Tear Film Dynamics in Floppy Eyelid Syndrome

Daniel Tzung-Shyue Liu,1,2,3 Mario A. Di Pascuare,1 Junki Sawai,1 Ying-Ying Gao,1,4 and Scheffer C. G. Tseng1

PURPOSE. Floppy eyelid syndrome (FES) presents nonspecific ocular surface irritation. The hypothesis for the current study was that one contributing factor is the abnormality in tear film dynamics.

METHODS. Sixteen patients with FES were consecutively examined. Tear film dynamics were evaluated by kinetic tear interference images, infrared thermometry, water evaporation rate, tear break-up time, and fluorescein clearance test. Data showing evaporation rate and thermometry were compared with those of 10 normal subjects.

RESULTS. There was a high correlation between the eye with the worse symptoms and the eyes with the more severe floppy lids ($P < 0.01$) and with ocular surface evaporation rate ($P = 0.02$). Except for one patient, all others showed abnormal tear film, with an average tear break-up time of 2.9 ± 3.7 seconds. Kinetic analysis of tear interference images revealed that lipid spread in a vertical or mixed pattern in 18 eyes (75%) with a delayed spread time ($P = 0.0007$), indicating that most of the patients had lipid tear deficiency. The ocular skin temperature and water evaporation rate were higher in the FES group ($P = 0.0003$ and 0.026, respectively). Nearly all patients with FES showed eyelid hyperpigmentation. The ocular surface evaporation rate in the FES group was also higher than that of the normal subjects ($P < 0.0001$). Multiple regression analysis showed that a vertical pattern of lipid spread had a significant influence on ocular surface evaporation rate ($P = 0.003$).

CONCLUSIONS. Tear film abnormality is prevalent in patients with FES and is characterized by lipid tear deficiency, leading to rapid tear evaporation. The FES lid skin is also characterized by high temperature, high water evaporation rate, and hyperpigmentation. Studies directed to investigating the linkage of lid changes and meibomian gland dysfunction may shed new light on the pathogenesis of FES. (Invest Ophthalmol Vis Sci. 2005;46:1188–1194) DOI:10.1167/iovs.04-0913

Floppy eyelid syndrome (FES) was first described by Culbertson and Ostler1 in 1981 in a male cohort that showed the triad of obesity; an easily everted, floppy upper eyelid; and papillary conjunctivitis of the upper palpebral conjunctiva. Although initially reported to be typical in middle-aged over-weight men,1–4 FES has also been found in women, different age groups, and nonobese patients.5–10 FES presents symptoms of nonspecific irritation, foreign body sensation, mucoid discharge, dryness, redness, photosensitivity, and eyelid swelling. Although the clinical features of FES are well described, the cause is still unknown. It is speculated that one pathogenic mechanism of FES is the conjunctiva-cornea-pillow contact during sleep, a notion supported by the fact that, in patients with FES, the worse floppy eyelid corresponds to the side of the body they sleep on, and a preference for sleeping on their stomachs.5–7,9,11–15

The role of tear film abnormality in the pathogenesis of FES has also been suspected. In a case series report, three of seven patients with FES showed evidence of both quantitative and qualitative tear film disorders.1 Other reports on FES include poor-quality tear film and tear film disorders.14,15 Meibomian gland abnormality including cystic degeneration, squamous metaplasia of the orifice, and atrophy of acini has been described.11 The tarsal plate of FES is frequently infested by Demodex brevis15,16 which may contribute to the dysfunction of meibomian glands.17 Because FES is associated with tear film disorders and a stable tear film dictates ocular surface health, we wanted to investigate the tear film dynamics in patients with FES to extend our knowledge regarding the pathogenesis of FES.

Although several conventional tests have been used to delineate different aspects of the aforementioned tear dynamics, they are static (one time point) and may generate artifacts by physically touching the eye to arouse ocular sensitivity or alter lid blinking. Furthermore, few tests are able to take accounts of both compositional and hydrodynamic factors at the same time. For these reasons, we used noninvasive, time-dependent kinetic tests to monitor the water evaporation rate,18–20 tear interference images,20–22 and ocular skin temperatures,23 so that we might probe more deeply the pathophysiology of tear film dysfunction in FES.

MATERIALS AND METHODS

Patients and Study Design

This study was approved by the Institutional Review Board of Baptist Hospital of Miami/South Miami Hospital, Inc. (Miami, FL), for retrospective analysis of a patient’s record with ocular irritation. The tenets of the Declaration of Helsinki were adhered to in full. In this study, we consecutively recruited 16 patients (9 men and 7 women) with FES diagnosed at the Ocular Surface Center (Miami, FL). Eleven of them were referred by other ophthalmologists because of chronic symptoms not well controlled by topical medications. Their mean ages (±SD) were 45.6 ± 15.9 years (range, 25–78; Table 1). The diagnosis of FES was made based on the finding that the upper eyelid was easily everted on lifting the upper lid skin with the examiner’s thumb while the patient looking down, as shown in Figure 1. The severity was graded as: 0 (no floppy eyelid); no tarsal conjunctiva visible; 1 (mild): less than one third of the upper tarsal conjunctiva visible; 2 (moderate): between one third and one half of the upper tarsal conjunctiva visible; and 3 (severe): more than one half of the tarsal conjunctiva visible (Fig.
TABLE 1. Summary of Case Profile, TBUT, FCT, and Lipid Layer Interference Image in Patients with FES

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Worse Eye</th>
<th>Floppy Grade</th>
<th>TBUT (s)</th>
<th>FCT (mm)</th>
<th>Pattern of Spread</th>
<th>Spread Time (s)</th>
<th>Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>F</td>
<td>OD</td>
<td>3+/2+</td>
<td>0/2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>M</td>
<td>OD</td>
<td>1+/2+</td>
<td>ND</td>
<td>ND</td>
<td>M/M</td>
<td>1.93/1.74</td>
<td>90.0/63.3</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>OD</td>
<td>1+/2+</td>
<td>2/1</td>
<td>9.3/8.3</td>
<td>H/V</td>
<td>0.77/1.35</td>
<td>96.7/93.3</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>OD</td>
<td>2+/1+</td>
<td>ND</td>
<td>0.8/0.8</td>
<td>V/V</td>
<td>1.54/1.35</td>
<td>23/26.7</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>M</td>
<td>OD</td>
<td>2+/3+</td>
<td>3/3</td>
<td>10.0/7.3</td>
<td>H/H</td>
<td>0.19/0.19</td>
<td>176.7/160.0</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>M</td>
<td>OD</td>
<td>3+/3+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>F</td>
<td>OD</td>
<td>3+/2+</td>
<td>ND</td>
<td>3.1/5.0</td>
<td>V/V</td>
<td>1.54/0.58</td>
<td>73.1/58.0</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>M</td>
<td>OD</td>
<td>2+/2+</td>
<td>3/0</td>
<td>6.3/1.0</td>
<td>V/H</td>
<td>1.53/0.39</td>
<td>76.7/166.7</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>M</td>
<td>OD</td>
<td>3+/3+</td>
<td>1/1</td>
<td>5.3/8.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>F</td>
<td>OD</td>
<td>2+/2+</td>
<td>ND</td>
<td>4.5/30.0</td>
<td>M/V</td>
<td>0.39/0.78</td>
<td>166.7/90.0</td>
</tr>
<tr>
<td>11</td>
<td>42</td>
<td>M</td>
<td>OD</td>
<td>2+/3+</td>
<td>10/15</td>
<td>13.3/18.5</td>
<td>H/H</td>
<td>0.39/0.39</td>
<td>66.7/63.3</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>M</td>
<td>OD</td>
<td>3+/3+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>2.51/1.93</td>
<td>43.1/33.3</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>F</td>
<td>OD</td>
<td>2+/2+</td>
<td>1/4</td>
<td>16.8/15.0</td>
<td>V/V</td>
<td>0.58/0.58</td>
<td>80.0/163.3</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>F</td>
<td>OD</td>
<td>3+/2+</td>
<td>ND</td>
<td>4.5/5.0</td>
<td>V/H</td>
<td>1.16/0.97</td>
<td>67.7/166.7</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>F</td>
<td>OD</td>
<td>1+/2+</td>
<td>1/0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>M</td>
<td>OD</td>
<td>1+/2+</td>
<td>1/1</td>
<td>0.8/0.0</td>
<td>V/M</td>
<td>2.51/1.74</td>
<td>40.0/43.3</td>
</tr>
</tbody>
</table>

Pattern of spread: H, horizontal pattern; V, vertical pattern; M, mixed horizontal and vertical pattern (see Fig. 2); ND, not done. Floppy grade: 1+ (mild), 2+ (moderate), 3+ (severe). Data are in the order of OD/OS.

1). External photographs were also taken to document the skin changes around the eyelids. Patients with such ocular surface diseases as Steven-Johnson syndrome, chemical or thermal burn, or ocular cicatricial pemphigoid, were excluded.

The following tear functional tests were performed in the order described below. Among these tests, tear break-up time (TBUT) and the fluorescein clearance test (FCT) have been well described, and the published normal data have been validated in previous papers.20 –22 We have also studied the tear interference images of normal subjects in previously published papers.27,28 The published normal data were referenced and used for comparison in this study. However, the data for tear skin temperature and tear evaporation rate were obtained in parallel from 20 eyes of 10 normal subjects and compared with those in patients with FES.

Kinetic Analysis of Tear Interference Images

We used an interference video camera (DR-1; Kowa Company, Nagoya, Japan) to capture the real-time interference image generated from the lipid tear film after each complete eyelid blink. We used the same instrument setup and operation as recently reported.18,19 Similarly, we analyzed these sequential interference images according to the following three parameters: The pattern of lipid spread after each blink was classified as “horizontal,” “vertical,” or “mixed” (i.e., a combination of horizontal and vertical) patterns (for representative examples, see Fig. 1).

2). The spread time (in seconds) is the time that the lipid film takes to reach a stable interference image after the onset of each blink. If the image did not achieve a stable pattern throughout the entire interblink interval, the entire interblink time was used to calculate the spread time. The lipid film thickness was determined by the simulated color tables described previously27–29 at the three positions: the center of the cornea and 2 mm above and below the center of the cornea. The average of these three values was used to denote the thickness of each eye, and the average of both eyes was used to compare different patients.

Ocular Skin Temperature by Infrared Thermometry

Because the tear evaporation rate is influenced by the temperature,30 we used an infrared thermometer (Thermal Vision Laird 3A; Nikon Co., Tokyo, Japan) that has been reported to detect ocular surface temperature30–34 to measure the ocular skin temperature. Specifically, we measured the temperature of four positions of the skin (i.e., the upper and lower eyelids, 0.5 cm medial to the medial canthus, and 1 cm lateral to the lateral canthus) and averaged them to denote the skin temperature of that eye. The average of the skin temperature of both eyes was compared among the different patients.

Water Evaporation Rate from the Skin and the Ocular Surface

Tear evaporation during normal blink was measured by a method previously reported16–19 with a highly sensitive humidity sensor machine manufactured by Analytical Research Center, KAO Corp.
We thus derived the following equation to calculate the exact evaporation rate of the ocular surface because \( J_{\text{open}} \) represents the weighted evaporation rate of both the ocular surface and the lid skin inside the measuring chamber, not the sum of them. \( J_{\text{open}} - J_{\text{closed}} \) will be much less than the exact evaporation rate of the ocular surface. We thus derived the following equation to calculate the exact evaporation rate of the ocular surface, \( J_{\text{eye}} \). \( J_{\text{open}} \) represents the weighted evaporation rate of the ocular surface, so

\[
J_{\text{open}} = \frac{A_{\text{eye}} \cdot J_{\text{eye}} + A_{\text{skin}} \cdot J_{\text{skin}}}{A_{\text{eye}} + A_{\text{skin}}},
\]

where \( A_{\text{eye}} \) is the surface area (in square centimeters) of the ocular surface, \( A_{\text{skin}} \) is the surface area (in square centimeters) of skin inside the chamber when the eye is open, and the sum of \( A_{\text{eye}} \) and \( A_{\text{skin}} \) is the total area of the chamber (14.2 cm\(^2\) in this study). \( J_{\text{skin}} \) is the evaporation rate of skin inside the chamber when the eye is open. \( J_{\text{eye}} \) can then be converted to equation 2:

\[
J_{\text{eye}} = \frac{14.2 \cdot J_{\text{open}} - (14.2 - A_{\text{eye}}) \cdot J_{\text{closed}}}{A_{\text{eye}}},
\]

We then used a previously published equation\(^{34} \) to calculate the ocular surface area \( (A_{\text{eye}}) \) based on the measurement of the eyelid fissure width (\( W \)) in millimeters, which was obtained at the slit lamp examination:

\[
A_{\text{eye}} = 0.28 \cdot W - 0.44.
\]

Besides the data from our patients with FES, we tested 20 eyes of 10 normal subjects (6 men and 4 women) and compared \( J_{\text{skin}} \) (equal to \( J_{\text{closed}} \)), \( \Delta J \), and \( J_{\text{eye}} \) between the two groups.

**TBUT and FCT**

We used fluorescein to measure TBUT in a conventional manner, followed by FCT, as previously described.\(^{24} \) After instillation of 1 drop of anesthetic with 0.5% proparacaine hydrochloride and 1 drop of 0.25% fluorescein sodium (Fluresse; Akorn, Inc., Buffalo Grove, IL) in each eye, sequential Schirmer strips were inserted for a 1-minute duration in each eye every 10 minutes during a period of 30 minutes, with the last one performed after nasal stimulation. These tests allowed us to determine basic and reflex tear secretion and tear clearance at the same time, based on the normal values established in a previous report,\(^{24} \) that have been used in other studies.\(^{20,25} \) The average of the wetting length (in millimeters) of the first and second Schirmer strips was used for analysis.

**Statistical Analysis**

Unless otherwise indicated, all data are expressed as the mean ± SD. We averaged the data from both eyes when we compared between the FES and normal groups. We used the Mann-Whitney test to analyze the data between the two groups. The Wilcoxon paired \( t \)-test was used to analyze data between the eyes of each subject. Linear regression analysis was applied to the relationship between evaporation rate and ocular temperature. Multiple regression analysis was performed between \( J_{\text{eye}} \) and three indices of lipid interference image (pattern, spread time, and thickness). \( P < 0.05 \) was considered statistically significant.

**Representative Case Report**

Patient 7: This 78-year-old woman noticed dryness in both eyes 3 to 4 months before enrollment. Her symptoms were worse in the morning and as the day progressed. She was treated with oral doxycycline, topical steroids, Restasis (Allergan, Inc., Irvine, CA), and insertion of punctal plugs, all without success. Dryness improved only temporarily with topical lubrication. She did not snore, but her sleep was poor, without REM sleep. She tended to sleep on the right side of her body. Examination showed that the skin around the eyelids was darkened with wrinkles (A, B). Her blink was poor, and closure was incomplete, as shown by the gap (B; A). Floppy eyelids were more severe in the right eye (3+) than the left eye (2+; A). Kinetic tear interference images showed a vertical lipid spread pattern in both eyes (C, D). The lipid was deficient and distributed unevenly, especially in the right eye. The small black spots (arrowheads) were superficial punctate keratitis. Infrared thermometry showed a higher ocular skin temperature in FES (E), compared with the normal subjects (F). The skin temperature of the mouth was also elevated.

**Results**

Among these 16 patients with FES, 9 (56%) had asymmetrical symptoms between the two eyes. The worse eye was the right
eye in three patients and the left eye in six. All worse eyes were on the same side of the body on which the patients preferred sleeping (Table 1). Using our grading system, the severity of floppy eyelid was mild in 5 (16%) eyes, moderate in 17 (53%), and severe in 10 (31%). There was a high correlation between the eye with the worse symptom and the eye with the more severe floppy lids \((P < 0.01)\). The worse symptomatic eye and the more severe floppy lids were on the same side in seven (78%) of nine patients. The other two patients had the same floppy grades in both eyes.

The results of TBSUT, FCT, and tear interference image in patients with FES are summarized in Table 1. Only patient 11 had normal test results; all other patients had abnormal results. The average TBSUT was 2.9\(\pm\)3.7 seconds, which was significantly less than the normal value of 3\(\pm\)10 seconds\(^{26}\). In 22 eyes with FCT, 5 (23%) showed a wetting length less than the normal range of 3 mm, indicating that nearly one fourth of our patients had aqueous tear deficiency (ATD).

### Kinetic Analysis of Tear Interference Images

The tear interference images of normal subjects in our previous studies\(^{20-22}\) showed that the lipid film spread rapidly in horizontal, propagating waves from the lower to the upper cornea in normal subjects after each blink. Nevertheless, the lipid film spread slowly in a vertical streaking pattern in patients with pure lipid tear deficiency (LTD),\(^{22}\) but spread in a mixed horizontal and vertical pattern in patients with ATD.\(^{21}\) In this study, we noted that 14 (58%) eyes showed a vertical pattern, 4 (17%) a mixed pattern, and 6 (25%) a horizontal pattern (Fig. 2, Table 1), indicating that the majority of patients had LTD. The result of lipid interference imaging in patients with FES is summarized in Table 2. The average spread time in our patients with FES was 1.12\(\pm\)0.67 seconds, which was significantly longer than the 0.43\(\pm\)0.22 seconds of normal control subjects (Table 2, \(P = 0.0004\)). The worse symptomatic eye and the more severe floppy lids were on the same side in seven (78%) of nine patients. The other two patients had the same floppy grades in both eyes.

The means showed no significant difference, but the F test of variances showed a significant difference (\(P < 0.0001\)), indicating that the range of lipid thickness is different.

### Ocular Skin Temperature and Water Evaporation Rate from the Skin and the Ocular Surface

As summarized in Table 3, the ocular skin temperature in patients with FES was 33.6\(\pm\)0.4°C, significantly higher than 32.9\(\pm\)0.3°C in normal subjects (\(P = 0.0003\)). The average variation of the ocular temperature at different points in the same eye was approximately 1.33°C to 1.36°C in patients with FES and normal control subjects. In general, the inner canthus was the warmest, and the inferior eyelid was coolest. The average of the four points revealed that the normal ocular temperature was 32.9\(\pm\)0.3°C, which was significantly lower than 33.6\(\pm\)0.4°C of patients with FES. The ocular skin evaporation rate \((J_{\text{skin}})\), defined by the water evaporation rate measured when the eye is closed, was 16.1\(\pm\)5.9 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second, which was significantly higher than 11.9\(\pm\)1.8 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second (\(P = 0.026\)). However, the correlation between the skin evaporation rate \((J_{\text{skin}})\) and ocular temperature was not significant (correlation coefficient of 0.36, \(P = 0.06\); Fig. 4).

The two indices of ocular surface tear evaporation rate \((\Delta J)\) and \((J_{\text{eye}})\) in FES group were significantly higher than those in the normal subjects (\(P = 0.024\) and \(\leq 0.0001\), respectively). The correlation between the skin temperature and tear evaporation rate \((J_{\text{eye}})\) was not statistical significant (correlation coefficient of 0.14, \(P = 0.47\); Fig. 4). The increase in skin temperature and evaporation rate also suggests that there may be some pathologic changes in the eyelids of patients with FES. In this regard, we noted that nearly all our patients with FES showed variable extents of skin hyperpigmentation around the eyelid (Fig. 5).

In the nine patients who presented with asymmetric symptoms between the two eyes, we also compared \(J_{\text{skin}}\) and \(J_{\text{eye}}\) between the two eyes. We noted that \(J_{\text{skin}}\) in the worse eyes was 20.2\(\pm\)8.7 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second, which was higher than 17.0\(\pm\)6.0 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second in the better eyes, but did not reach statistical significance (\(P = 0.21\)). On the other hand, \(J_{\text{eye}}\) in the worse eyes was 98.0\(\pm\)51.5 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second, which was significantly higher than the 66.2\(\pm\)26.1 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second in the better eyes (\(P = 0.02\)). \(J_{\text{eye}}\) was 70.7\(\pm\)33.1 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second in FES eyes with ATD, which was not significantly different from 70.8\(\pm\)38.2 \(\times\) 10\(^{-7}\) g/cm\(^2\) per second in FES eyes without ATD (\(P=0.99\)). To determine whether there may be some correlation between tear evaporation rate and lipid interference image, we performed multiple regression analysis between \(J_{\text{eye}}\) and the three indices of lipid interference image: pattern,

<table>
<thead>
<tr>
<th>Normal</th>
<th>FES</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J_{\text{skin}} = J_{\text{closed}}</td>
<td>11.9 (\pm) 1.8</td>
<td>16.1 (\pm) 5.9</td>
</tr>
<tr>
<td>(\Delta J) = (J_{\text{open}} - J_{\text{closed}})</td>
<td>4.6 (\pm) 3.0</td>
<td>7.4 (\pm) 3.2</td>
</tr>
<tr>
<td>J_{\text{eye}}</td>
<td>39.3 (\pm) 13.6</td>
<td>73.1 (\pm) 29.7</td>
</tr>
</tbody>
</table>

\(J_{\text{skin}}\) the water evaporation rate from eyelid skin surface, which is equal to \(J_{\text{closed}}\) (i.e., the water evaporation rates measured while the eye closed); \(J_{\text{open}}\), the water evaporation rates measured while the eye opened; \(\Delta J\): the difference of between \(J_{\text{open}}\) and \(J_{\text{closed}}\); \(J_{\text{eye}}\): the water evaporation rate from the ocular surface; All water evaporation rates are expressed as \(\times 10^{-7}\) g/cm\(^2\) per second.

### Table 2. Kinetic Analysis of Tear Interference Images in Patients with FES

<table>
<thead>
<tr>
<th>Pattern of Lipid Spread, n (%)</th>
<th>Horizontal</th>
<th>Mixed</th>
<th>Vertical</th>
<th>Spread Time (s)</th>
<th>Thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13 (81)</td>
<td>3 (19)</td>
<td>0 (0)</td>
<td>0.43 (\pm) 0.22</td>
<td>74.5 (\pm) 6.9</td>
</tr>
<tr>
<td>FES</td>
<td>6 (25)</td>
<td>4 (17)</td>
<td>14 (58)</td>
<td>1.12 (\pm) 0.67</td>
<td>82.1 (\pm) 40.7</td>
</tr>
<tr>
<td>(P)</td>
<td>0.0004</td>
<td></td>
<td></td>
<td>0.0007</td>
<td>0.61*</td>
</tr>
</tbody>
</table>
spread time, and thickness. We found that the pattern of lipid spread had a significant influence on $J_{\text{eye}}$ and the correlation coefficient was 0.59 ($P = 0.003$; Fig. 6). In contrast, $J_{\text{eye}}$ was not significantly influenced by the spread time ($r = 0.035, P = 0.87$) or the lipid thickness ($r = 0.029, P = 0.89$).

**DISCUSSION**

The complex tear dynamics necessary for maintenance of stable tear film involves both compositional and hydrodynamic factors that are unified by neuroanatomic integration. Compositionally, normal tears contain meibum lipids primarily derived from the meibomian glands, aqueous fluid mainly derived from lacrimal glands, and mucins secreted by ocular surface epithelial cells, including conjunctival goblet cells. Hydrodynamically, these tear components must spread to cover the entire ocular surface and clear into the nasolacrimal drainage system by frequent and effective eyelid blinking. Both compositional and hydrodynamic factors are integrated via two neural reflexes, mediated by the sensory input from the first branch of the trigeminal nerve (controlling the ocular sensitivity) and by the output from the parasympathetic or motor branch of the facial nerve (controlling compositional and hydrodynamic factors, respectively). Any violation of tear film dynamics causes ocular surface problems.

Initially FES was typically reported in middle-aged, overweight men but subsequently was found in different demographic groups. In a study of 60 patients with FES reported by Culbertson and Tseng, 22 (37%) were women and 19 (29%) were obese. Their ages ranged from 20 to 80 years (average, 54). In the present study of 16 patients with FES, 9 (56%) were men, 6 (38%) were obese, and their ages ranged from 25 to 78 years (average, 46). Studies are under way to determine whether gender, age, and body weight correlate with the severity of FES.

Similar to what has been reported, we noted that the worse eyes were on the same side of the body on which the patients preferred sleeping in all nine patients with asymmetric symptoms. Using a system to grade the severity of floppy eyelids (Fig. 1), we noted that eyes with more severe symptoms also had more severe floppy eyelids and higher tear and skin evaporation rates. These results collectively supported the notion that clinical morbidity of FES is correlated with the severity of FES and may be caused by dysfunctional tear film.

Indeed, all except for one patient showed a short TBUT of 2.9 ± 3.7 seconds. Because a short TBUT signifies the presence of an unstable tear film (i.e., the hallmark of dry eye), this finding confirmed the high prevalence of dry eye in FES. The high tear evaporation rate from the ocular surface correlated well with the pattern of the lipid spread based on kinetic analysis of tear interference images (Fig. 6), indicative of LTD. Specifically, the kinetic analysis of tear interference

**FIGURE 4.** Correlation between the evaporation rate and ocular temperature. There was no significant correlation between the linear regression analyses of $J_{\text{skin}}$ and ocular temperature (correlation coefficient = 0.36, $P = 0.06$, left) and between $J_{\text{eye}}$ and ocular temperature (correlation coefficient = 0.14, $P = 0.47$, right).

**FIGURE 5.** Skin changes in patients with FES. The skin of FDS patients showed variable extents of hyperpigmentation with brownish or dark coloration and wrinkles around the eyelid. (A) Patient 4; (B) patient 13; (C) patient 5; and (D) patient 15.

**FIGURE 6.** Multiple regression analysis between $J_{\text{eye}}$ and lipid spread pattern. Among the three indices—pattern, spread time, and thickness—multiple regression analyses showed that the lipid spread pattern was the only one with a significant influence on $J_{\text{eye}}$ (correlation coefficient = 0.59, $P = 0.003$).
images showed that the lipid film was abnormal in 75% of eyes that manifested LTD (58%) and ATD (23%), and the lipid spread time was significantly more prolonged in 13 (54%) FES eyes.

Although the average thickness of the lipid layer showed no significant difference, the F test of variances showed the range of lipid thickness to be much wider in the FES group (P < 0.0001). The thickness of the lipid layer depends on many factors. Meibomian gland dysfunction, aqueous tear deficiency, delayed tear clearance, ocular surface temperature, and eyelid diseases all can change the thickness of the lipid layer. Some make it thinner, others thicker. FES may involve several pathologic changes that make the variation in thickness much larger than in normal subjects.

The high evaporation rate from the ocular surface did not correlate with the results of FCT, which revealed the presence or absence of ATD. Two reports have shown that Schirmer test results do not correlate with the results of tear evaporation rate,34-36 whereas one report shows that patients with ATD have a lower tear evaporation rate.55 Collectively, our results support the notion that if the tear evaporation rate plays a key role in predicting tear film stability, the tear film dysfunction in FES is mainly caused by the LTD and not ATD. A stable lipid tear film helps maintain tear film stability by lowering the surface tension, facilitating tear spread, and retarding tear evaporation. Because eyelid blinking is an important driving force in spreading the tear film including the lipid layer and for “milking” the meibum from the meibomian glands,37 further studies are needed to determine whether the floppiness of eyelids in FES plays a direct pathogenic role in causing LTD.

Theoretically, high temperature causes a high water evaporation rate. One study shows significant correlation between high ocular temperature and high tear evaporation rate.29 In our study, we did not find this correlation. The water evaporation rate from the ocular surface is determined by several factors: tear and air temperatures, air humidity, air movement near the evaporation surface, tear production, and the lipid layer of tear film. The difference in ocular temperature between the FES and normal groups was minimal (0.7°C). Therefore, the evaporation rate was determined mainly by other factors. Most likely, the major factor was the lipid layer of the tear film.

Besides a high water evaporation rate from the ocular surface, we noted a significantly higher skin temperature and higher water evaporation rate from the ocular skin of patients with FES (Table 3). Intriguingly, we noted that such physiologic changes of the FES skin were also associated with morphologic changes of hyperpigmentation and wrinkles in the eyelid skin (Fig. 5). Previously, others have noted that some patients with FES have swollen eyelids.6,7 At the present time, we do not know whether such hyperpigmentation of the lid skin is primary or secondary to FES. If it is primary, the same mechanism leading to such hyperpigmentation should play an important role in causing floppy eyelids. One attractive hypothesis of FES is hypoxia. Hypoxia during sleep (via sleep apnea) not only can cause floppy eyelids (reviewed in Ref. 6), but also conceivably can cause damage to the eyelid skin by ischemia–reperfusion injury. As a result, the skin becomes chronically inflamed, leading to a higher temperature, and loses the normal barrier against water evaporation. Collectively, these changes may then lead to a higher water evaporation, which in turn causes additional damage to the skin. Such a vicious cycle may aggravate lid inflammation, which in turn may contribute to meibomian gland dysfunction and lid floppiness. Future studies directed to investigating this hypothesis may shed new lights on the pathogenesis of FES.

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