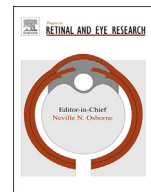




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Dynamics and function of the tear film in relation to the blink cycle



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ABSTRACT

Great strides have recently been made in quantitative measurements of tear film thickness and thinning, mathematical modeling thereof and linking these to sensory perception. This paper summarizes recent progress in these areas and reports on new results. The complete blink cycle is used as a framework that attempts to unify the results that are currently available. Understanding of tear film dynamics is aided by combining information from different imaging methods, including fluorescence, retroillumination and a new high-speed stroboscopic imaging system developed for studying the tear film during the blink cycle. During the downstroke of the blink, lipid is compressed as a thick layer just under the upper lid which is often released as a narrow thick band of lipid at the beginning of the upstroke. “Rippling” of the tear film/air interface due to motion of the tear film over the corneal surface, somewhat like the flow of water in a shallow stream over a rocky streambed, was observed during lid motion and treated theoretically here. New mathematical predictions of tear film osmolarity over the exposed ocular surface and in tear breakup are presented; the latter is closely linked to new *in vivo* observations. Models include the effects of evaporation, osmotic flow through the cornea and conjunctiva, quenching of fluorescence, tangential flow of aqueous tears and diffusion of tear solutes and fluorescein. These and other combinations of experiment and theory increase our understanding of the fluid dynamics of the tear film and its potential impact on the ocular surface.

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1. Introduction

The human tear film is a very thin layer of fluid, approximately 3 microns thick (King-Smith et al., 2000). Although thin, it provides a critical function in the eye's optical system and serves to nourish, protect and enhance the differentiation of surface epithelial cells (Bron et al., 2004; Govindarajan and Gipson, 2010; Montes-Mico et al., 2010; Tutt et al., 2000). When unstable, the tear film may stress and potentially alter the underlying ocular surface, resulting in a common condition known as dry eye (DE), which affects millions in the U.S and elsewhere (DEWS, 2007; Schaumberg et al., 2003; Uchino et al., 2011; Viso et al., 2009). However, despite the common occurrence of the DE condition, knowledge of tear film dynamics remains inadequate to understand fluid dynamics during the complete blink cycle, perhaps due to the rapidity of the changes taking place in the very thin film. This review combines recent imaging of tear film dynamics and other experimental measures with mathematical modeling of tear film parameters to deepen our understanding of the dynamic processes taking place in the tear film during the complete blink cycle.

Tear film instability, which includes both rapid tear thinning and tear break-up (TBU), is considered a core mechanism of DE, along with tear film hyperosmolarity (DEWS, 2007). It is thought that tear film instability occurs due to increased evaporation and leads to increased tear film osmolarity, which stresses the ocular surface and leads to a vicious cycle of inflammation and hyperalgesia. Ultimately this repeated stress can lead to the surface alterations and neural and cellular damage seen in severe dry eye (Baudouin et al., 2013; DEWS, 2007).

Traditionally, the lipid layer has been thought to retard evaporation of the tear film, so that a more stable lipid layer should theoretically increase tear film stability. Mishima and Maurice (1961) provided evidence that the tear film lipid layer of the

rabbit can reduce the rate of evaporation by a factor of 15. However, some *in vitro* studies show that meibum (meibomian lipid) has little or no effect on evaporation when spread on the surface of saline (Borchman et al., 2009; Brown and Dervichian, 1969; Cerretani et al., 2013). This discrepancy between *in vivo* and *in vitro* studies of evaporation may be due to differences between the tear film lipid layer and meibum spread on saline. In support of this idea, *in vivo* studies show an inverse correlation between lipid layer thickness and both tear film thinning rates and tear break-up time. As discussed at the beginning of Section 5, there is additional extensive evidence for the role of evaporation through the lipid layer in tear film instability and dry eye; however, the altered viscoelastic properties in dry eye disorders (Georgiev et al., 2014) may also contribute to tear film instability directly, or by alterations in the lipid layer which cause increased evaporation.

Recent imaging of TBU combined with sensory measures have linked TBU to discomfort, pain and increased DE-like symptoms and suggested that tear film osmolarity may reach 800–900 mOsM within local areas of TBU (Liu et al., 2009). However, tear film osmolarity is difficult to measure directly over the ocular surface and is currently estimated by sampling tears from the lower meniscus (Bron et al., 2014; Lemp et al., 2011). Mathematical modeling of changes in tear film fluorescence within areas of tear film instability has provided a method to estimate tear film hyperosmolarity within the same regions over the ocular surface (Braun et al., 2014). In this paper, we add to previous results from mathematical models of TBU (Peng et al., 2014) and we present new results for osmolarity all over the exposed ocular surface. We also include mathematical models for the fluorescent intensity, in order to help understand this process quantitatively and how fluorescence is related to the osmolarity. Since solute concentrations are not measured outside the meniscus, these quantitative estimates may currently be the best source of concentrations available.

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