Experimental Eye Research 120 (2014) 97–102

Contents lists available at ScienceDirect

Experimental Eye Research

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

Thermal fluctuation based study of aqueous deficient dry eyes by non-invasive thermal imaging

Mohammad Azharuddin [a], Sumanta Kr. Bera [b], Himadri Datta [b,*], Anjan Kr. Dasgupta [a]

[a] Department of Biochemistry, University of Calcutta, 35 ballygunge circular road, Kolkata 700019, India
[b] Regional Institute of Ophthalmology (RIO), Calcutta Medical College, Kolkata 700073, India

ARTICLE INFO

Article history:
Received 3 September 2013
Accepted in revised form 9 January 2014
Available online 21 January 2014

Keywords:
ocular surface temperature
left eye
right eye
thermal fluctuation
aqueous deficient dry eye
thermal imaging

ABSTRACT

In this paper we have studied the thermal fluctuation patterns occurring at the ocular surface of the left and right eyes for aqueous deficient dry eye (ADDE) patients and control subjects by thermal imaging. We conducted our experiment on 42 patients (84 eyes) with aqueous deficient dry eyes and compared with 36 healthy volunteers (72 eyes) without any history of ocular surface disorder. Schirmer's test, Tear Break-up Time, tear Meniscus height and fluorescein staining tests were conducted. Ocular surface temperature measurement was done, using an FL-IR thermal camera and thermal fluctuation in left and right eyes was calculated and analyzed using MATLAB. The time series containing the sum of squares of the temperature fluctuation on the ocular surface were compared for aqueous deficient dry eye and control subjects. Significant statistical difference between the fluctuation patterns for control and ADDE was observed ($p < 0.001$ at 95% confidence interval). Thermal fluctuations in left and right eyes are significantly correlated in controls but not in ADDE subjects. The possible origin of such correlation in control and lack of correlation in the ADDE subjects is discussed in the text.

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1. Introduction

Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation (Craig and Tomlinson, 1997; Iwata et al., 1969; Mishima and Maurice, 1961), which causes damage and discomfort to the ocular surface. However, recent review by Savini et al. (Savini et al., 2008) points out that the term "dry eye" includes spectra of alterations of the ocular surface with varying etiology and pathophysiology. While the exact definition of dry eye is debated, the general consensus that was accepted in International Dry Eye workshop is that the dry eye is a part of the ocular surface disease, which includes both Aqueous Deficient Dry Eye (ADDE) and Evaporative Dry Eye (EDE), lid related diseases (such as Meibomian Gland Dysfunction (MGD) and anterior blepharitis), allergic conjunctivitis and other inflammatory, infective or iatrogenic conditions (Lemp, 2007). In most cases, dry eye patients suffer from excessive tear evaporation rate because of the instability of the tear film (Craig et al., 2000; Mathers et al., 1993; Rolando et al., 1983). The cause of ADDE is a lack of aqueous tear secretion by the lacrimal glands, whereas EDE is most often caused by MGD, in which the lipid secretion required to control evaporation and maintain a normal tear film is abnormal.

Interestingly, like the problems in the disease definition, the methods to detect and score dry eyes are also non-unique. Staining based techniques, Schirmer's test (ST) and the staining based tests are mostly semi-invasive in nature. The techniques commonly used in diagnosis are ST, Tear Break-up Time (TBUT) and ocular surface staining, but such tests are imperfect and may lead to incorrect diagnosis (Morgan et al., 1995; Paschides et al., 1989). The film stability test (TSAS) on the other hand is based on complex refractometric measurements (Savini et al., 2008). Apart from this the dynamics of the tear film by different biophysical aspects have been studied but they still possess some limitations (Tomlinson and Khanal, 2005).

In this paper we describe an independent approach for identification and scoring of dry eye disease (in this case ADDE). The method is based on Infrared (IR) thermography or IR thermal imaging (Arora et al., 2008; Gowen et al., 2010). The reason behind this is its non-invasive nature as well as its accuracy in measuring a wide range of temperatures on the macro as well as on the micro level. Measurement of the ocular surface temperature (OST) using an IR- based thermal camera- known as ocular thermography (Keeney and Guibor, 1970; Mapstone, 1970; Morgan et al., 1993; Purslow and Wolffsohn, 2005; Purslow et al., 2005), was first introduced by Mapstone (Mapstone, 1968a,b,c,d). Recently, there

* Corresponding author. Tel.: +91 9380127929 (mobile).
E-mail address: himadri.datta@gmail.com (H. Datta).

0014-4835/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.exer.2014.01.007

has been a rapid advancement in infrared thermography and its application in Ophthalmology has paved the way for measurements of OST. Infrared thermography is a non-contact and non-intrusive, temperature measuring technique, capable of displaying real-time surface temperature distribution (Mackie and Seal, 1981; Tan et al., 2009a). The growing fascination with OST is primarily due to the information gained from it, which may reflect the physical as well as physiological state of the eye (Keeney and Guibor, 1970; Purslow and Wolffsohn, 2005; Yang and Yang, 1992). Infrared cameras have earlier been used to analyze normal eyes in different age groups (Acharya et al., 2009) and in addition have been used to detect patients with dry eye syndrome and it has been reported that dry eye patients have a greater decrease in the OST than the normal individuals under normal circumstances (Su et al., 2011). However, in a later study it was observed that there is a smaller decrease in the OST as compared to normal individuals (Chiang et al., 2006; Morgan et al., 1996). This discrepancy in IR thermal imaging has not been studied extensively, although the patterns of thermal images of dry eye patients appeared to be more irregular as compared to the control group (Mathers, 2004; Mori et al., 1997; Tan et al., 2011a). Recently, it has been shown that the temperature profile is smoother for normal individual as compared to the dry eye patients (Tan et al., 2010c). It has been reported earlier that cooling of the ocular surface occurs more predominantly in dry eye patients than in normal individuals. Earlier researchers have reported the absolute temperature difference between dry eyes and normal subjects; also to be noted is the fact that they analyzed the data based on single eye. The expected result that the higher cooling of the ocular surface as a result of lesser tear film stability was what was reported. Apart from the above study various mathematical models and algorithms have been developed in order to correctly localize the corneal surface for accurate measurement of OST in disease states (Ooi and Ng, 2009; Tan et al., 2010a, 2011b; 2009b).

2. Methods

In this paper we have studied ocular surface thermal fluctuation in left ($\Delta T(t)_L$) and right ($\Delta T(t)_R$) eyes for 42 ADDE patients and comparing it with 36 normal individuals without any symptoms of ocular surface disorder. Here, $\Delta T(t)$ refers to the temperature fluctuation of the ocular surface.

This study was approved by the institutional ethics committee prior to its commencement. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

2.1. Subjects

Forty two (84 eyes) ADDE patients (17 male; 25 female: mean age 35.2 ± 4.3 years) were recruited from the outpatients department. Thirty six (72 eyes) control subjects (16 male; 20 female: mean age 28.4 ± 3.1 years) were recruited from the staff of the hospital. Inclusion criteria were devised such that all patients had ADDE symptoms, were not taking any artificial tear supplement, had either a Tear break-up time and fluorescein score of more than 3 out of 15 (Bron et al., 2003), a Schirmer's test result of less than 10 mm in 5 min, Tear meniscus height of 0.18 mm or less (Farrell et al., 2003) and two or more symptoms of dry eye according to the McMonnies Dry Eye questionnaire (McMonnies, 1986). Patients suffering from Meibomian gland dysfunction (MGD) were excluded from the study. Diagnostic criteria for MGD (Nichols et al., 2011) include (a) slit lamp microscopy to detect any abnormality of meibomian gland mass, (b) gland expressibility, (c) quantification of gland dropout, (d) Telangiectasia of meibomian gland orifice. The control subjects were asymptomatic of ADDE, Schirmer's test of >20 mm, tear breakup time of >10 s, had no previous history of ocular or general pathology and were not taking any topical or systemic medication that could interfere with tear production.

2.2. Testing condition

Infrared thermal camera (Model no. FLIR SC 305, FLIR SYSTEMS AB, Sweden) was used to monitor the OST for ADDE patients and the control group. The camera has a thermal sensitivity of <0.05 °C at + 30 °C, spatial, temporal and image resolution of 1.36 mrad, 9 frames per second and 320 × 240 pixels respectively, with spectral range between 7.5 and 13 μm. Subjects adapted to the prevailing room temperature for at least 10 min before OST of the right and left eye were recorded (Purslow and Wolffsohn, 2007). Room temperature and humidity were monitored and controlled at 22.0 ± 0.5 °C and 45 ± 5%. Subjects were restricted from (a) topical application of any eye drop (b) any food or drinks intake within 2 h prior to experiment (c) and any strenuous physical activity that would affect the ocular surface temperature. $\Delta T(t)$ was calculated by using MATLAB analysis software, MATLAB version 7.9.0. R2009b, Mathworks USA.

2.3. OST measurement parameters

During the measurement the participants were asked to keep their eyes open for 15 s without blinking and in this condition thermal sequence of the ocular surface were obtained. The reading was acquired after 2 s of eye opening. For pseudo code and MATLAB code please refer to the Supplementary section (S).

2.4. Statistical test

The temperature fluctuation for 72 control eyes (36 X2) and 84 ADDE eyes (42X2) were respectively combined to produce two arrays one representing the control and the other ADDE. The unpaired student t test was then performed. Validity of the null hypothesis (implying no difference between the control and the ADDE groups) was then tested at 95% confidence interval (H = 0, implying null hypothesis, and H = 1 implying significant difference between control and ADDE).

3. Results

Fig. 1A and B represents a typical thermogram of an individual and the region of the ocular surface (i.e. the cornea) for which temperature is measured. Fig. 2A represents $\Delta T(t)$ (left and right eye) of a given control, whereas Fig. 2B shows the $T(t)$ of the OST for the same control subject. Similarly, Fig. 3A and B depicts the $\Delta T(t)$ and $T(t)$ (left and right eye) for an ADDE patient. The above Figs. 2A, B and 3A, B describe the variation in temperature of the ocular surface along with the actual OST.

Interesting results were obtained when the time course for all the control (36) and ADDE patients (42) data were plotted against $\Delta T(t)_L$ and $\Delta T(t)_R$ as shown in Fig. 4A and B, from these figures it may be noted that ADDE individuals exhibit an irregular ocular surface thermal variation (which may be either more heating or cooling compared to the control group) in contrary to the earlier report (which only considered cooling, taking about 11subjects). The range of temperature fluctuation for ADDE patients ($\Delta T(t)_L$ and $\Delta T(t)_R$) and control is provided in Table 1 ($p < 0.001$). Irregular temperature fluctuation rather than monotonic decay was observed for ADDE patients when time course for $T(t) - \mu$ was plotted as shown in Supplementary figs. (S1 and S2).

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