Non invasive assessment of the tear film stability in patients with tear dysfunction using the Tear Film Stability Analysis System (TSAS)

Koray Gumus, MD, FEBO*, 1Charlene Hong Crockett, MD*, 1Kavita Rao, MD, 1Elizabeth Yeu Lin, MD, 1Mitchell P. Weikert, MD, 1Mariko Shirayama, MD, 2Shigeki Hada, 1Stephen C. Pflugfelder, MD

* Dr. Gumus and Dr. Crockett should be considered as equal first authors

1 Ocular Surface Center, Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, Houston, TX, US and 2Tomey Corporation, Nagoya, Japan

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The authors have had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Correspondence and request for reprints:

Stephen C. Pflugfelder, MD
Ocular Surface Center, Cullen Eye Institute
Baylor College of Medicine
6565 Fannin, NC205, Houston, Texas 77030, USA

Telephone: 713-798-4732
Fax: 713-798-1457
E-mail: stevenp@bcm.tmc.edu
**Purpose:** To evaluate the tear film stability in patients with tear dysfunction and an asymptomatic control group using the new non-invasive Tear Stability Analysis System (TSAS).

**Methods:** In this prospective case control study, 45 patients with dysfunctional tear syndrome (DTS) were stratified into 3 groups (1, 2, and 3/4), based on clinical severity, with higher scores indicating more severe symptoms and 25 asymptomatic control subjects were evaluated. TSAS measurements were performed using the RT-7000 Auto Refractor-Keratometer (Tomey Corporation, Nagoya, Japan). Images of ring mires projected on to the cornea every second for 6 seconds were captured and analyzed. Focal changes in brightness were calculated as numerical Ring Break-Up (RBU) values and the elapsed time when the cumulative values (RBU Sum) exceeded a threshold was defined as the Ring Break-Up Time (RBUT).

**Results:** RBUT in DTS groups were all significantly lower than those of control subjects, with the lowest values found in DTS 3/4. RBUT was significantly shorter in DTS 3/4 than DTS 1 (P< 0.001). The change of RBU Sum over a 6-second period in DTS groups combined or among the individual groups was found to be statistically significant (p<0.001) as was the difference between the 1 and 6 second values. For distinguishing between asymptomatic controls and DTS, the sensitivity and specificity of a 5.0 second RBUT cut-off were 82.0% and 60.0%, respectively.

**Conclusions:** The TSAS may be a useful non invasive instrument for evaluating tear stability and for classifying DTS severity.
INTRODUCTION

Dry eye and tear dysfunction are among the most common ocular diseases, estimated to affect 14% to 33% of adults and having increased with age.\(^1\) The air/tear film interface is the primary refractive surface of the eye, and thus its integrity and stability is crucial for maintaining high quality vision and ocular comfort.\(^1\)-\(^5\) Traditionally, the precorneal tear film was considered to consist of separate mucin, aqueous, and lipid layers. Soluble mucins are important structural components of the precorneal tear film and the hydrated mucus layer occupies most of the film thickness.\(^6\),\(^7\),\(^8\) Instability of tear film may be due to qualitative or quantitative abnormalities of any of these components. Other factors that can also affect tear film stability include concentrations of stabilizing factors (e.g. mucins), integrity of the surface epithelia, and overlying lipid layer, activity of proteolytic enzymes in tears and reflex blink mechanisms.\(^8\)

Tear break-up test with fluorescein is one of the most commonly used measures of tear stability.\(^10\),\(^11\) However, it has numerous limitations including the need to instill fluorescein, lack of standardization of fluorescein concentration, induction of reflex tearing, subjective assessment, and difficulty in simultaneous assessment of tear break-up across the entire cornea.\(^11\) It is possible to assess tear break-up with noninvasive methods which include tear film lipid layer interferometry,\(^12\),\(^13\) xeroscope and Tearscope.\(^14\) A limitation of these methods is they do not provide standardized objective measurement of tear stability.

Topographical regularity indices of the Tomey TMS-2N corneal topography instrument (Tomey Corporation, Nagoya, Japan) have also been used as objective
diagnostic parameters of tear stability and corneal surface regularity in patients with tear dysfunction, but these topographic examinations provide data at only one time point. For kinetic noninvasive assessment of tear stability, Tear Stability Analysis System (TSAS) software was developed for the TMS-2N and its utility for measuring tear stability in dry eye was studied. This particular software is not commercially available; however, a modified version has been developed for the RT-7000 Auto Refractor-Keratometer (Tomey Corporation, Nagoya, Japan). Basically, this system works on the principle of capturing images of mire rings projected onto the cornea every second for up to 10 seconds. Points along a radial line are converted into a wave pattern based on the light intensity of the reflected points at that second. The instrument’s software uses these waves to calculate tear stability parameters.

The purpose of this study was to evaluate tear film stability in patients with dysfunctional tear syndrome (DTS) using this new non-invasive TSAS in the RT-7000 instrument and compare the results with those of normal control subjects.

**PATIENTS and METHODS**

This study was approved by the Baylor College of Medicine, Institutional Review Board (IRB). It also adhered to the tenets of the Declaration of Helsinki for clinical research, and written informed consent was obtained from all the participants after explanation of the purpose and possible consequences of the study.

Forty five consecutive patients with newly diagnosed DTS meeting the inclusion and exclusion criteria were enrolled for the study at the Ocular Surface Center at Baylor College of Medicine, Houston, Texas. Patients were excluded if they were using any
topical medications other than preservative-free artificial tears, wearing a contact lens, had ocular surgery in the past year, or had evidence of any other ocular surface diseases, systemic disease and medications that would alter the ocular surface. Twenty-five subjects were recruited as asymptomatic controls. Inclusion criteria for the control subjects were absence of corneal and conjunctival dye staining and a symptom severity score ≤ 20. Diagnosis of DTS was based on complaints of eye discomfort (symptom severity score > 20 and tear break-up time ≤ 7 seconds).

DTS patients recruited for this study were referred by three members of the cornea service in our department. Asymptomatic control subjects and DTS patients all underwent the same ocular surface and tear evaluations. Patients completed a dry eye symptom severity questionnaire, followed by a complete ocular surface examination of both eyes in the following sequence: TSAS of the right eye by the RT-7000 Auto Refractor-Keratometer (Tomey Corporation, Nagoya, Japan), topographic measurement of surface regularity index (SRI) in both eyes (right eye followed by the left eye), biomicroscopic examination of the lid margins and meibomian glands, fluorescein tear break-up time (TBUT), corneal fluorescein staining, conjunctival lissamine green staining, and Schirmer 1 test. With the exception of the TSAS, these tests were performed by a single investigator (S.C.P) as previously described. Symptom severity score was measured by the ocular surface disease index (OSDI) questionnaire that contains 12 questions evaluating the character and severity of dry eye symptoms. Briefly, the questionnaire inquired about the frequency of occurrence of each symptom, rating it from “none” to “all the time.” The questionnaire scores ranged from 12 (no symptoms) to a maximum of 59. Criteria for grading DTS severity were modified from
the Dry Eye Workshop (DEWS) based on the symptom severity scores, TBUT values and corneal and conjunctival staining scores (Table 1). If all criteria of a severity group were not met, assignment to a severity grading was based on the worst parameter. Meibomian gland disease (MGD) was diagnosed by evidence of dysfunction (lack of expressible meibum from ≥ 75 % of glands on the central lower lid margin) and the presence of one or more morphological changes of the meibomian glands, including acinar atrophy, vascular dilation on or scalloping of the posterior lid margin. The United States European Study Group consensus criteria were used for diagnosis of Sjögren’s syndrome (SS).

**Principle of Tear Film Stability Analysis System of the RT-7000**

TSAS software had previously been designed for the Tomey Topographic Modeling System (TMS-2N; Tomey Corporation, Nagoya, Japan), but it was never released commercially. We explored a newer version of the TSAS that was developed for the Tomey RT-7000 Auto Refractor-Keratometer. In this version, 15 mire rings from a lighted cone are projected onto the corneal surface. To minimize the interference of lids and lashes, only the 11 central rings are analyzed. The software captures images of the reflected rings each second for up to 10 consecutive seconds. This study examined the right eye for 6 seconds. Data points for analysis consist of the intersections of 256 lines radiating from the center with the 11 reflected rings, yielding a total of 2816 points. Each line of points is converted into a wave pattern based on the light intensity of the reflected points at that second. Waves at time 0 are set as the standard. The instrument’s software uses these waves to calculate parameters which include Ring Break-Up Sum (RBU Sum), Ring Break-Up Time (RBUT), and Ring Break-Up value.
(RBU value). Detailed explanations of these parameters are provided in Figures 1 and 2.

**Ring Break-Up (RBU) value and Ring Break-Up Sum (RBU Sum)**

A Ring Break-Up (RBU) value is the change of ring brightness level of the data points compared to the previous second. The sum of the RBU value at any given second and those of the previous seconds is defined as the RBU Sum at that second. RBU Sum corresponds to the area of tear film breakup. An eye with an RBU Sum of 700, for example, has ten times the area of tear film breakup as one with 70.

**Ring Break-Up Time (RBUT)**

The time in seconds after the last blink when the RBU sum exceeds a specified threshold value (20) is considered the Ring Break-Up Time. Based on preclinical testing the manufacturer found a RBUT less than or equal to 5 seconds to be suggestive of dry eye.

**Statistical Analysis**

SPSS 15.0 for Windows evaluation version (LEAD Technologies Inc., Chicago, IL) was used for statistical analysis. The Pearson Chi-square test was applied to analyze sex differences among the groups. A Shapiro-Wilk test was carried out to determine whether data were normally distributed. If a distribution could not be normalized by logarithmic transformation, the Kruskal-Wallis test was used. Normally distributed continuous parameters were analyzed among the groups (control and three DTS groups) by one-way ANOVA and Welch ANOVA tests. Tukey and Tamhane multiple comparison tests were also applied for the homogenous and nonhomogenous
parameters, respectively. Spearman’s correlation test was carried out to analyze the association among the study parameters. The change over time among the groups was analyzed using repeated measures of ANOVA. The right eye values were used for statistical comparison of clinical parameters and the Ring Break-Up parameters. A p value $\leq 0.05$ was considered statistically significant.

**RESULTS**

The demographic data and clinical parameters for control subjects and DTS patients are presented in Table 2. Etiological subclassification of DTS patients is also provided in Table 3. For statistical analysis, data from patients meeting DTS 3 and DTS 4 severity criteria were combined to form one group, DTS 3/4. Thus, a total of four groups were compared: control, DTS 1, DTS 2, and DTS 3/4. Even though the mean age of control subjects was slightly younger than that of DTS patients, the difference did not reach statistical significance. There was also no significant difference in gender distribution among the control and three DTS subgroups.

**Clinical parameters**

Compared with the control group, the symptom severity scores were significantly greater in all DTS groups combined ($p\leq 0.001$); however, there were no significant differences in symptom severity scores among the three DTS groups ($p= 0.897$ for DTS 1 vs DTS 2, $p= 1.00$ for DTS 1 vs DTS 3/4, $p= 0.870$ for DTS 2 vs DTS 3/4). The Schirmer 1 values were lower in each DTS group compared to those of control subjects, though the difference reached statistical significance only in the DTS 3/4 ($p= 0.002$). There was a statistically significant difference in the SRI among the four groups ($p<$
0.001). In post hoc analysis, the control (p< 0.001), DTS 1 (p= 0.016), and DTS 2 (p=
0.030) groups were all significantly lower than DTS 3/4. The fluorescein TBUT values
were statistically significant among the groups, except for DTS 2 versus DTS ¾ (p>
0.05). Corneal fluorescein staining scores were significantly greater in the DTS groups
compared to the control group (all p values< 0.05). Conjunctival staining scores were
significantly greater in DTS 2 and DTS 3/4 groups compared to the control subjects and
DTS 1 group. Detailed statistical comparisons between groups are provided in the Table
2 legend.

**TSAS Analysis**

The RBUT results are presented in Table 2. RBUT values in DTS groups were all
significantly lower than the values in control subjects, with the lowest values found in
DTS 3/4. RBUT was significantly shorter in DTS 3/4 than DTS 1.

The RBU Sum over time in the asymptomatic control group and three DTS
groups is presented in Figure 3. The change of RBU Sum over a 6-second period in
DTS groups combined or among the individual groups was found to be statistically
significant (p<0.001). This difference was found to be significant from second 1 to
second 6.

When the cut-off point was 5.0 seconds for RBUT as the manufacturer
recommended, the sensitivity and specificity of the current TSAS method were 82.0%
and 60.0%, respectively. Moreover, while the positive predictive value was 0.79, the
negative predictive value was 0.65. Sensitivity and specificity ratios were re-analyzed
using RBUT cut-off points ranging from 2.5 to 5.0 seconds (Table 4). The optimum
sensitivity (82.2%) and specificity (88.0%) were obtained when the cut-off point was lowered to 3.0 seconds.

**DISCUSSION**

This study evaluated a recently released non-invasive tear stability analysis system in patients with dysfunctional tear syndrome (DTS). We found that similar to conventional fluorescein tear break-up time, RIBUT measured with the TSAS became progressively shorter with worsening severity. Furthermore, the RBU Sum values showed greater increase over the 6 second evaluation time in DTS patients than in the control group, and the rate of increase was greater with worsening disease severity. A cut-off point for RIBUT of 3.0 seconds was found to have the optimum sensitivity and specificity of 82.2% and 88.0%, respectively.

In response to the increasing prevalence of dry eye and increasing recognition of its impact on quality of life, numerous technological advancements have been made in studying disease pathogenesis, diagnosis and treatment. Development of a non-invasive diagnostic method to measure tear stability and to identify eyes with tear dysfunction with high specificity and sensitivity has been a major goal.

In both research studies and in clinical practice, the use of corneal topographic systems for identifying tear dysfunction has gradually increased. For example, a number of studies\textsuperscript{15, 17, 23, 24} have documented corneal surface irregularity detected by computerized videokeratoscopy (CVK) indices in patients with DTS. These studies established that indices such as surface regularity index (SRI), surface asymmetry index (SAI), potential visual acuity index (PVA) and irregular astigmatism index (IAI) of
the Tomey TMS-2N had good sensitivity and specificity for predicting the presence of tear dysfunction identified by corneal fluorescein staining.\textsuperscript{15} Other studies have reported that increases in SRI were correlated with decreased functional visual acuity and contrast sensitivity.\textsuperscript{25, 26, 27}

A number of non-invasive techniques for assessing precorneal tear film break-up time without use of fluorescein have been reported. Indeed, instruments such as the grid xeroscope and Tearscope (Keeler, Windsor, UK) are capable of non-invasive measurement of tear break-up time. However, identifying tear break-up is still a subjective assessment with these instruments.\textsuperscript{11}

Over the last 5 years, several studies have reported the use of CVK systems to assess tear film stability.\textsuperscript{11, 18, 28, 29} Kojima and associates described the Tear Stability Analysis System (TSAS) software for the TMS – 2N which was programmed to capture Placido ring images sequentially for 10 seconds.\textsuperscript{11} In this system, disruption of tear film stability was identified as a change in corneal power. Change of corneal power more than 0.5 diopter (D) was designated an area of break-up. Two parameters were established to evaluate the tear film stability: 1) tear break-up time (TMS-BUT) and 2) tear break-up area (TMS-BUA). The system provided a summary of the individual breakup points in a single display.\textsuperscript{18}

Kojima et al evaluated the effectiveness of the TSAS for the TMS-2N before and after the insertion of punctual plugs in patients with tear dysfunction and control subjects.\textsuperscript{11} In eyes with DTS, both tear stability regularity and asymmetry indices (TSRI, TSAI) derived from SRI and SAI were found to be greater than in control subjects. The
authors concluded that TSAS was effective in objectively assessing the tear stability in patients with DTS.

Two studies by Goto and colleagues documented that TMS-BUT and TMS-BUA had similar specificity to conventional fluorescein TBUT, but videokeratoskopic indices had significantly higher sensitivity in identifying tear film in stability.\textsuperscript{18, 29} They reported TMS break-up time to be shorter than break-up identified by biomicroscopy.\textsuperscript{29} Moreover, they suggested that TSAS for the TMS-2N may be used as a new sensitive method for diagnosing tear dysfunction before and after LASIK.\textsuperscript{18, 29}

In the present study, a newer version of the TSAS developed for the Tomey RT-7000 Auto Refractor-Keratometer was evaluated. This system projects mire rings onto the cornea and captures images of the mires every second for up to 10 seconds. Our study examined the right eye for 6 seconds. The instrument’s software evaluates ring brightness to generate parameters which include Ring Break-Up value (RBU value), \textit{Ring Break-Up Sum (RBU Sum) and Ring Break-Up Time (RBUT)}. A detailed explanation of the methods used to calculate these indices is provided in the Materials and Methods section and in Figures 1 and 2. The manufacturer suggests that an RBUT less than or equal to 5 seconds is suggestive of dry eye.

Several key differences in the two versions of TSAS software deserve to be highlighted. The TSAS for TMS-2N calculates breakup by changes in corneal power as measured by corneal topography, while the TSAS for the RT-7000 calculates tear break-up based on the brightness difference of data points on mire rings. Additionally, the TSAS for the RT-7000 includes an auto-alignment feature to correct for unstable
fixation of the patient’s eye over the duration of the test. According to the manufacturer that designed both versions, results of the TSAS of the RT-7000 have been found to be more stable.

Using the new system we found that the RBUT was significantly lower in all DTS severity groups combined (p< 0.001) and in each of the subgroups compared to the asymptomatic control group (p= 0.001, p= 0.003 and p< 0.001, respectively). The RBU Sum was significantly higher in the entire DTS group at each time interval from 1 to 6 seconds compared to the control group (p= 0.001 at 1 sec and other p values < 0.001)

A distinct difference in the pattern of RBU Sum was noted between the control subjects and the DTS groups. While the RBU Sum remained relatively constant in the control group, the RBU Sum in each of the DTS group progressively increased over the 6-second evaluation period. Among the DTS groups, the DTS 3/4 group had the highest RBU Sum over time, followed by the DTS 2 and DTS 1 groups. These differences in RBU Sum noted between DTS and control subjects and between the DTS severity groups indicate the TSAS is objective method to detect tear film instability and it may prove to be a useful method to monitor efficacy of therapies for DTS.

When we evaluated the sensitivity and specificity of the TSAS model currently used in this study, sensitivity was found to be as high as 82.0%, but specificity was 60.0% using the cut-off RBUT of 5.0 seconds suggested by the manufacturer. While this test is useful for identifying DTS patients, it is not as strong at discriminating between normal individuals from DTS patients. We therefore investigated other cut-off values for RBUT to eliminate this deficiency. Based on these data, the cut-off point of 3.0 seconds
for RBUT seems to have greater sensitivity (82.2 %) and specificity (88.0 %) ratios compared to the cut-off point of 5.0 seconds. Therefore, an RBUT of less than 3.0 seconds appears to be appropriate for identifying an unstable tear film.

One of the most important disadvantages of this new method is the high variability of RBU Sum. Based on the present data, this variability significantly increased with the level of clinical severity of DTS and increased in all groups over time. This was consistent with our observation of minimal variability of the results in repeated exams of normal eyes. Fortunately, the change in RBU Sum over time between the control group and DTS groups became statistically significant at the first second, revealing that the instrument is efficient and reliable method for identifying tear instability in patients complaining of eye irritation. Squinting, flinching, lid movement and looking away from the target were actions observed to increase the RBU readings and thus decrease the RBUT. To minimize the impact of these factors, subjects were encouraged to keep their eyes wide open and focused on the target for the duration of the test. It should be noted, however, that doing so for 6 seconds can be a challenge especially for patients experiencing irritation and photophobia, hence these movements may contribute to the variability of the measurement.

For some subjects, facial anatomy, notably the brow and nose, necessitated repositioning of the head to allow for proper alignment of the lighted cone. Even with repositioning, a few subjects still could not be tested due to prominent facial features. This is a limitation that the manufacturer may want to address in future devices.
In conclusion, the TSAS system for the RT-7000 provides valuable information regarding tear film stability in patients with tear dysfunction. It appears to be a useful non-invasive tool for diagnosing and stratifying DTS. It may also help as an objective indicator for monitoring therapies for tear dysfunction.
REFERENCES


**Table 1.** Severity Grading Criteria for Dysfunctional Tear Syndrome (DTS).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>DTS1</th>
<th>DTS2</th>
<th>DTS3</th>
<th>DTS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom severity score *</td>
<td>≤ 20</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Tear break-up time (seconds)</td>
<td>&gt; 7</td>
<td>≤ 7</td>
<td>≤ 7</td>
<td>≤ 7</td>
<td>≤ 7</td>
</tr>
<tr>
<td>Conjunctival staining score</td>
<td>0</td>
<td>≤ 3</td>
<td>≥ 3</td>
<td>≥ 3</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Corneal staining score</td>
<td>0</td>
<td>≤ 2</td>
<td>≤ 8</td>
<td>&gt; 8, including central cornea or filaments</td>
<td>≥ 12</td>
</tr>
</tbody>
</table>

*Symptom severity score was measured by ocular surface disease index (OSDI) questionnaire
DTS: Dysfunctional tear syndrome
DTS 1-4: Dysfunctional tear syndrome severity levels from 1 to 4.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n:25)</th>
<th>DTS 1 (n:23)</th>
<th>DTS 2 (n:11)</th>
<th>DTS 3/4 (n:11)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.20 ± 16.55</td>
<td>52.48 ± 16.14</td>
<td>59.36 ± 19.54</td>
<td>55.36 ± 14.14</td>
<td>0.282</td>
</tr>
<tr>
<td>Sex (m/f) (%)</td>
<td>56 / 44</td>
<td>21.7 / 78.3</td>
<td>36.4 / 63.6</td>
<td>36.4 / 63.6</td>
<td>0.112</td>
</tr>
<tr>
<td>OSDI scores</td>
<td>10.40 ± 4.65</td>
<td>35.65 ± 11.95</td>
<td>31.27 ± 11.45</td>
<td>35.73 ± 7.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBUT</td>
<td>9.12 ± 0.97</td>
<td>5.91 ± 3.10</td>
<td>3.10 ± 1.52</td>
<td>2.91 ± 1.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conjunctival SS.</td>
<td>0 ± 0</td>
<td>0.09 ± 0.29</td>
<td>1.73 ± 2.19</td>
<td>2.36 ± 3.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Corneal SS.</td>
<td>0 ± 0</td>
<td>0.77 ± 0.97</td>
<td>3.73 ± 1.35</td>
<td>9.36 ± 4.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Schirmer 1</td>
<td>22.63 ± 9.66</td>
<td>14.68 ± 10.72</td>
<td>12.67 ± 8.17</td>
<td>8.50 ± 8.76</td>
<td>0.002</td>
</tr>
<tr>
<td>SRI</td>
<td>0.13 ± 0.14</td>
<td>0.42 ± 0.38</td>
<td>0.37 ± 0.34</td>
<td>1.04 ± 0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBUT</td>
<td>4.91 ± 1.62</td>
<td>2.40 ± 2.47</td>
<td>1.24 ± 1.75</td>
<td>0.36 ± 0.45</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TBUT: Tear Break up time (seconds), Conjunctival SS: Conjunctival Staining Score, Corneal SS: Corneal Staining Score, SRI: Surface Regulatory Index, RBUT: Ring Break-up Time, DTS: Dysfunctional Tear Syndrome

*P values, among A, B, C, and D groups

Age: One-way ANOVA, Sex: Chi-square, OSDI scores: Welch ANOVA, TBUT: Kruskal-Wallis H, Corneal and Conjunctival SS: Kruskal-Wallis H, Schirmer 1: One-way ANOVA (after logarithmic transformation), SRI: One-way ANOVA (after logarithmic transformation), RBUT: Welch ANOVA (after logarithmic transformation)

**Post Hoc p values:**
OSDI: p< 0.001 (A-B), p= 0.001 (A-C), p< 0.001 (A-D), p= 0.897 (B-C), p= 1.00 (B-D), p= 0.870 (C-D)
TBUT: p< 0.05 (A-B), p< 0.05 (A-C), p< 0.05 (A-D), p< 0.05 (B-C), p< 0.05 (B-D), p< 0.05 (C-D)
Conjunctival SS: p> 0.05 (A-B), p< 0.05 (A-C), p< 0.05 (A-D), p> 0.05 (B-C), p> 0.05 (B-D), p> 0.05 (C-D)
Corneal SS: p< 0.05 (A-B), p< 0.05 (A-C), p< 0.05 (A-D), p< 0.05 (B-C), p< 0.05 (B-D), p< 0.05 (C-D)
Schirmer 1: p= 0.076 (A-B), p= 0.078 (A-C), p= 0.002 (A-D), p= 0.967 (B-C), p= 0.217 (B-D), p= 0.576 (C-D)
SRI: p= 0.082 (A-B), p= 0.229 (A-C), p< 0.001 (A-D), p= 0.997 (B-C), p= 0.016 (B-D), p= 0.030 (C-D)
RBUT: p= 0.001 (A-B), p= 0.003 (A-C), p< 0.001 (A-D), p= 0.700 (B-C), p= 0.004 (B-D), p= 0.522 (C-D)
Table 3. Etiological Subclassification of Dysfunctional Tear Syndrome (DTS) Patients.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>All DTS (n:45)</th>
<th>DTS 1 (n:23)</th>
<th>DTS 2 (n:11)</th>
<th>DTS 3 / 4 (n:11)</th>
</tr>
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<tbody>
<tr>
<td>MGD</td>
<td>27 (60.0)</td>
<td>15 (65.2)</td>
<td>7 (63.6)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>SS</td>
<td>5 (11.1)</td>
<td>-</td>
<td>1 (9.1)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Non-SS ATD</td>
<td>13 (28.9)</td>
<td>8 (34.8)</td>
<td>3 (27.3)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

MGD: Meibomian gland disease; SS: Sjögren’s Syndrome; Non-SS ATD: Non Sjögren’s Syndrome Aqueous Tear Deficiency
Table 4. Sensitivity and Specificity Ratios for Tear Film Stability Analysis System (TSAS) at Different Cut-off Points.

<table>
<thead>
<tr>
<th>Cut-off point for RBUT (sec)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5.0</td>
<td>82.0 %</td>
<td>60.0 %</td>
</tr>
<tr>
<td>≤ 4.5</td>
<td>82.2 %</td>
<td>76.0 %</td>
</tr>
<tr>
<td>≤ 4.0</td>
<td>82.2 %</td>
<td>76.0 %</td>
</tr>
<tr>
<td>≤ 3.5</td>
<td>82.2 %</td>
<td>80.0 %</td>
</tr>
<tr>
<td>≤ 3.0</td>
<td><strong>82.2 %</strong></td>
<td><strong>88.0 %</strong></td>
</tr>
<tr>
<td>≤ 2.5</td>
<td>80.0 %</td>
<td>88.0 %</td>
</tr>
</tbody>
</table>

RBUT: Ring break-up time
FIGURE LEGENDS

Figure 1. There are 256 points evenly distributed on each of the 11 central mire rings. These points are radially connected by lines to make 256 lines. Each line of points is converted into a wave based on the light intensity of the reflected points at that second. The waves are also regularized, or normalized, to account for peripheral rings not reflecting as brightly as central ones due to a greater distance from the light source.

The difference of the area under the curves of each point at n seconds and 0 seconds is calculated (example: the shaded area between the solid and dashed lines of “Ring 4” above). When the difference reaches a designated threshold, the point is considered to be a “break-up point”. Peripheral break-up points are weighted more heavily to compensate for a lower density of points. The total break-up points in the 11 central rings, after being weighted, is the Ring Break-Up Sum (RBU Sum) for n seconds. The time at which RBU Sum exceeds 20.0 is the Ring Break-Up Time (RBUT). A RBUT of less than 5.0 seconds is suggestive of dry eye.

Figure 2. Ring Break-Up (RBU) values represent the changes of RBU Sum between consecutive seconds. For example, at second 2, the value 12.5 on the printout (Figure 2A) indicates an increase of 12.5 RBU from second 1, thus the RBU Sum at second 2 is 7.1+12.5=19.6. At second 3, the value 6.8 means an increase of 6.8 RBU, so the RBU Sum at second 3 is 7.1+12.5+6.8=27.4 (Figure 2B).
The time at which RBU Sum crosses the threshold of 20.0 is the Ring Break-Up Time (RBUT), at 2.1 seconds in this example (Figure 2C). An RBUT less than 5.0 seconds, as in this case, suggests dry eye.

**Figure 3.** The graph is revealing RBU Sum over time. Control group values had the lowest RBU Sum throughout the 6 seconds. RBU Sum increased each second with increasing severity of DTS. Variability increased with increasing severity of DTS and also increased over time in each DTS group. Bars indicate 95% confidence intervals.
Figure 1.
Figure 2.

NAME:  
ID:  No ID  
DATE:  2009/12/31 10:05  
Exam. No.:  000615

<RIGHT>  
[TSAS]  
<<<<Ring Breakup>>>>  
RIBUT:  2.1 sec

AS Time: 0.5 sec  
Time Mode: 6 sec  
Interval: 1.0 sec  
RBU Level1: 0.010  
RBU Level2: 20.00

<table>
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<th>RIBUT*</th>
<th>sec</th>
<th>RIBUT*</th>
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<td>9.4</td>
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</tr>
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<td>8</td>
<td></td>
</tr>
<tr>
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<td>6.8</td>
<td>8</td>
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<tr>
<td>5</td>
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<td>10</td>
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</tbody>
</table>

*TOMEY CORP. RT-7000

*RBU in the table refers to Ring Break Up (RBU) value.
Figure 3.