Predicting Dry Eye Using Noninvasive Techniques of Tear Film Surface Assessment

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PURPOSE. To measure tear film surface quality in healthy and dry eye subjects using three noninvasive techniques of tear film quality assessment and to establish the ability of these noninvasive techniques to predict dry eye.

METHODS. Thirty-four subjects participated in the study and were classified as dry eye or normal, based on standard clinical assessments. Three noninvasive techniques were applied for measurement of tear film surface quality: dynamic-area high-speed videokeratoscopy (HSV), wavefront sensing (DWS), and lateral shearing interferometry (LSI). The measurements were performed in both natural (NBC) and suppressed (SBC) blinking conditions.

RESULTS. To investigate the capability of each method to discriminate dry eye subjects from normal subjects, the receiver operating curve (ROC) was calculated and then the area under the curve (AUC) was extracted. The best result was obtained for the LSI technique (AUC = 0.80 in SBC and AUC = 0.75 in NBC), which was followed by HSV (AUC = 0.72 in SBC and AUC = 0.71 in NBC). The best result for DWS was an AUC of 0.64 obtained for changes in vertical coma in SBC, whereas for NBC, the results were poorer.

CONCLUSIONS. Noninvasive techniques of tear film surface assessment can be used for predicting dry eye, and such an assay can be achieved in NBC as well as SBC. In this study, LSI showed the best detection performance, closely followed by the dynamic-area HSV. The DWS technique was less powerful, particularly in NBC. (Invest Ophthalmol Vis Sci. 2011;52: 751–756) DOI:10.1167/iovs.10-5173

There are many well-established techniques and tests for diagnosing dry eye.1–6 One of the major diagnostic tests for identifying global features of dry eye is the assessment of tear film surface quality and the measurement of tear film break-up time.4

The slit lamp biomicroscopy technique that involves the instillation of a fluorescent dye into the tear film is a method still favored by many clinicians.7 However, the reliability of many of the traditional clinical tests for dry eye diagnosis has been brought into question.8 As pointed out by Mengher et al.,9 the addition of any substance to the tears will decrease their stability and may produce biased and unreliable estimates of tear film break-up times.8 Hence, significant efforts have been made toward developing methods of noninvasive characterization of tear film surface quality, from which estimates of tear film break-up time could be derived.

The noninvasive methods of assessing the tear film defined herein are those in which no substance is instilled into the eye, there is no forced blinking or forcible holding of the eyelids, and there is no contact between the measuring instrument and the eye or eyelids. An important characteristic of any potential method for tear film quality assessment is its ability to detect dry eye. In this article, we consider the efficacy of three noninvasive techniques in detecting dry eye. These methods are based on measuring the temporal changes in the specular reflection of a grid pattern projected onto the tear film,10–14 in the monochromatic wavefront aberrations of the total eye,15–18 and in recorded interferometric patterns on the tear film surface.19–21 Throughout the article, these three methods will be referred to as dynamic-area high-speed videokeratoscopy (HSV), dynamic wavefront sensing (DWS), and lateral shearing interferometry (LSI), respectively.

Recently, these three noninvasive techniques have been compared in a prospective study involving a cohort of subjects with healthy tear film,22 in whom the tear film surface characteristics were measured during natural blinking conditions (NBC). It was established in that study that HSV is the most precise method for measuring tear film surface quality; LSI is the most sensitive method for analyzing tear film build-up; and DWS, on the basis of the temporal changes in vertical coma and higher order RMS values, also has potential for describing tear film kinetics.

While it has been established that these noninvasive techniques can provide reliable assessments of normal tear film,23 there have been only limited previous studies investigating measurements from these noninvasive techniques in dry eye.11,18,24 Although these studies established reductions in tear film quality associated with dry eye, none of them specifically evaluated these techniques for the purpose of diagnosing dry eye. In addition, they did not assess the tear film under NBC. The purpose of this study was therefore to measure tear film surface quality by using noninvasive techniques in both NBC and suppressed blinking conditions (SBC) in a cohort of healthy control subjects and a cohort of subjects with clinically diagnosed dry eye and to investigate the potential of the three considered noninvasive techniques in terms of discriminating dry eye.

MATERIALS AND METHODS

Subjects

Thirty-four Caucasian subjects, 23 women and 11 men, from 20 to 68 years of age (mean, 38 ± 16) were recruited from among the students and staff members of the School of Optometry and patients of a dry eye
table 1. the group average of the objective clinical measurements

<table>
<thead>
<tr>
<th>measurement</th>
<th>group</th>
<th>group mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol wet thread length, mm*</td>
<td>Normal</td>
<td>23.4 ± 6.21</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>17.1 ± 8.58</td>
</tr>
<tr>
<td>FTBUT, s</td>
<td>Normal</td>
<td>14.3 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>6.3 ± 2.2</td>
</tr>
<tr>
<td>Corneal (fluorescein) stain score (0–15)</td>
<td>Normal</td>
<td>1.19 ± 0.99</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>5.62 ± 2.85</td>
</tr>
<tr>
<td>Conjunctival (lissamine green) stain score (0–18)</td>
<td>Normal</td>
<td>0.67 ± 0.89</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>7.75 ± 4.9</td>
</tr>
<tr>
<td>Tear meniscus height, mm*</td>
<td>Normal</td>
<td>0.25 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>0.23 ± 0.24</td>
</tr>
<tr>
<td>McMonnies questionnaire</td>
<td>Normal</td>
<td>8.7 ± 6.0</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>22.2 ± 6.1</td>
</tr>
</tbody>
</table>

*p values denote the results of a two-sample t test between the normal and dry eyes. Data are the mean ± SD.
* Measurements not used for the diagnosis of dry eye.

A standard clinical assessment of dry eye symptoms and signs was performed on all subjects. It included clinical history, McMonnies questionnaire, a slit lamp examination, a phenol red thread test of tear film break-up time (FTBUT). The slit lamp assessment included examination of the lid margins and meibomian glands, the bulbar and tarsal conjunctiva, and staining of the ocular surface with fluorescein and lissamine green dye. The central lower tear meniscus height was measured with a slit lamp graticule. Three measurements of FTBUT were conducted, and the average was taken. Fluorescein staining of the cornea and lissamine green staining of the bulbar conjunctiva were graded according to the National Eye Institute (NEI) grading scale.

All clinical measurements were performed in a sequence after the measurements with the three considered noninvasive methods. They were conducted by one experienced clinician who was masked with respect to the measurements performed with the noninvasive methods. Dry eye was diagnosed if the subject exhibited all three of the following characteristics of dry eye: significant subjective dry eye symptoms (McMonnies test score, >14), objective signs of tear film instability (FTBUT, <10 seconds), and surface staining (corneal and/or conjunctiva stain score, >3). According to this classification, 22 normal subjects (31 ± 10 [mean ± SD] years of age) and 12 dry eye subjects (52 ± 17 years) participated in the experiment. The normal group was 55% female and the dry eye group was 92% female. The differences in the group demographics were not considered to be relevant, because they should not sufficiently influence the comparison between the three considered noninvasive techniques. The group average statistics of the clinical measurements (mean ± SD) for normal and dry eyes are shown in Table 1.

Measurement Protocol

The assessment of tear film surface quality was performed with three noninvasive methods mentioned earlier: dynamic-area HSV, DWS, and LSI. All measurements were taken in the afternoon between 2:30 and 5:00 PM. All three instruments were located in the same room, so that the room’s environmental conditions did not significantly affect the tear film quality (Fig. 1). Temperature and humidity of the room were controlled and recorded at the beginning of each measurement session. The average (mean ± SD) temperature in the measurement room was 23 ± 1°C, and the average humidity was 53% ± 5%.

The order of use of the instruments was standardized to optimize time management and reduce the subject’s fatigue, because of the need to save large amounts of digital data. Two sets of measurements were performed in the following order: HSV, followed by DWS, and finally LSI. In the first step, tear film surface quality was assessed in SBC and after a 10-minute break, again in NBC. In SBC, three measurements were taken with each instrument. The subjects were asked to blink several times before the beginning of the measurement and then to...
TABLE 2. The Group Average of the Interblink Interval Duration across the Instruments for Normal and Dry Eye Subjects, under NBC.

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV</td>
<td>Normal</td>
<td>3.72 ± 2.81</td>
<td>P = 0.0029</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>2.44 ± 2.03</td>
<td></td>
</tr>
<tr>
<td>DWS</td>
<td>Normal</td>
<td>2.90 ± 2.53</td>
<td>P = 0.0019</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>2.12 ± 2.06</td>
<td></td>
</tr>
<tr>
<td>LSI</td>
<td>Normal</td>
<td>3.53 ± 1.91</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Dry Eye</td>
<td>2.57 ± 2.53</td>
<td></td>
</tr>
</tbody>
</table>

P values denote the results of a two sample t-test between the normal and dry eye. Data are the mean ± SD.

focus on the instrument’s fixation target and keep their eyes open as long as they could. The maximum time of the recording sequence was 30 seconds; a 5-minute break was given between measurements. In the NBC experiment, the subjects were asked to blink naturally without deliberately keeping their eyes open during two 30-second measurements. A break of 60 seconds was allowed before the next measurement was taken.

Instrumentation

In this article a short summary of the technical aspects of each of the three procedures is provided. For a more detail description of each of the methods, the reader is referred to works on HSV,27,28 DWS,28,29 and LSI.30

The dynamic-area HSV method27 is based on the projection of a Placido disc pattern onto the cornea’s outer layer, the tear film, and capturing the reflection with a video camera. Over time, the quality of the reflected image provides a time-varied indicator of tear film surface quality.

For DWS, a wavefront aberrometer (COAS; WaveFront Sciences, Inc., Albuquerque, NM) was used. Wavefront aberrations were rescaled to the smallest common pupil diameter in each of the recordings. The wavefront dynamic measure was provided as a time series of higher order aberrations (HOAs), total comatic terms (Coma_v and Coma_h), and the Zernike polynomial RMS fit error. The total comatic terms include the third-, the fifth-, and the seventh-order comatic terms.

In the LSI apparatus, the wavefront coming from an HeNe laser reflects from the tear film surface and creates an interferogram. The shape of interference fringes corresponds to the temporal stage of precorneal tear film surface. The method of numerical analysis is based on a fast Fourier transform combined with image-processing techniques.30

The HSV and LSI techniques captured images at a constant rate of 25 Hz, whereas the DWS provided a sampling frequency that fluctuated around 7.5 Hz.28

Statistical Analysis

ROC curves were calculated to show the capability of each of the three noninvasive techniques to discriminate between dry eye and normal subjects. The ROC curves determined the sensitivity and specificity of the measurement in diagnosing dry eye.6

To create the ROC curves, we first fitted all the raw time series of tear film surface quality (TFSQ) indicators provided by the three instruments with a polynomial function, to smooth any noise. The optimal order of the polynomial was chosen based on Mallow’s Cp information criterion,31 in which the penalty function is modified by a factor of 3 to avoid the overfitting of the polynomial function.52 At a given sampling time point, the data of the smoothed TFSQ indicators from each of the two groups of subjects (i.e., normal and dry eye) were used to estimate the probability density function. This procedure was achieved by using a kernel density estimator with an Epanechnikov window.53 The ROCs were then numerically evaluated from each such pair of nonparametric kernel density estimators.

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From the ROC curve, the AUC was also extracted by using numerical integration. AUC provides an overview of the characteristics of the ROC. The AUC is contained between 0 and 1—the closer to 1, the better the detector’s performance. Despite the significance of the AUC, it is still important to present the plot of the ROC to fully understand the detection behavior.

RESULTS

Interblink Interval Duration

The group statistics of the interblink interval duration, acquired by the three instruments, are shown in Table 2 for NBC. It is worth noting, that the interblink interval duration was, as expected, slightly shorter in the dry eye subjects than in the normal ones.

Figure 2 illustrates the interblink interval duration under SBC. The dry eye subjects showed less ability to keep their eyes open for longer intervals, when compared with the normal subjects. For example, examining the 50% level of subjects who could not suppress blinking until the 30-second measurement, we noted that for the dry eye subjects, the interblink intervals were approximately 11 seconds for LSI and HSV and 12 seconds for DWS. In the normal subjects, the intervals were 24 seconds for LSI, 26 seconds for HSV, and 17 seconds for DWS.

ROC Curves

To arrive at the best possible ROC for each of the noninvasive methods, a group of ROC curves were evaluated at different sampling intervals. Figure 3 shows a representative example for LSI. The range of times was kept between 1 and 11 seconds for all the methods, to ensure that the measurements were undertaken after the tear film build-up phase and that at least 50% of the subjects were included in each group (i.e., subjects who blinked within 11 seconds were excluded). In the case of the LSI, it is easy to observe the increase of the AUC as the time interval is increased, achieving an optimal value at ~9 seconds. The other two instruments showed similar behavior, but with the LSI, this effect was particularly pronounced.

Figure 4 shows the power to discriminate dry eye subjects from normal subjects for each of the three noninvasive techniques in the SBC. LSI shows the best performance (AUC = 0.80, for t = 9 seconds) follow by the HSV (AUC = 0.72, for t = 8 seconds), whereas the DWS achieved lower values (AUC_coma vertical = 0.64, for t = 8 seconds; AUC_coma horizon-
tal = 0.56, for $t = 2$ seconds; AUC_RMS [fit] = 0.57, for $t = 2$
seconds; AUC_HOA = 0.60, for $t = 10$ seconds).

The development of ROC curves by time to blink induces bias. However, this problem is not an issue, as we were inter-
ested in establishing the best possible performance of each of
the methods in terms of separating the two classes (i.e., the
normal and the dry eye subjects). The results produced in this
way and shown in Figure 4 provide additional information in
terms of class separability for a given tear film surface quality
indicator. For example, horizontal coma or RMS fit error
achieved the highest separability at 2 seconds (i.e., immedi-
aply post blink), whereas the other indicators performed best
at a much later stage of the interblink interval.

Figure 5 shows the power to discriminate dry eye subjects
from normal ones for the LSI and HSV under NBC and SBC.
DWS data have not been included because of their poor per-
formance. LSI presented the best performance for SBC data
(AUC = 0.80), whereas in NBC, it was slightly lower (AUC =
0.73). HSV also showed its best performance for SBC (AUC =
0.72) but the difference between SBC and NBC (AUC = 0.71)
was small.

**DISCUSSION**

The reliable diagnosis of dry eye can be a clinical challenge.
The invasive nature and relatively poor repeatability of tradi-
tional clinical tests for tear film assessment has led to the
development of several newer noninvasive tests of tear film
quality. The clinical utility of these new tests depends on a
range of factors including their repeatability, their ease of use,
and their ability to detect dry eye in the clinical setting.

We have compared the ability of three noninvasive instruments
to detect dry eye. The intent was to assess whether each of
the three noninvasive techniques—HSV, DWS, and LSI—is capable
of consistently and reliably detecting dry eye under different
blinking conditions (i.e., NBC versus SBC). Each of the three
techniques that we considered is based on different physical
principles, different tear film surface quality estimators, and the
size and location of the area of analysis. However, this study
demonstrates for the first time, using established statistical
techniques, some potential for each of the three techniques to
objectively detect dry eye.

The LSI technique appeared to exhibit the best performance
of the three considered techniques for the detection of dry eye,
achieving area under the ROC curve close to that reported for the
tear turnover rate method. Previous studies have demonstrated
that the LSI technique can be used for dynamic, repeatable quanti-
titative tear film assessment in normal subjects, with alterations
in tear film quality noted previously to be associated with dry eye
and contact lens wear. This study is the first investigation of the
ability of LSI to detect clinically diagnosed dry eye. While the LSI
technique is not a commercially available instrument, our findings
of good discriminative ability support the potential for this tech-
nique in the clinical assessment of the tear film. One potential
drawback of the LSI apparatus that we used is that it analyzed only
a small portion of the ocular surface ($\sim 4 \times 4$ mm); however, this
limitation did not appear to detract significantly from the ability
of the instrument to detect dry eye, when it exhibited slightly
superior AUCs compared with HSV, which assesses a larger area
of the ocular surface. A larger analysis area can be achieved with
the LSI technique if optical elements with large apertures are
used.

Although it has been established that the level of higher
order ocular wavefront aberrations are typically higher in dry
eye and increase in the postblink interval, there have been
relatively limited investigations of the ability of dynamic wave-
front analysis to detect dry eye. We have illustrated that dy-
namic wavefront sensing exhibits some diagnostic ability un-
der SBC, particularly in terms of analysis of vertical coma and higher order aberrations. However, the other techniques (i.e., LSI and HSV) appeared to exhibit superior performance in dry eye detection under both SBC and NBC, compared with DWS. The increased variability associated with DWS\textsuperscript{22} and the potential for confounding of the wavefront data by non-tear-film-related ocular factors (accommodation microfluctuations, among others) are the likely reasons underlying the performance of DWS compared with the other two instruments, which more directly measure the ocular surface.

For each of the techniques, the dry eye detection performance tended to improve with the length of time that elapsed after a blink. The best discrimination between normal and dry eye subjects was typically observed for tear film surface quality estimates derived approximately 8 to 10 seconds after a blink. This finding highlights the difference in tear-film dynamics associated with dry eye disease. The tear film quality of dry eye patients deteriorates more rapidly after a blink compared with that of normal persons, and therefore the largest difference in tear film quality between normal and dry eye subjects appears to occur 8 to 9 seconds after a blink. This finding is also consistent with the average measured FTBUT in the two groups.

An advantage of the three techniques over traditional dry eye diagnostic tests is the noninvasive nature of the tests and their ability to obtain information regarding the quality of the tear film even under NBC. Of particular interest is the fact that HSV and LSI methods provide good dry eye detection under both NBC and SBC. LSI showed better discrimination in SBC, because it is more sensitive than HSV. Recently, it was shown that LSI could clearly identify the build-up phase in 99% of cases.\textsuperscript{22} Similarly, LSI is the only current technique that can detect up to five phases of tear film surface kinetics.\textsuperscript{34} Hence, in SBC, it is likely that the differences in the tear film thinning phase between normal and dry eye subjects are sufficiently large to be detected by LSI, but not by HSV. Although both LSI and HSV displayed slightly higher discriminative ability under SBC, the performance under NBC approached those of the SBC closely. This result highlights a potential for these techniques for detecting dry eye during NBC. In contrast to this, the DWS did not perform as well in NBC, with AUCs of ~0.50.

Dry eye is a multifactorial ocular disease with a wide array of etiologies and clinical presentations.\textsuperscript{3} The dry eye subjects in our present study exhibited a range of clinical severities and etiologies (i.e., subjects with both aqueous-deficient dry eye and evaporative dry eye were included). Because of the relatively small number of dry eye subjects included in our present study, we did not consider clinical dry eye subclassification or grading in our analysis. However, future research using these noninvasive techniques for tear film assessment with a larger sample of dry eye subjects may be able to determine whether the noninvasive assessment of the dynamic behavior of the tear film can provide further information regarding the severity or underlying dry eye etiology or can discriminate between different subtypes of dry eye.

In conclusion, we investigated the performance of three noninvasive techniques for tear film assessment in the detection of dry eye. Overall, in our study, the LSI technique showed the best detection performance, closely followed by the dynamic-area HSV. Wavefront-sensing techniques were less powerful, particularly in NBC. In both SBC and NBC, measures of tear film surface quality from the LSI and HSV instruments demonstrated clear potential to detect dry eye. Previous studies investigating the ability of clinical tests to detect dry eye have primarily used invasive techniques (e.g., Ref. 6) that involve contact with the eye, the instillation of drops, and/or suppressed blinking patterns. Importantly, our current findings showed that noncontact techniques for assessing tear film surface quality in NBC (i.e., truly noninvasive measurement conditions) have considerable potential for the objective detection of dry eye.

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References


