The Interblink Interval I: The Relationship between Sensation Intensity and Tear Film Disruption

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PURPOSE. To find the relationship between tear film drying and sensation during the interblink period.

METHODS. One eye was taped shut, and after a blink the subjects were asked to keep the other eye open. Digital video images of the ocular surface (with fluorescein) were obtained using a slit lamp biomicroscope while 23 subjects rated the intensity of the ocular surface sensation by adjusting a one-turn potentiometer to represent the strength of the sensation. They were trained to use the potentiometer before the data were collected. In addition, the characteristics of the sensation as spoken by the subject were recorded.

RESULTS. The sensation was generally triphasic, with initial constant sensation and a subsequent biphasic period, with intensity increasing slowly followed by a rapid increase before the subjects blinked (correlations were all \( r > 0.95 \)). Tear film drying dynamics were also biphasic, and drying and sensation were strongly associated, with a correlation of 0.94 between drying dynamics and sensation during the interblink period.

CONCLUSIONS. The methods provide novel information about the development of ocular sensation during ocular surface drying. As evidenced by the complex functions required to adequately describe the relationships, tear film drying and ocular surface sensations are associated in complex ways. (Invest Ophthalmol Vis Sci. 2009;50:1087–1092) DOI:10.1167/iovs.08-18413

Skin and mouth dryness are often associated with the symptoms of dry eye, and such symptoms are especially prominent in the elderly and in those with conditions such as the sicca syndrome. 1–3 Dryness and the perception of roughness of the skin are dependent on the state of its hydration. Skin hydration studies indicate that dryness and the resultant sensation of roughness have a linear relationship. 4–6 In the mouth the physical drying of the oral surface or the exposure of the oral surface to an astringent substance gives a feeling of dryness. 7 The symptoms of ocular discomfort are related to ocular surface dryness and an altered relationship between the tear film and the ocular surface. 8,9 Ocular surface dryness may be due to tasks that reduce spontaneous blinking and increase tear evaporation, such as occupational factors and visual information processing. 10–13 In computer users ocular surface dryness due to increased tear evaporation has been proposed as the cause of ocular discomfort. 14 Tear film factors associated with dry eye symptoms include reduced tear turnover, delayed tear clearance, increased tear evaporation, and desiccation of the ocular surface. 17–20 But unlike the skin and mouth, symptoms of dry eye have a poor association with these clinical signs. 8,21–24

At present, methods of assessing the sensations arising from the ocular surface representing the experience of ocular discomfort are limited. 25–28 Recently, ocular surface drying occurring during forced eye opening has been used to elicit acute discomfort in an attempt to understand corneal sensations in provoked dry eye. 7–20 We used this as a point of departure to characterize the dynamics of tear film drying and describe the nature of the associated changing sensations.

With a view toward simultaneously acquire the intensity and qualitative attributes of sensations produced during forced eye opening and to quantify the tear film drying during this interval, we developed an instrument to acquire continuous ratings of intensity, spoken attributes of sensations, and images of fluorescein patterns of tear breakup and surface drying when blinks were voluntarily suppressed.

METHODS

Twenty-three subjects (11 men and 12 women), whose ages ranged from 20 to 30 years, participated in the study. None of them had any symptoms of dry eye and they did not use contact lenses during the study. They gave informed consent to a protocol approved by the Office of Research Ethics at the University of Waterloo and in compliance with the Declaration of Helsinki. All subjects were informed that they were free to interrupt the measurement process at any time during the experiment.

An instrument was developed to collect continuous intensity ratings, spoken data, and digital video, the details of which have been described before (Varikooty JP, et al. Invest Ophthalmol Vis Sci. 2001;42:ARVO Abstract 50/88). It was used to record intensity and other verbal characteristics of the sensations arising during the tear film drying as well as dynamic fluorescein patterns on the same time scale. Software written in a commercial program (MatLab, ver. 5.0; The MathWorks, Natick, MA) was used to sample the data acquired via a National Instruments card (NI PCI6035E; Austin TX) from a potentiometer, video camera, microphone, and an infrared thermometer. All the data were collected and plotted on the same time frame at 0.2-second intervals.

Subjective Data

Subjects were seated in front of the slit lamp, and a drop of fluorescein was instilled into the conjunctival sac of the lower lid. After instillation, they blinked once or twice for an even spread of the fluorescein to occur over the ocular surface and then kept the eye open for as long as possible. The left eye was used for data collection and the right eye was closed with a gauze pad and a patch during the experiment. Subjects were trained before data were collected to use the rotary potentiometer while viewing a color-coded circle, and a pointer controlled by the potentiometer. The pointer and circle were not visible to the subjects during the data collection sessions. After training, the subjects were asked to rate the sensation intensity with the potentiometer while voluntarily not blinking, forcing the eye to remain open. Rotating full turn counterclockwise represented “no sensation” and full clockwise rotation represented “so intense that I must blink immediately.” Although subjects rated the intensity of the sensation with
the potentiometer, they described the characteristics of the sensation verbally into a microphone. (The analysis of their descriptions is not reported in this article). Instructions to the subjects included the necessity that they focus on performing the sensation intensity ratings to minimize the lag between the sensations they experienced and their response when using the potentiometer. Only individual full sets of scaling, imaging, and verbal data were used. During data collection, the subjects received no feedback other than the kinesthesis from the potentiometer position. The room temperature and humidity were approximately constant during the experiment.

Analysis

The symptom intensity data were extracted with a program written in the commercial software (MatLab; The MathWorks). The video slit lamp images were processed with a macro written in Object-Image 2.08 software. The program identified the cornea and, within this region of interest, estimated thinning areas (indicated by dark pixels) in each video frame. The tear break-up time (TBUT) was the time taken for the first appearance of a dark spot on the fluorescein image. The sensory intensity and tear film data were analyzed by using a nonlinear regression analysis (Statistica ver. 5.0; StatSoft, Inc., Tulsa, OK).

Results

General

An examination of the intensity settings showed at least three phases. In 68% of subjects the typical sensation rating that preceded the blink was triphasic (Fig. 1). On opening the eye, there was a brief period with no alteration in the intensity. The second was a slowly rising phase with a relatively flat slope. The third rapidly rising phase was characterized by a steep slope of the intensity time function. A bilinear function (each with its own slope and intercept) with a variable-position intersection (the “elbow”) was used to describe the two phases of ascending data (not the first, unchanging phase). The functions fit well, with correlation coefficients of at least 0.95 (Fig. 2). The associations between the various components of the bilinear fits (described in Fig. 1) to each subject’s data are shown in Table 1.

In 17% of the subjects, the sensation rating was atypical with a rapid increase during the second phase followed by a third phase of slowly increasing sensation (Fig. 3). In 8% of the ratings, there was a mixed response consisting of a typical pattern during the first forced eye opening followed by an

![Figure 1. The three phases of sensation intensity rating accompanying ocular surface drying. Circled numbers indicate the variables in Table 1: 1, Start (time in seconds from eye opening) of second phase; 2, Slope 1; 3, Elbow (sensation intensity); 4, Break (time in seconds from eye opening); 5, Slope 2.](image1)

![Figure 2. Nonselected examples of typical sensation intensity versus time after eye opening in two subjects with short and long interblink intervals.](image2)
atypical pattern in the second forced eye opening or an atypical pattern in the first rating followed by a typical pattern in the second trail. An incomplete response where the subject was not able to rate the sensation due to an inadvertent sudden closure of the eye was seen in 7% of the ratings.

An examination of the tear film drying showed a similar multiphasic relationship between time and the area of drying (Figs. 4, 5). Therefore, a bilinear function was also fit to each subject’s tear film data.

Association of Tear Film Changes with Sensations

The similarity between tear film drying and sensation intensity on the same time scale is illustrated in Figures 4 and 5. The bilinear functions with a variable “elbow” position that described the intensity of sensation were also used to describe the tear drying on the ocular surface. When the “sensation break” was plotted against the “image break” for all subjects the correlation between the sensation break and image break was 0.94 (Fig. 6), and the shift from slow to rapid drying preceded the shift from a slow to a rapid increase in intensity.

Correlations between the clinical tear-breakup time (TBUT), tear drying characterized by the components of the bilinear fits extracted using nonlinear regression as illustrated in Figure 1 are shown in the Table 1. Data were fit with a bilinear function as this provided information regarding the slopes of the phases. We realize that this may be a simplistic approach but fitting other functions gave similar high correlations. For example we also realized that this may be a simplistic approach but fitting other functions gave similar high correlations. For example we also fit data with monotonic nonlinear quadratic functions. Although the fit statistics were similar ($r^2 = 0.89 - 0.99$) the benefit of the nonmonotonic functions in their identification of the discontinuities that were strongly correlated with other clinical discontinuities (e.g., TBUT) convinced us of the utility of these bilinear functions.

In the first phase, on eye opening there was a brief period with no change in the intensity of the ocular surface sensation. Eye closure therefore not only reestablished the tear film, but the slope of the initial drying phase. A relatively rapid increase in sensation (of both phases) in a subject with a short TBUT is illustrated in Figure 2, left.

### Table 1. Associations between TBUT and the Components of the Bilinear Fits Extracted Using Nonlinear Regression as Illustrated in Figure 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>TBUT</th>
<th>Sensation</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Start</td>
<td>Break</td>
</tr>
<tr>
<td>TBUT</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.53</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Break</td>
<td>0.71</td>
<td>0.45</td>
<td>1.00</td>
</tr>
<tr>
<td>Elbow</td>
<td>-0.16</td>
<td>-0.38</td>
<td>0.08</td>
</tr>
<tr>
<td>Slope 1</td>
<td>-0.48</td>
<td>-0.39</td>
<td>-0.56</td>
</tr>
<tr>
<td>Slope 2</td>
<td>-0.38</td>
<td>-0.28</td>
<td>-0.48</td>
</tr>
<tr>
<td>Image</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>0.23</td>
<td>0.32</td>
<td>0.59</td>
</tr>
<tr>
<td>Break</td>
<td>0.68</td>
<td>0.53</td>
<td>0.94</td>
</tr>
<tr>
<td>Elbow</td>
<td>-0.18</td>
<td>0.32</td>
<td>0.12</td>
</tr>
<tr>
<td>Slope 1</td>
<td>-0.66</td>
<td>-0.45</td>
<td>-0.70</td>
</tr>
<tr>
<td>Slope 2</td>
<td>0.01</td>
<td>-0.08</td>
<td>-0.22</td>
</tr>
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</table>

Correlations, $N = 23$. Bold indicates significant correlations ($P \leq 0.05$).
it also reduced the intensity of sensation caused by the previous tear film changes. During normal eye opening, the sensory level is returned to a “basal” state and remains at this level during minimal or no tear film alteration on the ocular surface. It is possible that an inability to establish this symptom-free basal state may result in discomfort symptoms reported in dry eye disease.

The second phase was characterized by an increase in intensity, and the slope of this phase was typically less steep than the slope of the following phase in two thirds of the subjects. As evidenced by the correlations (Table 1), this second phase had strong associations with clinical TBUT.

The third phase was characterized by a more steep intensity slope that preceded eye closure. Prolonged eye opening caused a rate of intensity change that signaled the eye to blink urgently. Since in the experiment, blinking did not follow the initial, slower change in intensity but rather the more rapid phase, it is possible that overall comfort for an individual is related to the rate of change in intensity. Those whose rates of change are high (that is they go from moderate to intense sensations rapidly) have to blink more frequently and are perhaps symptomatic.

In approximately 17% of the subjects with the atypical triphasic pattern of sensory events, the rapid change during the second phase appeared similar to the more steep third phase seen in the majority of subjects. Because nociceptive systems have a low gain it is possible that the rapid rise in discomfort was perceived as an impending nociceptive threat by the ocular surface functional unit and this, perhaps, led to a rapid reflex tearing and increased mucin secretion by the conjunctival and corneal epithelium. It is possible that this increase in tear volume and mucin glycoproteins altered the tear rheology, aided in stabilizing the mechanical tear disruption, and minimized the nociceptive effects. These physiological mechanisms may then have been reflected in the less steep third sensory phase.

At present, the different models of tear breakup and subsequent drying caused by initial occurrences such as lipid contamination of mucous layer or a mucous rupture of the tear film do not clearly explain the events underlying the psychophysical ratings. However, as shown in Table 1, a short TBUT was associated with steeper slopes of sensation functions.

These negative correlations between the TBUT and the slopes as well as the data presented in Figure 6 make it tempt-
leading to an increased perceived texture. Although it is friction, and it is suggested that alterations of the surface drug are also unclear.

The strong correlations between the rate of change of tear film and rate of change of sensation (slopes in Table 1) point to an influence of spatial summation mechanisms. As greater amounts of tear film drying occur, a greater sensation is reported. Similarly, spatial summation has been proposed to account for the relationship between perceived roughness and area of drying in the skin.

In conclusion, this is the first study to report simultaneous measures of the various aspects of sensation intensity occurring during ocular surface drying. The technique provided novel information about the changes in sensory intensity and ocular surface drying. There were strong associations between tear film characteristics (TBUT and tear drying dynamics) and the accompanying sensory events.

References
11. Wieslander G, Norback D, Nordstrom K, Walinder R, Venge P. Nasal and ocular symptoms, tear film stability and biomarkers in by the subjects. If tear film thinning is a physical measure of ocular surface dryness and the sensations experienced by the subjects were caused by the increasing intensity of ocular dryness, these results would appear to point to a direct stimulus-response function relating the tear film’s physical chemistry to the sensation information arising from the cornea, such as has been reported in the mouth. Unfortunately, this was not the case. The sensations induced by the tear film changes during forced eye opening are often not of dryness (particularly at the latter stages of forced eye opening, Vankooty and Simpson, manuscript submitted), and this, in relationship to how poorly perceived dryness and physical dryness are related, is perhaps not surprising. The areal extent (in pixels) of thinning as quantified using our image processing algorithm does not capture the “depth” of dryness in each dark area in the fluorescein picture. It may or may not be that the area of dryness and the thickness of the tear film in these dry areas are related. In addition, how the extent of dryness and depth of dryness are related to the attributes of the sensation (e.g., perceived dryness) and the intensity of the sensation reported in this experiment are also unclear. 
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