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Purpose. To evaluate spontaneous eye blink patterns and their correlations with clinical tests in dry eye disease (DED).

Methods. Twenty-five DED patients and 25 healthy subjects were included in this prospective case-controlled study. Clinical evaluations included the Ocular Surface Disease Index (OSDI), lipid layer thickness (LLT), spontaneous eye blink pattern analysis, fluorescein tear film break-up time (FBUT), and so on. Eye blinks were recorded for 20 seconds with a high-speed camera. Eye blink patterns were divided into the following five phases: the eyelid closing phase (ECP), eyelid closed phase (CDP), early opening phase (EOP), late opening phase (LOP), and interblink intervals (IBI). The correlations between blink parameters and clinical tests were analyzed.

Results. Compared with the control group, mean ECP, CDP, and EOP were significantly longer in DED patients ($P < 0.001$, $P = 0.029$, and $P < 0.001$, respectively). DED patients also had significantly shorter LOP and blink intervals (both $P < 0.001$) and more partial blinks as compared with control subjects ($P = 0.001$). FBUT was negatively correlated with ECP ($r = -0.618$, P=0.001) and the number of partial blinks ($r = -0.413$, $P = 0.040$). There was a positive correlation between OSDI and the number of partial blinks ($r = 0.446$, $P = 0.026$). The LLT coefficient of variation (LLT-CV) also showed a positive correlation with ECP, CDP, and LOP ($P = 0.001$, $P = 0.050$, $P = 0.049$, respectively). Corneal and conjunctival staining was positively correlated with ECP, CDP, and the number of blinks ($r = 0.449$, $P = 0.024$; $r = 0.526$, $P = 0.007$; $r = 0.456$, $P = 0.022$, respectively) and negatively correlated with IBI ($r = -0.420$, $P = 0.037$).

Conclusions. Partial blinks, prolonged eyelid closed time and short blink intervals were the three main characteristics of DED patients' spontaneous blink patterns.

Keywords: dry eye, partial blink, blink patterns, inter-blink interval

Dry eye disease (DED) is a common ocular surface disease characterized by a loss of homeostasis of the tear film, ocular surface inflammation, and hyperosmolarity, and associated with ocular surface irritation symptoms, visual disturbance, and quality of life impairment.[1] Maintaining a stable tear film over the ocular surface depends on tear secretion and lipid quality, but also on spontaneous eye blinks. Different from reflex and voluntary blink, a spontaneous blink is a rapid, automatic, and unconscious closing and opening movement of the eyelids.[2] It is essential for tear film spreading over the ocular surface, including lipid secretion into the tear film and tear drainage. Moreover, a spontaneous blink has implications for the optical quality of the eye.[3]

Spontaneous blinking is influenced by age[4] and mental activity,[5] and has complex interactions with the ocular surface.[6] Although the stimulation of the ocular surface increases the spontaneous blink rate, a low blink rate is also a risk factor for the development of DED by increasing tear film evaporation.[7,8] Consequently, changes in the blink rate have been considered both a cause and a consequence of DED.[7] Recent research has focused on the relationship between DED and spontaneous blink. It has been shown that DED patients have a higher spontaneous blink rate (SBR) and a shorter eye-opening time than healthy controls.[9] Similarly, fluorescein tear break-up time (FBUT) was negatively correlated with the SBR.[6] Abnormal blinks could also participate in the poor quality of vision observed in DED patients.[10,11]

Because of the high speed of a spontaneous blink (one blink in <100 ms), it is difficult to measure and analyze blink parameters. Therefore, most studies used the blink rate and the interblink interval (IBI) as the main parameters to evaluate spontaneous blinks in DED.[7] However, these parameters only provide means and variances and do not describe a continuous dynamic change in the blink process. In fact, more complex patterns of blinks appear in DED patients and each phase of the blink process might be important to understand the relationship between DED and blinking. Hence, the objectives of the present study were to establish a method to analyze the blink pattern and to evaluate the correlations between blink parameters and clinical parameters in DED patients.

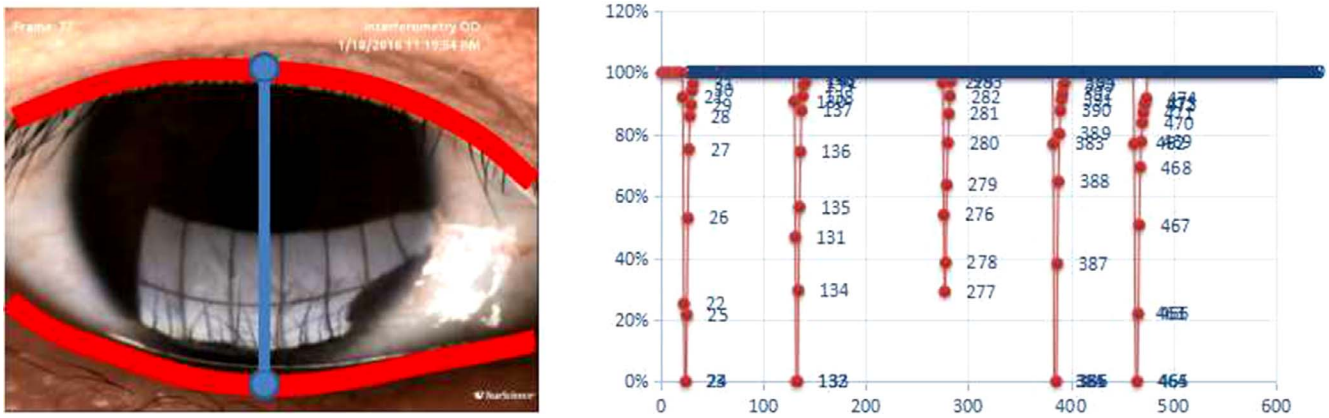


FIGURE 1. Measurement of POH and the blink pattern. (*Left panel*) POH was defined by the vertical distance between the central points of the upper and lower eyelid margins; (*Right panel*) the blink pattern was obtained with 600 scatter points (POH %) in 20 seconds.

METHODS

Subjects

This study was conducted at the Beijing Institute of Ophthalmology with the approval of the Medical Ethics Committee of Beijing Tongren Hospital (TREC-2017-KY031). All subjects were informed of the aims of the study and their consent was obtained according to the declaration of Helsinki. Twenty-five patients (13 men and 12 women; mean age: 41.16 ± 16.28 years; range, 19–66 years) with DED and 25 age-matched control subjects (11 men and 14 women; 42.72 ± 9.62 years; range, 25–65 years) were included in this study. DED patients were consecutively recruited from the Cornea Unit of Beijing Tongren Hospital in April 2017. According to the consensus report by the International Dry Eye Workshop (2007),[12] the inclusion criteria for the DED group were as follows: (1) age older than 18 years; (2) Ocular Surface Disease Index (OSDI) score greater than 12; (3) FBUT less than 10 seconds; and (4) the Schirmer I test less than 10 mm. All control subjects had a FBUT >10 seconds, with no complaint of ocular surface irritation and no abnormality on biomicroscopic examination and ocular surface tests. The exclusion criteria for both groups were as follows: (1) age younger than 18 years; (2) subjects unable to complete the questionnaire or to understand the procedures; and (3) the presence of ocular or systemic disease or the use of topical or systemic medications that may affect the ocular surface and previous history of eye surgery or contact lens wear.

Clinical Evaluation

All subjects underwent quantification of ocular surface symptoms using the OSDI questionnaire with a score ranging from 0 to 100 (0–12, asymptomatic; 13–32, mild to moderate symptoms; 33–100, severe symptoms).[13] Then clinical examinations were performed in the following order: lipid layer thickness measurement (LLT) and blink pattern analysis, infrared Meibomian gland (MG) photography, FBUT, corneal and conjunctival fluorescein staining, and the Schirmer test.

The LLT and blink pattern were analyzed with the Lipiview II (TearScience, Morrisville, NC, USA). The patients' eyes were positioned in front of an illumination source and a 20-second video with 600 frames (800 × 600-pixel resolution) was captured and recorded. The participants were asked to blink freely during examination. The interferometric color unit (ICU) value reflected the local LLT with 1 ICU equivalent to 1 nm of lipid layer thickness. The accuracy was evaluated with the conformance factor (CF) value, which had to be above 0.7 in all subjects. To evaluate the lipid layer thickness heterogeneity over the ocular surface, the tear film LLT coefficient of variation (LLT-CV)[14] was calculated for each eye as the result of the SD divided by the mean value. The integrity of the MGs was assessed using a noncontact infrared meibography system (BG-4M; Topcon, Tokyo, Japan). This system employs a background illumination device with an infrared light transmittance filter that illuminates the MGs to assess their integrity. Meibography of the upper eyelids was then analyzed using ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) software as previously described.[15] MG loss (MGL, expressed as %), representing the ratio of the MG dropout area over the total MG area, was calculated for each eye. FBUT was measured using sterile fluorescein strips impregnated with 0.6 mg fluorescein sodium (Alcon Laboratories, St. Louis, MO, USA). After applying 50 µL of normal saline solution to the paper strip, it was applied to the inferior fornix. The interval between a complete blink and the appearance of the first dry spot was noted. Two measurements were consecutively taken and the average of the two break-up times was calculated. Corneal and conjunctival staining was evaluated using the Oxford scale after instillation of fluorescein under a yellow filter. The Schirmer test was performed without anesthesia for 5 minutes with the patient's eyes closed.

Spontaneous Blink Pattern Analysis

The spontaneous blink pattern was analyzed on the 600 frames provided by the 20-second video of the Lipiview II (TearScience, Morrisville, NC, USA). With the ImageJ software, the palpebral opening height (POH), defined by the vertical distance between the central points of the upper and lower eyelid margins, was measured. Considering the variance of POH in different subjects, the POH percentage (POH %) was evaluated as the POH divided by the maximum POH opening observed during the recorded blinks (POH % = POH / POH_{max}). For every subject, 600 POH values were measured from the 600 frames and scatter points were obtained (Fig. 1). The blink pattern was divided into five consecutive segments, including the eyelid closing phase (ECP), the closed phase (CDP), the early opening phase (EOP), the late opening phase (LOP), and the IBI (Fig. 2). As previously described, the EOP and LOP were defined as the period from the beginning of eyelid opening to 97% of complete opening and the period covering the last 3% of eyelid opening, respectively.[16] During the 20-second exam-

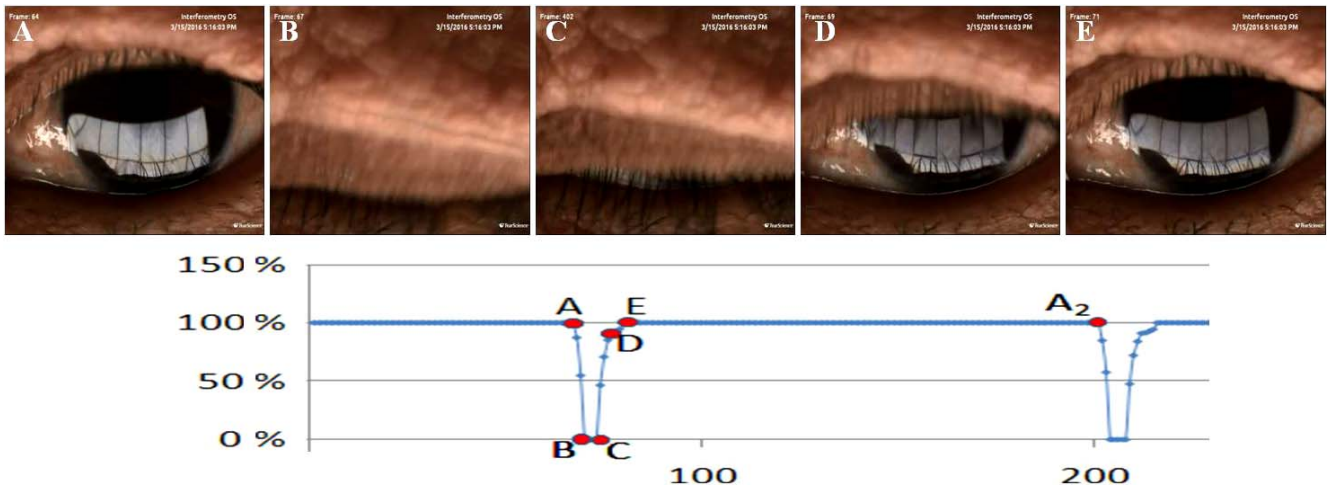


Figure 2. The blink pattern plotting procedure. With the measurements of POH, the blink pattern was plotted on the graph below (images **A–E**). Phases of the normal blink: AB segment: ECP; BC segment: CDP; CD segment: EOP; DE segment: LOP; EA_2 segment: IBI.

ination, the duration of every phase in the blinking cycle was quantified. The definitions of blink phases are summarized in Table 1. The number of blinks and the rate of partial blinks were also evaluated during the 20-second video analysis. Partial blinks were defined as blinks with no contact between the upper and lower eyelids.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 16.0 (SPSS, Inc., Chicago, IL, USA). For each patient, one eye was randomly selected for statistical analysis. The mean ± SD values of all parameters were compared between DED patients and the control group, and the correlations were

Table 1. Definition and Graphic Depiction of Blink Segment and Pattern

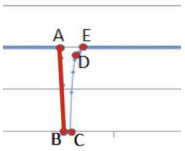
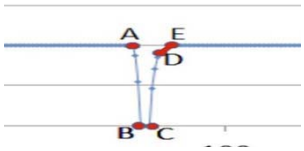
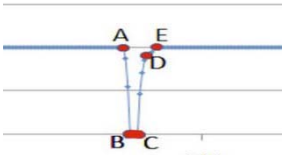
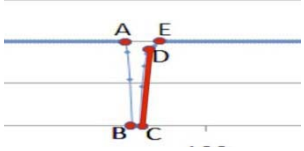
Blink Segment	Graphic Depiction	Definition
AB segment		ECP: From the opening to the closure of the eyelid. This was the indicator of the partial blink rate.
BC segment		CDP: From the beginning of closing the eye to the beginning of opening the eye.
CD segment		EOP: From the beginning of eyelid opening to 97% of complete opening.[19]
DE segment		LOP: The last 3% of eyelid opening.[19]
EA_2 segment		IBL: From the eyelid complete opening to the beginning of a new blink.

Table 2. Demographic Information and Results of Clinical Tests

	Healthy Controls	DED Patients	t / χ^2	Cohen's D	*P* Value
Male, *n* (%)	11 (44.0)	13 (52.0)	0.321	0.08	0.571
Female, *n* (%)	14 (56.0)	12 (48.0)			
Age, y	42.72 ± 9.62	41.16 ± 16.28	0.677	0.12	0.055
OSDI, units	7.36 ± 3.45	33.64 ± 13.26	−9.588	2.71	<0.001
FBUT, s	11.52 ± 1.87	4.52 ± 1.48	14.677	4.15	<0.001
Schirmer I, mm	15.24 ± 6.84	4.56 ± 2.23	7.421	1.86	<0.001
Oxford score, unit	0.08 ± 0.28	0.52 ± 0.71	−2.611	0.74	0.014
LLT, μm	75.04 ± 17.98	61.88 ± 18.34	2.562	0.72	0.014
LLT-CV	0.10 ± 0.06	0.18 ± 0.11	−2.963	0.90	0.005
MGL rate, %	22.64 ± 16.39	34.36 ± 15.70	−2.802	0.73	0.007
Number of blinks, *n*/20s	5.52 ± 2.52	15.32 ± 10.99	−4.347	1.23	<0.001
Number of partial blink, *n*/20s	3.52 ± 2.62	7.16 ± 4.11	−3.736	1.06	0.001

Cohen's d value was used to quantify the effect size of the difference between two groups.

analyzed between blink parameters and clinical ocular surface examinations. A *t*-test was performed to compare the mean value difference between the two groups. A Spearman correlation test was applied to analyze the relationship between ocular surface parameters and blinking characteristics in the DED group. A *P* value less than 0.05 was considered statistically significant.

Results

Subject Characteristics

There was no difference regarding sex ($P = 0.571$) and age ($P = 0.055$) between the DED and control groups. Concerning ocular surface clinical tests, compared with the control group, DED patients had more symptoms (OSDI score, 33.64 ± 13.26 vs. 7.36 ± 3.45, $P < 0.001$), lower FBUT (4.52 ± 1.48 vs. 11.52 ± 1.87 seconds, $P < 0.001$), a lower Schirmer test score (4.56 ± 2.23 vs. 15.24 ± 6.84 mm, $P < 0.001$), and a higher Oxford score (0.52 ± 0.71 vs. 0.08 ± 0.28, $P = 0.014$). MGL (34.36 ± 15.70% vs. 22.64 ± 16.39%, $P = 0.007$) and the LLT-CV (0.18 ± 0.11% vs. 0.10 ± 0.06, $P = 0.005$) was significantly increased in the DED group, while the LLT significantly decreased (61.88 ± 18.34 vs. 75.04 ± 17.98, $P = 0.014$). The demographic information and clinical results were presented in Table 2.

Spontaneous Blink Pattern Analysis

In the control group, the blink patterns were regular with a similar morphology of the five blinking phases within subjects (Fig. 3A). Although several partial blinks were observed in control patients, the number of blinks and partial blinks were both significantly higher in DED patients (15.32 ± 10.99 vs. 5.52 ± 2.52, $P < 0.001$; 7.16 ± 4.11 vs. 3.52 ± 2.62, $P = 0.001$, respectively).

In DED patients, the blink pattern was irregular (Fig. 3B). Partial blinks, prolonged CDP, and short IBI were the three main characteristics of their spontaneous blink patterns. Partial blinks are shown in Figures 4A and 4B. In DED patients, the mean ECP was longer than it in control patients (1.93 ± 1.24 vs. 0.59 ± 0.30 seconds, $P < 0.001$). Sometimes the double peak curve of the ECP phase was detected in several severe partial blink patients (Fig. 4C). Mean CDP, EOP, and LOP were

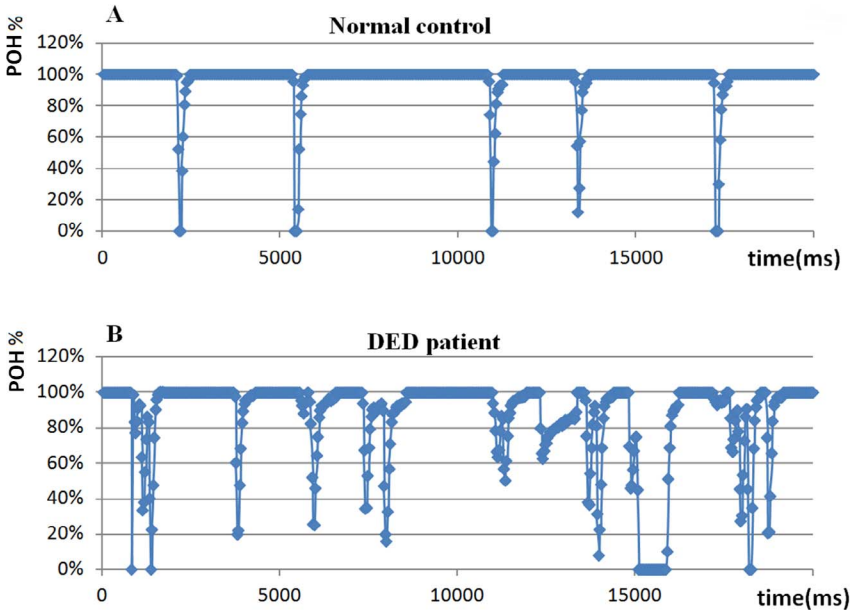


Figure 3. The blink pattern of a normal control and a DED patient. (**A**) The blink pattern was regular and symmetric in normal controls; (**B**) the blink pattern of a DED patient showing irregular and partial blinks and asymmetric patterns.

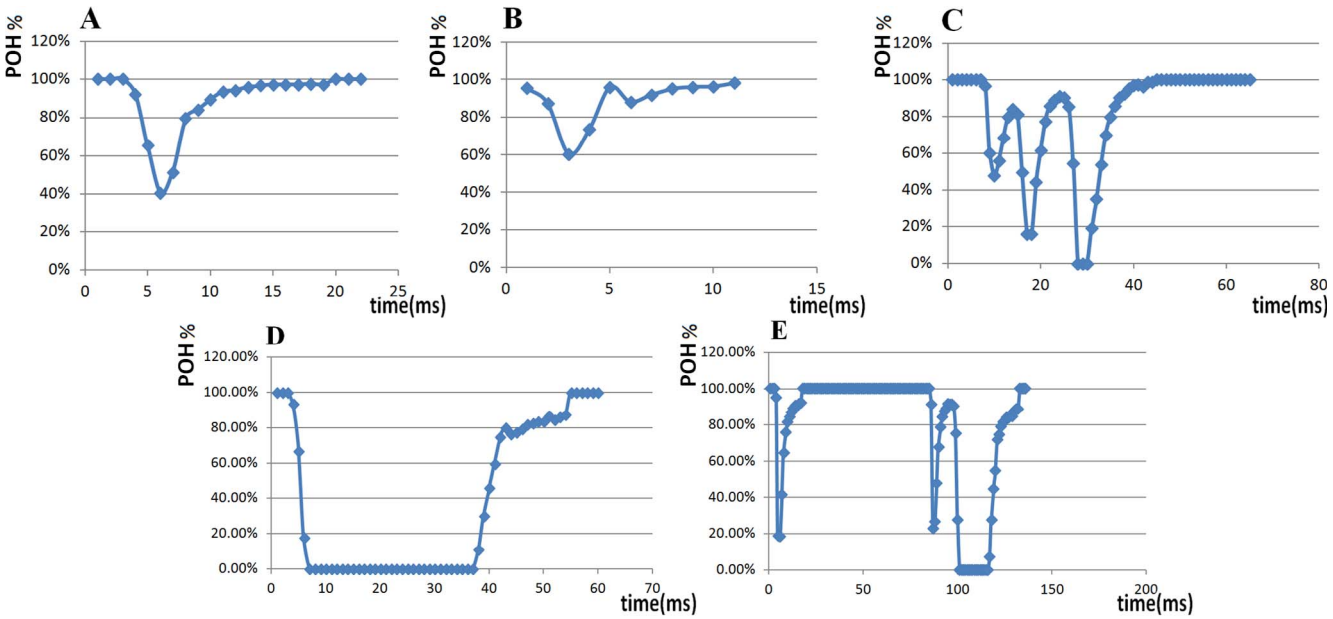


FIGURE 4. Abnormal blink pattern from typical DED cases. Partial blinks: (**A**) the blinking amplitude was 60%; (**B**) the blinking amplitude was only 40%; (**C**) double-peak curve for the ECP segment in severe partial blinks. Prolonged CDP segment and pathologic EOP and LOP are presented in (**D**, **E**).

also longer in the DED group than in the control group (0.56 ± 0.89 vs. 0.14 ± 0.22 seconds, $P = 0.029$; 3.20 ± 1.44 vs. 1.09 ± 0.79 seconds, $P < 0.001$; 1.90 ± 0.85 vs. 0.73 ± 0.49 seconds, $P < 0.001$, respectively, Fig. 4B, 4E). In addition, the IBI was shorter in DED patients than in the control group (12.52 ± 3.49 vs. 17.37 ± 1.59 seconds, $P < 0.001$). The results were summarized in Table 3.

Correlation Between Blink Patterns and Clinical Tests

When evaluating the relationship between spontaneous blink pattern parameters and DED clinical tests, OSDI scores were correlated with ECP, the number of partial blinks and the number of blinks ($r = 0.443$, $P = 0.027$; $r = 0.553$, $P = 0.004$; $r =$

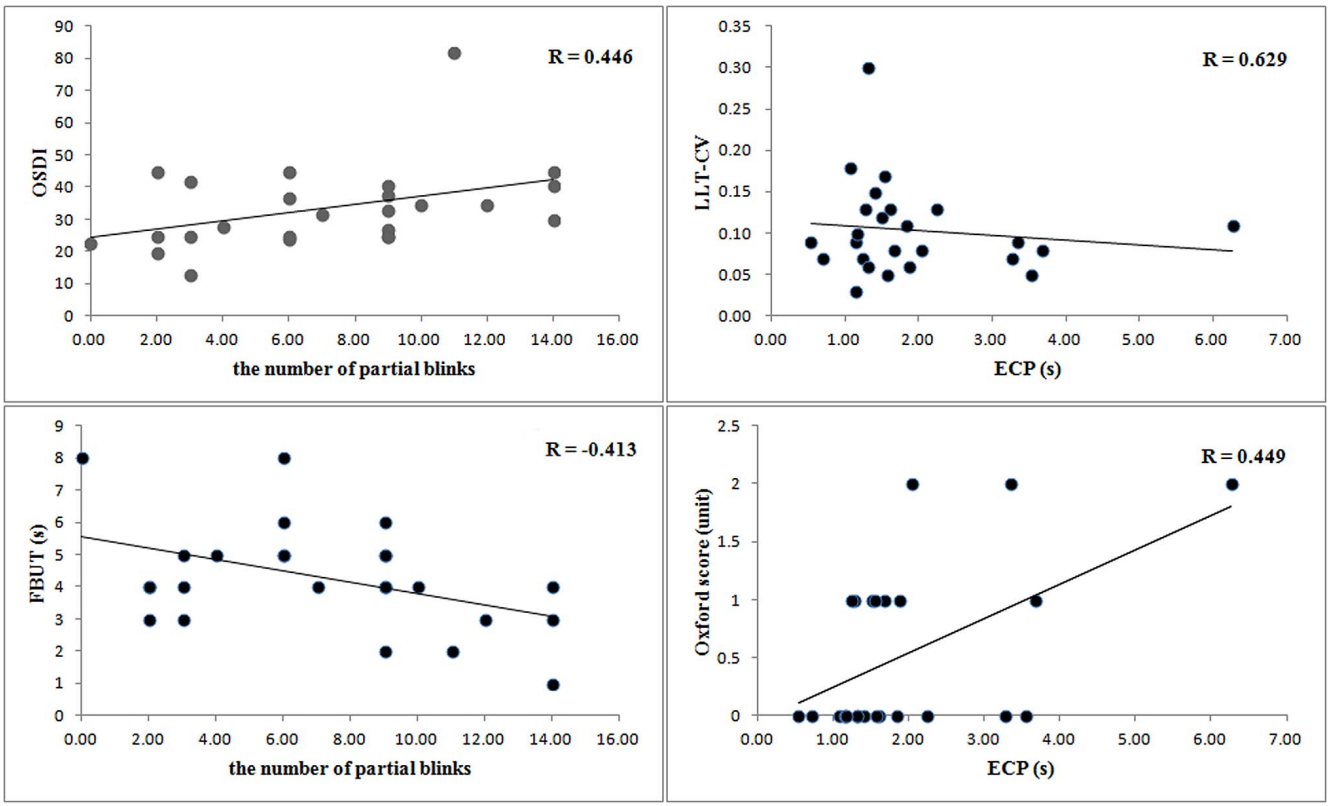


FIGURE 5. Correlation between blink parameters and clinical examinations in DED patients.

Table 3. Mean Duration (Over the 20-Seconds Evaluation) of the Five Components of the Blink Pattern in DED Patients and the Control Group

Parameters	Healthy Controls	DED Patients	*t*-Value	*P* Value
ECP (s)	0.59 ± 0.30	1.93 ± 1.24	−5.238	<0.001
CDP (s)	0.14 ± 0.22	0.56 ± 0.89	−2.307	0.029
EOP (s)	1.09 ± 0.79	3.20 ± 1.44	−6.397	<0.001
LOP (s)	0.73 ± 0.49	1.90 ± 0.85	−5.996	<0.001
IBI (s)	17.37 ± 1.59	12.52 ± 3.49	6.328	<0.001

0.446, $P = 0.026$). The FBUT had a negative correlation with ECP ($r = -0.618$, $P = 0.001$) and the number of partial blinks ($r = -0.413$, $P = 0.040$). The LLT showed no correlation with the others, but the LLT-CV was positively correlated with ECP, CDP, and LOP ($r = 0.629$, $P = 0.001$; $r = 0.396$, $P = 0.050$; $r = 0.397$, $P = 0.049$). The corneal and conjunctival staining (the Oxford score) was positively correlated with ECP, CDP, and the number of blinks ($P = 0.024$, 0.007, and 0.022), and negatively correlated with IBI ($P = 0.037$). The correlation results were summarized in Table 4 and Figure 5.

Discussion

Spontaneous eye blinking is influenced by ocular surface health status and its observation might be a useful parameter to evaluate ocular surface diseases. Exposure keratopathy appeared to be associated with incomplete blinking and the precipitation of the contact lens surface may be accelerated by incomplete blinking.[17] DED is the most common ocular surface disease and an abnormal spontaneous blink pattern has been considered as part of DED pathogenesis. Previous studies mostly focused on the spontaneous blink rate and the incomplete blink rate, but more complex patterns of blinks appeared in DED patients and each phase of the blink procedure might be important to understand the relationship between DED and blinking. The study from Ousler et al.[18] indicated that extended lid closures and increased blink rates were the main differences between DED and healthy subjects. Rahman et al.[19] found that rapid blinking was associated with worse ocular surface and tear film instability. Although these studies have raised interesting issues about the relationship between spontaneous eye blinking and DED, the blink pattern and the different phases of blinking need to be further analyzed. Some studies divided the blinking process into three phases, as did Bologna et al.[20] (closing phase, opening phase, and interphase) and others, such as Kwon et al.,[16] divided it into four phases (closing, closed, early-opening, and late-opening phase). The latter study analyzed the palpebral aperture, peak blinking speed, average blinking speed, and the duration of spontaneous blinking in 25 healthy volunteers. The mean duration of one blink in their study was 572 ± 25 ms and the blink motion was asymmetric with a much faster closing action compared with the opening action. The opening phase included 97% of the early opening and the last 3% recovery during the late opening. In our study, a high-speed camera was used to record the details of blink motion and the blink pattern could be divided into five phases (including closing phase, closed phase, early-opening phase, late-opening phase, and blink interval). Interestingly, in the present study, the closed phase and the blink interval, which were not evaluated previously, appeared to be sensitive parameters to differentiate DED from healthy controls (Fig. 6; Table 5).

From this study, partial blinks, prolonged CDP and short IBI were the three main characteristics of the DED blink pattern. Longer ECP and partial blinks indicate that the blink is incomplete and this type of blink is not sufficient to refresh the tear film, to induce lipid secretion and to clean the corneal surface. With insufficient tears and lipid secretion, tear film renewal might be only located in the important optical region

Table 4. Correlation Analysis of the Blink Phases With the Results of Clinical Tests in the DED Group

	OSDI	FBUT	Schirmer Test	Oxford Score	LLT	LLT-CV	MGL
ECP							
R	0.443*	−0.618*	0.186	0.449*	0.013	0.629*	0.172
P	0.027*	0.001*	0.374	0.024*	0.953	0.001*	0.411
CDP							
R	0.152	−0.042	−0.089	0.526*	−0.095	0.396*	0.094
P	0.469	0.842	0.671	0.007*	0.651	0.050*	0.657
EOP							
R	0.088	−0.158	−0.090	0.332	0.028	0.347	0.251
P	0.677	0.452	0.670	0.104	0.893	0.090	0.225
LOP							
R	0.109	0.033	−0.331	0.336	0.133	0.397*	0.316
P	0.605	0.876	0.107	0.100	0.527	0.049*	0.124
IBI							
R	−0.143	0.213	0.111	−0.420*	−0.001	−0.361	−0.271
P	0.495	0.308	0.599	0.037*	0.997	0.076	0.190
Number of blinks							
R	0.553*	−0.279	0.372	0.456*	−0.084	0.535	0.214
P	0.004*	0.176	0.067	0.022*	0.689	0.006	0.304
Number of partial blinks							
R	0.446*	−0.413*	0.348	0.328	0.019	0.310	0.225
P	0.026*	0.040*	0.088	0.109	0.926	0.132	0.279

* The correlation between two parameters was statistically significant.

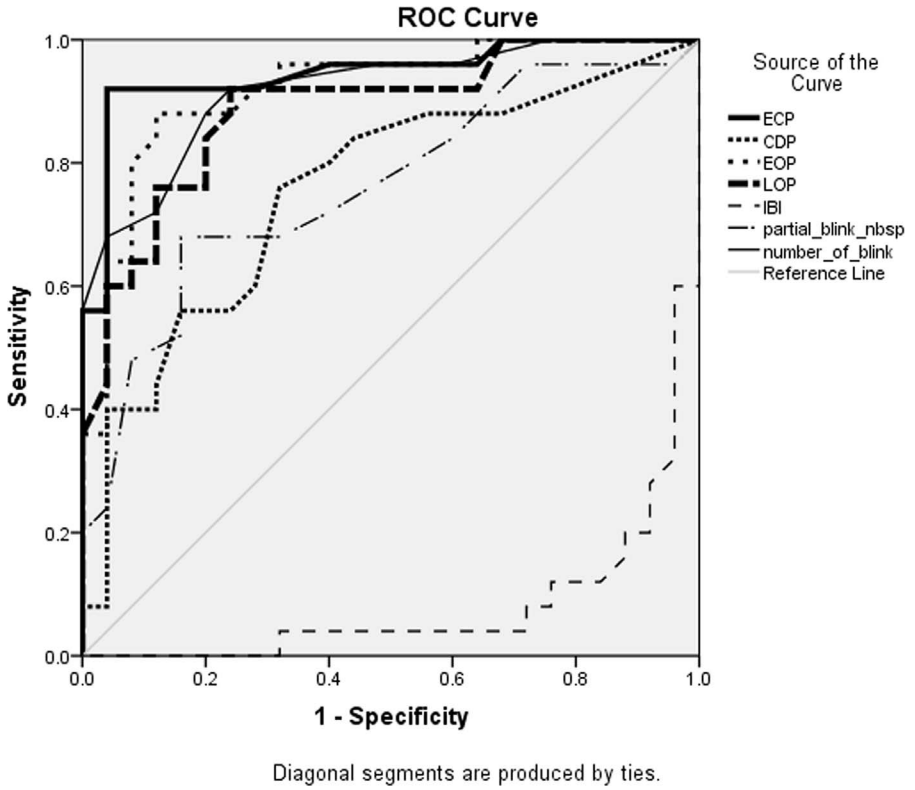


Figure 6. Receiver operating curves of spontaneous blink phases, the number of partial blink, the number of blink, and IBI.

(central cornea). Consequently, partial blinks might become a compensatory response to an abnormal tear film in DED patients. In accordance, Harrison et al.[21] showed that DED patients had greater stability of the newly deposited tear film after an incomplete blink as compared with a complete blink. Although partial blinks could be an adaptive protective response, it might aggravate, in a vicious circle, tear film dysfunction with less lipid secretion from MGs. Meanwhile, partial blinks might also induce thinning and destabilization of the tear film in the proximity of the upper eyelid and might result in an "imprint" of the thinning over the corneal surface, as proposed by Yokoi et al.[22] Interestingly, the partial blink rate has a positive correlation with the OSDI, and a negative correlation with FBUT, confirming its close relationship with ocular surface status in DED.

In DED patients, the total eyelid closed time (CDP) lengthened. Compared with healthy controls, the CDP of DED patients was five times longer. Our results were similar to the results from McMonnies[17] that showed 4.5% versus less than 1% eyelid closing time between DED and healthy subjects, respectively. In addition, the EOP, which accounted for 97% of the eyelid opening phase, was also longer in DED patients as compared with the control group (3.20 vs. 1.09 seconds). DED patients may need more closed time to renew the altered tear film and maintain ocular surface hydration. This could also be a protective response aiming at covering an altered and painful ocular surface and decreasing DED symptoms.

In addition, it is obvious that a shorter IBI duration and higher frequency of blinking was observed in the DED group. The results were consistent with the findings from the Tsubota et al.[23] study. Because DED patients have a longer closing time, closed time and opening time, and an increased blinking frequency, this will naturally decrease IBI time. Therefore, the short IBI is more a compensating process than an initial mechanism in the blink pattern.

The main limitation of this pilot study was the limited number of subjects included. The blink pattern was measured manually frame by frame (600 measurements for each subject), a fastidious task for this number of subjects. With the development of automatic analysis software, further studies could be completed more easily on a large number of subjects and the clinical significance of these results could be clarified.

Table 5. Area Under the Curve Evaluation of Blink Parameters in the DED Group

Parameter	Area	SE	Asymptotic Significance	Asymptotic 95% CI	
				Lower Bound	Upper Bound
ECP	0.946	0.033	0.000	0.880	1.000
CDP	0.755	0.070	0.002	0.618	0.892
EOP	0.918	0.040	0.000	0.840	0.996
LOP	0.887	0.047	0.000	0.792	1.000
IBI	0.077	0.054	0.000	0.002	0.155
Partial blinks	0.762	0.068	0.002	0.627	0.896
Number of blinks	0.918	0.038	0.000	0.843	0.993

Nevertheless, despite the small number of subjects, the results were robust, with significant results differentiating DED from controls. Consequently, it would be very advantageous to include patients with other ocular surface diseases, such as allergic conjunctivitis, dry eye following refractive surgery, or MG dysfunction, to better understand the role of blinking in these pathologies. Moreover, if different diseases have different blink patterns, the analysis of the blink process could also be a useful diagnostic tool.

Although spontaneous blinking is a complex phenomenon, new devices today provide a complete evaluation of the blinking process. Partial blinks, prolonged closed eyelid time, and short blink intervals were the three main characteristics observed in DED patients that were also correlated with clinical signs and symptoms of DED. This study highlights the importance of analyzing the blink pattern in ocular surface diseases.

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