Experimental Eye Research 117 (2013) 28–38

Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Review

Tear film stability: A review

Deborah F. Sweeney [a,*], Thomas J. Millar [b], Shiwani R. Raju [b]

[a] Office of the Pro-Vice Chancellor, University of Western Sydney, Locked Bag 1797, Sydney, Penrith, 2751 NSW, Australia
[b] School of Science and Health, University of Western Sydney, Parramatta Campus, Locked Bag 1797, Sydney, Penrith, 2751 NSW, Australia

ARTICLE INFO

Article history:
Received 27 March 2013
Accepted in revised form 13 August 2013
Available online 22 August 2013

Keywords:
tear film stability
tear break-up time
non-invasive break-up time
lipid layer
dewetting
ocular mucins
ocular proteins
tear film assessment

ABSTRACT

Tear film stability can be assessed via a number of tools designed for clinical as well as research purposes. These techniques can give us insights into the tear film, and allow assessment of conditions that can lead to dry eye symptoms, and in severe cases, to significant ocular surface damage and deterioration of vision. Understanding what drives tear film instability and its assessment is also crucial for evaluating existing and new therapies. This review examines various techniques that are used to assess tear film instability: evaluation of tear break-up time and non-invasive break-time; topographic and interferometric techniques; confocal microscopic methods; aberrometry; and visual function tests. It also describes possible contributions of different tear film components; namely meibomian lipids, ocular mucins and proteins, and factors such as age, contact lens wear, ocular surgery and environmental stimuli, that may influence tear film instability.

1. Introduction

The ocular surface is a complex unit comprising various epithelial and glandular tissues (cornea, bulbar and palpebral conjunctiva, and lacrimal and accessory eyelid glands). These tissues secrete the tear film that coats and protects the ocular surface and allows clear vision (Holly, 1973; Stern et al., 1998; Tutt et al., 2000; Gipson, 2007). Its complexity is highlighted by observations that the composition of tears varies between open eye and closed eye (Sack et al., 2000), stimulated and non-stimulated (Fullard and Snyder, 1990), and in diseased versus normal (Li et al., 2005; Tomosugi et al., 2005; Green-Church et al., 2008; Lema et al., 2010; Versura et al., 2010; Acera et al., 2011; Zhou et al., 2012) states. Therefore, deciphering the components of the tear film that are irregular and inadequate when it is unstable is a challenge for both scientists and clinicians, and the effects of a stable tear film on the ocular surface health is paramount. The purpose of this review is to bring to the forefront the current technologies and methods used to assess tear film stability, both in the clinical and laboratory setting, as well as critically revisit the literature on some of the concepts regarding tear film stability and what factors can influence tear film stability.

2. Measurement of tear film stability

In general, tear film stability is measured by its lack of stability, which is important clinically because it can be used for both diagnosis and assessment of treatments for dry eye states (Nichols et al., 2000; Bron, 2001). Its measurement is of importance to both clinicians and researchers. Clinicians are looking for evidence to support diagnosis of conditions that affect ocular health and patient comfort and quality of life, and to assess and monitor the effectiveness of treatments and interventions. Researchers are seeking techniques to better understand what drives tear film instability not only to guide the to guide development of effective therapies, but also to evaluate surface characteristics of new contact lenses materials.

A range of methods is now available to assess aspects of the tear film to provide insights into its “stability”. The direction of the development has been towards techniques that are non-invasive, assess a wide area of the ocular surface, and allow the dynamic nature and temporal instability of the tear film to be captured and analysed. As a consequence, many of the developing techniques are complex and unsuitable for routine clinical use. This section reviews the developments that have occurred.

* Corresponding author. Tel.: +61 2 9678 7417, +61 414 339 206.
E-mail addresses: D.Sweeney@uws.edu.au (D.F. Sweeney), T.Millar@uws.edu.au (T.J. Millar), S.Raju@uws.edu.au (S.R. Raju).

0014-4835/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.exer.2013.08.010

2.1. Tear break-up time (TBUT)

TBUT was first introduced by Norn (1969) and remains the most frequently used diagnostic test to determine tear film instability (Smith et al., 2008; Korb, 2000). Currently, the technique involves instilling sodium fluorescein into the tear film using a moistened strip or a pipette and observing the tear film with a biomicroscope, cobalt blue light and a wratten 12 yellow barrier filter (Cho and Douthwaite, 1995). The patient avoids blinking and TBUT is the time interval between a complete blink and the appearance of the first break, discontinuity or dry spot observed in the tear film following a blink. Break-up occurs most frequently in the inferior or central cornea (data from 22 healthy subjects) and least frequently in the superior quadrant (Elliott et al., 1998). In normal eyes, the values for TBUT can range from 3s to 132s, with an average of 27s (Norn, 1969b). In contrast, TBUTs less than 10s suggest an abnormal tear film (Mengher et al., 1985a), with values of 5s to 10s, considered marginal, and less than 5s, indicative of dry eye symptoms (Pflugfelder et al., 1998). According to Goto et al. (2004a), based on a sample of 80 eyes of 48 healthy subjects, the sensitivity and specificity of TBUT measurements were 75% and 60% respectively, for categorization of dry eye symptoms.

Despite its widespread use, it is recognised that TBUT measurements have poor reproducibility (Vanley et al., 1977). Lee and Kee (1988) in a group of 30 normals and 20 dry eye patients reported the reproducibility to be 65% in normals and 95% in dry eye patients. BUT was determined on 4 visit occasions and the mean of the first and second were compared to the mean of the third and fourth visits to calculate reproducibility. BUT can be affected by clinician expertise, partial blinking, illumination techniques (Cho et al., 1992) uneven tear mixing (Vanley et al., 1977), and by the amount, concentration, pH, drop size, presence of preservatives and the type of fluorescein used (Mengher et al., 1985b).

Using a volume of fluorescein that exceeds the average tear volume of ~ 6 to 7 μL can affect tear film stability and increase TBUT artificially. Marquardt et al. (1986) found that pipetting 1 μL of 2% fluorescein solution into the tear film improved the repeatability of TBUT measurement. Similarly, Korb et al. (2001) showed that using strips that delivered 5 times less fluorescein than normal strips gave improved reproducibility. Pult and Riede-Pult (2012) reported that using a narrow (1 mm) fluorescein strip also improved repeatability. Abelson et al. (2012) using a reduced volume of fluorescein determined TBUT to be greater than 5s in normals (mean 7.1 (1.17) s) and less than 5s in dry eye patients (mean 2.2 (0.82)s).

Cho (1991) recommended that a mean of multiple measures is a more reliable indication of TBUT and later reported that if fluorescein TBUT were repeated, the first measurement was significantly different from the second; but the second and third were similar (Cho et al., 1998). Nichols et al. (2004) reported high repeatability (95% limits of agreement −5.71 to 5.83 s, upto ±8s difference between visits) when TBUT was measured on two occasions by a single examiner in a group of mild to moderate dry eye patients. The second measurement at each visit was significantly longer and interclass correlation coefficient for the average of two readings taken at a visit demonstrated better reliability than either the first or second TBUT measurement alone.

Papas's (1999) analysis of Cho et al.'s data (1998) suggested that differences between first and subsequent measures of TBUT are unlikely to be of clinical significance. Sullivan et al. (2012) also reported on the clinical utility of objective tests for dry eye disease including TBUT. Fifty-two subjects were monitored for 3 months in a longitudinal observational case series. Break-up times were determined using a slitlamp. Results of 3 consecutive measurements timed with a stopwatch were averaged. Results confirmed those of Lemp et al. (2011) illustrating that patients with mild/moderate dry eye have broadly distributed TBUT values making it difficult to differentiate these from normal subjects. In addition, during the therapeutic intervention arm of the Sullivan study, the variability or dynamic range in TBUT increased, suggesting either its resolution was insufficient to discern subtle changes or that it is a lagging indicator of ocular surface health and may need to be monitored for several months following cessation of chronic inflammation. These studies highlight the importance of both the use and reporting of standardized and detailed protocols to allow results from various studies to be compared.

Automation of the TBUT methodology has also been investigated. The technique involves location of different areas from a video of the tear film, determining regions of interest and measurement of BUT in these areas. Cebreiro et al. (2012) reported the automatic measurement values to be in the same range as that determined by a trained expert observer.

2.1.1. Tear film break-up dynamics (TBUD)

To obtain more information about tear film break-up, the overall patterns have been examined. After instilling fluorescein, Begley et al. (2005) videotaped changes occurring after the first break in the tear film. By digitising individual frames and converting to grayscale, MATLAB was used to assess the total area of tear break-up (AB) of the exposed cornea along with TBUT and the maximum blink interval. Using a sample of 10 control and 10 dry eye subjects, TBUDs, which involves keeping the eye open for as long as possible, showed higher correlations (sensitivity and specificity) with symptoms compared to TBUT. For dry eye subjects, TBUT was faster and more extensive (24.5% vs 13.7% area) than for controls. The rate of tear break-up or dry area growth rate (DAGR) have been reported to be four times greater in dry eye subjects, who also demonstrate greater break-up in the central cornea than controls (Liu et al., 2006).

Similarly, using digital images, Ousler et al. (2005a) identified five distinct tear film break-up patterns (TFBUPs) that occurred after instilling fluorescein into the tear film: amorphous blob (frequency 26%), linear (22%), spot (20%), fractured (20%) and wispy (12%). These TFBUPs were remarkably reproducible (93.8%) and the linear pattern was most frequently associated with dry eye.

2.2. Non-invasive break-up time (NIBUT)

Given the lack of reproducibility of TBUT numerous "non-invasive" techniques have been reported. However, it is important to define precisely what is non-invasive (Szczesna and Iskander, 2010). These techniques should not involve instillation of fluorescein, blinking should be natural not forced or suppressed and there should be no contact between the measuring instrument and the eye or eyelids. In addition, it is important that the methodology does not substantially alter the ocular environment such as by increased temperature from illumination systems. It has been noted that changes in meniscus curvature can be observed using non-invasive methods, indicating that some minor degree of reflex tearing is present (DEWS Diagnostic Methodology, 2007a).

Generally, non-invasive techniques involve the observation of an illuminated grid pattern reflected from the anterior tear surface. A regular image of the reflected target indicates a stable tear film and the time in seconds from the last blink to the appearance of the first discontinuity or break in the reflected image is recorded (Lamble et al., 1976; Holly, 1981; Little and Bruce, 1994a; Craig et al., 1995). Generally, comparisons of TBUT and NIBUT in the same group are poorly correlated with NIBUT being longer (Cho and Douthwaite, 1995; Nichols et al., 2002).

One advantage of using a reflected mire to examine tear stability is that events before break-up can be examined. One such