean ± SD SBR (controls, 19.8 ± 4.9 blinks/min; Graves’, 17.6 ± 5.4 blinks/min) nor the IBI time (controls, 5.2 ± 3.1 seconds; Graves’, 7.9 ± 3.5 seconds) differed between the two groups. When the number of blinks was plotted in bins of 5 minutes’ duration, it was apparent that both parameters were quite variable along the time of obser-

FIGURE 1. Control subjects. Variation of the mean spontaneous blink rate and mean interblink time along 1 hour of observation. Each symbol represents the blink rate measured in a bin of 5 minutes.
vation. The coefficient of variation of the means for controls and Graves’ patients, respectively, were SBR, 29.6% and 36.7%, and IBI, 44.9% and 44.6% (Figs. 1, 2).

When the whole time of observation was considered, the IBI distribution of all subjects was positively skewed with coefficients greater than 1.0 (Fig. 3). This type of distribution, which corresponds to the J-shape type of Ponder and Kennedy¹ tends to be symmetric when the logarithm time is considered.

A significant number of bin distributions deviated from the highly positive pattern of the entire period. In 9.3% and 12.5% of distributions of the controls and patients, respectively, the coefficient of skewness was lower than 1.0, and for a small number of bins, the coefficients were symmetric or negative (controls, 1.25% and Graves’, 3.6%). Figure 4 displays different patterns of IBI distributions when a small sample size is considered.

**DISCUSSION**

There is a general agreement that SBR is modulated by central dopaminergic activity.¹² In fact, clinical studies of diseases with dopamine dysfunction have shown that SBR is low in conditions with hypodopamine activity, such as Parkinson’s disease¹³,¹⁴ and high when there is hyperdopaminergic activity as in schizophrenia.¹⁵–¹⁷ Besides, it has been experimentally demonstrated in monkeys that higher levels of dopamine are associated with high SBR.¹⁸ There is a large body of literature showing that the so-called normal SBR is highly variable across subjects and testing conditions.⁵,¹⁹ Normative adult values when the subject is sitting silently and in primary gaze position range from 10 to 22.4 blinks/min.⁵ In all studies on SBR the time of observation is quite short, typically a few minutes. We are not aware of any study that has assessed the within-subject variability during a long period of observation.

**FIGURE 2.** Graves’ patients. Variation of the mean spontaneous blink rate and mean interblink time along 1 hour of observation. Each symbol represents the blink rate measured in a bin of 5 minutes.
Mental effects may explain the high variability shown by our subjects during 1 hour of video observation. SBR is increased during conversation, states of anxiety, and fatigue and is reduced when the subject reads or views a text on a video display. It is possible that attentional factors, fatigue, and fluctuations in interest in the video interacted here to produce the variability displayed in Figures 1 and 2.

Despite the high variability of the SBR over time, all IBI distributions were positively skewed including those of the patients with GO. This means that the blinking process is characterized by a high number of blinks with short time intervals followed by a decreasing number of longer interblink intervals. This type of distribution becomes symmetric when the logarithm of the interblink interval is considered. This finding is surprising, because the existence of different classes of IBI distribution has been accepted as a scientific fact. However, a close inspection of the literature reveals that our results concur well with the few data that have been published on this subject. For instance, the IBI distribution of 31 (62%) of the 50 Ponder and Kennedy subjects was positively skewed and 8 were bimodal or symmetrical. However, in their experiment, the period of observation was from 30 minutes to 2 hours in duration, the first 10 or 15 minutes being disregarded for the purpose of measurement. Therefore, we do not know the time used to test each subject, and it is impossible to draw any conclusions on the relationship between time of observation and the shape of IBI distribution. Working with infants, Bacher and Allen noticed that the IBI of the distributions were highly positively skewed, and therefore the scores had to be transformed by using a logarithmic function for statistical analysis. Two studies on the effect of topical anesthesia on SBR have shown that when subjects are assessed over a period of 5 minutes, different types of IBI distributions are seen. However, when the data are averaged in just one histogram, the resulting distributions are clearly positively skewed. Our results indicate that the sampling size is an important factor when distribution shapes are analyzed, and the degree of symmetry changes when small samples are considered. If we accept that only the distributions with less than or more than +1 are highly skewed and those with coefficients between −1/2 and +1/2 are approximately symmetric, a significant number of subjects could be labeled as having symmetric distributions if a 5-minute period was considered. We believe that the skewness variations are random and do not depend on blink rate in each bin. In fact we found no correlation between the number of blinks in each bin and the degree of skewness of the IBI distributions.

Traditional knowledge in ophthalmology has consistently shown that the ocular surface is also important in blink rate modulation. Besides the classic experiments with topical anesthesia, recent investigations conducted with large samples under controlled environmental conditions (humidity, light, and temperature) have found significant negative correlations between tear breakup time and SBR. It has also been shown that the SBR of dry eye patients is higher than that of the normal population. The maximum time during which the subjects can keep their eyes open is also decreased among dry eye patients.
The resting position of the upper eyelid of patients with Graves’ disease is abnormally high. In addition, the metrics of the upper eyelid motion during spontaneous blinks is not normal. Despite these abnormalities, the IBI distributions of the patients were also positively skewed, showing that the occurrence of a large number of blinks with short intervals followed by a smaller number of movements with longer interblink intervals is a robust mark of the spontaneous blink process. Since the chronology of the spontaneous blink activity is lost when IBI histograms are plotted, further research is needed to examine a possible temporal order of the interblink intervals. A temporal series analysis of spontaneous blinks remains to be undertaken.

References


