The effects of the tear-film dynamics in healthy subjects and dry eye patients

Thesis of the postdoctoral paper

Erdélyi Béla MD

Semmelweis University
School of Doctoral Studies, Clinical Medicine

Tutor: Prof. Németh János MD, PhD, DSc

Opponents: Prof. Nagy Zoltán Zsolt MD, PhD, DSc
Prof. Módis László MD, PhD

Head of the final exam board: Prof. Hatvani István MD, PhD, DSc
Members of the final exam board: Prof. Fidy Judit MD, PhD, DSc
Füst Ágnes MD, PhD

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Introduction

The tear-film overlying the ocular surface has significant optical role, because the air–tear-film interface accounts for two-thirds of the total refraction of the eye. This surface is continuously changing between two blinks. The tear-film builds up gradually after blinking and attains its optimally regular and smooth shape, then evaporation makes it thinner and finally it breaks up. Irregularity significantly decreases visual acuity. The most simple demonstration of this is provided during the visualization of the retinal vessels. The image becomes distorted with time because of the break up of the tear-film.

For in vivo analysis of the ocular surface only non-invasive methods are acceptable. Corneal topography is a map based on the reflection of concentric rings from the corneal surface. Alterations between two blinks happen due to the changes of the tear-film, therefore its dynamics can be indirectly observed with this method.

The recognition of the ocular surface dynamics is important, as the treatments executed in corneal refractive surgery are partly based on a momentary image of the ocular surface. This is considerably influenced by the elapsed time after blinking. It is unknown which time point represents best the real ocular surface. In certain departments examinations are performed after instillation of an artificial tear drop, which is a rough intervention into the physiological status of the tear-film, the results do not reflect the true condition. On the other hand the administration of artificial tears in dry eye can be definitively useful from the optical point of view, besides the improvement of subjective symptoms in the patients. Visual acuity improves, because the artificial tear smoothens the ocular surface.

Dry eye is endemic throughout the world. The tear-film becomes unstable which can be observed with corneal topography. The abnormalities are not limited to the ocular surface, the disorder induces alterations in the deeper layers of the cornea on the long run. For the assessment of those alterations another instrument is necessary, which is capable of visualizing the layers of the cornea. Such method is the confocal microscope – used in several fields of medicine – it makes in-vivo histological images, in 3 dimensions if needed.

Our research can be divided into two sections, in the first part the postblink changes of the tear-film were observed, in the second we performed the description of corneal disorders in dry eye disease.

Purpose

In healthy subjects:

1. To study if the ocular surface topography changes after blinking or this is a constant microenvironment?

If changes are detectable the aim is to consider:

2. How can these changes be classified and do typical trends exist?

The topographic pattern of the ocular surface was earlier determined to be a constant property of the eye. Our aim was to detect:

3. Is this statement true, or the changes include the pattern as well?

In patients:

4. To observe the effect of artificial tear therapy on the regularity of the ocular surface in dry eye patients.

Our previous investigations – performed in healthy and dry eyes – raise the question, when to perform corneal topographic measurements after blinking. We further need to know:

5. Is the reproducibility of measurements altered with time after blinking?

The commercially available videokeratograph is capable of making only four images in one series, which is not satisfactory for studying the dynamics of the tear-film. Therefore development of an instrument capable of capturing several images per second was necessary.

6. We intended to observe the tear-film dynamics with the help of the newly developed videotopograph. The questions below were also planned to be answered:

a) Does the process differ in healthy and dry eyes?

b) Incomplete blinks are common in everyday practice. Does the tear-film dynamics change in this situation?

c) How does instillation of artificial tear gel influence the tear-film dynamics?

Dry eye disease is not only the disorder of the ocular surface.

7. Our aim was to observe if there are certain pathognomic signs in the layers of the cornea and if the morphology of the cornea differs in dry eye conditions with different etiology?

Methods

We followed the tenets of the Declaration of Helsinki in all our investigations. The healthy volunteers and the patients signed an informed consent before being involved in the study.

The alterations of the ocular surface topography in the interblink interval

Computerised videokeratography determines the refractive power and the radius of curvature in several thousand points of the corneal surface. The alterations of the ocular surface topography were investigated following the blink using this method. We examined the right eye of 12 healthy young volunteers (8 females, 4 males, age: 21.4±1.1 years). The topographic images were captured in series 5, 15, 30 and 60 seconds after blinking.

Based on the results of the first study our purpose was to find the tendencies of the alterations in the ocular surface topography after blinking. The examinations were performed again in series of four in 36 young healthy subjects (21 females, 15 males, age: 25.0±5.4 years).

The corneal topographic pattern in healthy eyes was classified into five groups based on the color-coded power maps: round, oval, symmetric bow-tie, asymmetric bow-tie, irregular (*Bogan et al, 1990*). We investigated whether the pattern is a stable characteristic of the eye, or it may change in the interblink period.

The effect of artificial tear gel on corneal topography was observed in five healthy subjects (3 females and 2 males, age: 24.4±5.2 years) and five dry eye patients (5 females, age: 57.4±7.4 years). One eye was treated, in the patients it was the one with more severe symptoms. Images were captured from both eyes before treatment 15 seconds after blinking. Then the treated and the control eye were examined in a parallel manner 1, 5, 15, 30, 45 and 60 minutes after application of the artificial tear drop, each time at 15 seconds postblink.

The postblink changes of the ocular surface may alter the reproducibility of the videokeratographic measurements with time after blinking. To reveal this we performed 3 series of examinations on 30 healthy eyes (17 females, 13 males, age: 25.7±5.6 years), 5, 15, 30 and 60 seconds postblink. Between two series the subject was requested to blink naturally, for sufficient regeneration of the tear-film.

Paired t-test was utilized for the comparison of the data of the same group at two different time points. For more than two samples – with normal distribution – ANOVA was performed with Bonferroni post-hoc test. Non-Gaussian distributed samples were compared using the Kruskal-Wallis test with Dunn post-hoc test. Friedman test was applied if the samples were not independent (multiple measurements on the same population). χ^2 test was used for assessment of the difference in the ratio of "irregular" and "regular" topographic patterns in the stable and changing subgroups. In the analysis of the reproducibility of topographic parameters variation coefficient was determined using the following formula: (SD/mean) x100.

Tear-film dynamics

A new device was developed on the basis of a videokeratograph, which is suitable for non-invasive observation of the tear-film dynamics. Fifteen ohthalmologically healthy subjects were recruited (12 females, 3 males, age: 31.5±10.4 years). Four images were captured per second for 30 seconds after a complete blink in each examined eye. For the statistical analysis of the alterations of SRI, SAI and keratometric values two different methods were used: fourth order polynomial approximation for the first 15 seconds and moving average assessment for the whole 30 seconds period after the complete blink. The time after the blink needed to attain the lowest SRI was considered tear-film build-up time. Videotopographic tear-film break-up time was provided if the increase of SRI after the minimum reached the value of the standard deviation of the SRI trendline.

Tear-film dynamics were examined only after complete blink so far, but in everyday life incomplete blinks occur frequently; therefore in a subsequent study we performed measurements after complete and incomplete blinks as well in another group of 15 healthy subjects (9 females, 6 males, age: 27.5±5.1 years). In this investigation 2 images per second were captured during a postblink period of 30 seconds. The observed parameters were SRI, PVA and simulated keratometry values (K_1, K_2). The results obtained under the two different circumstances were compared. The topographic parameters were used according to the principle of the moving average. We determined the topographic tear-film build-up- and break-up time. Besides the videotopographic measurements dr eye tests were performed in each subject (Schirmer's test, fluorescein tear break-up time).

Tear-film dynamics was also observed in 7 dry eye patients (7 females, age: 58.6±7.7 years) using our new method. Diagnosis was based on the subjective symptoms, the anterior segment findings and the results of dry eye tests (Schirmer's test<10mm/5 minutes, fluorescein tear break-up time < 10seconds, fluorescein staining > 4 points). Videotopographic measurement was performed at least 14 hours after the application of artificial tears. The recording was repeated three minutes after the instillation of an artificial tear drop.

The trends of the alterations of the SRI and the SAI were depicted as fourth order polynomial trendlines. In case of larger random fluctuations of the results moving average was applied; the data were replaced by the mean of a given interval of data (window). The latter method reduces the random fluctuations, and the distortion of the trendline is only dependent on the chosen width of the window.

Corneal findings in dry eye

The Heidelberg Retina Tomograph II (Heidelberg Engineering Inc.) fitted with the Rostock Cornea Module (RCM) is a confocal corneal microscope, suitable for in-vivo high magnification imaging of each layer of the cornea. A descriptive study was performed, the individual layers of the cornea were examined in healthy subjects and in patients suffering from dry eye.

For our purposes 26 patients with dry eye symptoms (16 females, 10 males; age: 61.7±10.0 years) and 10 age-matched healthy subjects (5 females, 5 males; age: 61.5±10.5 years) were recruited. Healthy subjects with ophthalmologic disorders or operations in their history and contact lens wearers were excluded.

After the assessment of the best spectacle corrected visual acuity and biomicroscopic examination of the anterior segment dry eye tests were performed: tear-film break-up time (BUT), fluorescein staining, and Schirmer's I test without topical anaesthesia. Lid-parallel conjunctival folds (LIPCOF) were also observed. The subjective symptoms of the patients were scored according to a simple severity scale. Finally confocal microscopy was carried out.

Diagnosis of dry eye was based on the typical symptoms, the presence of LIPCOFs, and the abnormal results of dry eye tests. Patients were divided into three subgroups. The first group included 10 patients with aqeuous tear deficiency (5 females, 5 males). None of them used artificial tears. The second group presented 8 patients with dysthyroid ophthalmopathy (8 females). Protrusion was not detected, all patients were in the chronic phase of the disease and none of them were on artificial tears before the examination. The third group contained 8 patients treated because of lagophthalmos (5 females, 3 males). The mean duration of the condition was 55 months (24- 108 months). Four of them used artificial tears. The cornea was examined at three locations: centrally and at the lower and upper paralimbal area. Besides the quantitative assessment morphological features were also noted at the layer of the subbasal nerves, the stroma and the endothelium.

For comparison of the groups ANOVA was applied with Bonferroni post-hoc test. Non-Gaussian distributed samples were compared using the Kruskal-Wallis test with Dunn post-hoc test. Calculation of correlation between the parameters was executed with Pearson's test for data of normal distribution or Spearman test for non-Gaussian distribution. Multiple regresssion analysis was performed to compare the results of dry eye tests and confocal microscopic findings.

Corneal topographic measures

Quantitative analysis of corneal topography is posssible with available mathematically calculated parameters. We used the following in our investigations. The surface regularity index (**SRI**) describes the regularity of the optically important central part of the cornea. The more regular the center of the examined ocular surface the smaller the value of the SRI. The surface asymmetry index (**SAI**) is a measure of the total corneal surface asymmetry. The more symmetric the surface the smaller the value of the SAI, for a perfect sphere it would be zero. The potential visual acuity (**PVA**) is the visual acuity based solely on the regularity of the ocular surface. The simulated keratometric values ($\mathbf{K_1}$, $\mathbf{K_2}$, $\mathbf{K_{min}}$) provide the powers and axes of the steepest ($\mathbf{K_1}$) and flattest meridians ($\mathbf{K_{min}}$) and the power and axis of the meridian perpendicular to the steepest meridian ($\mathbf{K_2}$). The color-coded power maps were used with the normalized scale from the various types of scales available.

Confocal microscopic outcome measures

Various quantitative measures were observed during confocal microscopy as follows: the epithelial cell density at three different layers (superficial cells, intermediate or wing cells and basal cells), the number of subbasal nerves (total number of parallel nerves visible from one side of the image and continuing to the other), the number of subbasal nerve branches (sum of the number of nerve branches seen in one image), the number of beadlike formations (number of such formations along 1mm of nerve fibre), the epithelial thickness, the corneal thickness, and the endothelial cell density.

Other parameters

The best spectacle corrected visual acuity was checked at the distance of 5 meters using Kettesy decimal visual acuity chart. The Schirmer's test was performed with filter-paper placed into the lower fornix without topical anesthesia. The wetting of the paper was measured after five minutes. The tear-film build up time was performed using fluorescein impregnated filter paper, touched gently to the lower tarsal conjunctiva, then after a few blinks the appearance of dry spots on the ocular surface was observed under the cobalt-blue filter of the slitlamp. The fluorescein staining of the ocular surface was examined under the same conditions in blue illumination. Biomicroscopic anterior segment examination was done, including the assessment of the lid-parallel conjunctival folds.

Results and their clinical significance

1. Due to the alterations of the preocular tear-film the corneal topography changes even 15 seconds after the blink. The SRI and the SAI increased with time after blinking. This increase was significant in the 5-15 (only for SRI) and 5-60 second intervals ($p<0.05$). The PVA decreased after the blink, significantly ($p<0.05$) between 5 and 60 seconds. The refractive power values did not change significantly. The SRI was normal (<1.01) in each eye 5 seconds after the blink and only two eyes became suspect (1.01-1.96) at 60 seconds. The SAI was normal in each cornea (<0.42) at 5 seconds. One eye became suspect at 15 seconds (0.42-0.49), 2 suspect and one abnormal eye (>0.5) were seen at 30 seconds. Only 7 normal corneal surfaces were found at 60 seconds and 5 changed to abnormal. The SRI, SAI and PVA proved to be suitable parameters for the assessment of the alterations of the tear-film.

2. As seen above the change of the mean SRI showed an obvious tendency after the blink, but the changes were not similar in each eye. Therefore groups were created. Most often the SRI increased continuously (31%), in others the SRI did not change (25%). In 18% of the eyes it hardly changed during the first 30 seconds, then increased. In the next group we found transient decrease of the SRI at 15 seconds, it increased at later times (17%). The SRI continuously decreased in 8% of the eyes. Similar groups could be introduced based on the changes of the SAI. The existence of the different groups means that tear-film stability might be vastly different in healthy eyes. In most of the cases the tear-film was ruptured and the ocular surface became irregular during the examination, but there were few cases when the tear-film remained stable for 60 seconds, the ocular surface remained regular and the SRI was unchanged.

3. The color-coded refractive power map of the ocular surface was considered a characteristic, stable quality of the eye. Our investigations showed that the topographic pattern changes in more than half of the cases in healthy eyes during a one minute pause in blinking. Analysing the group of subjects as a whole the ratio of the regular and irregular topographic patterns changed significantly during 60 seconds after blinking. The rate of regular patterns increased at 15 seconds; but

afterwards, less regular and more irregular patterns appeared with time ($p<0.001$). These results remind us, that it is important to capture the image at an appropriate time after the blink.

4. On those eyes of dry eye patients treated with artificial tear gel the SRI decreased under the level of the initial value ($p<0.05$) after transient significant increase ($p<0.001$) and it remained low until the end of the examination. The PVA transiently decreased at 1 minute after the blink compared with the value before instillation ($p<0.001$), later it significantly increased ($p<0.05$) and remained better throughout the examination ($p<0.01$ at 45 minutes). The SRI and PVA values of the diseased and healthy eyes were significantly different before application of the artificial tear drop ($p<0.05$ and $p<0.01$), the difference vanished after treatment. The method was found suitable for individual testing of artificial tear drops in dry eye patients. The positive changes in ocular surface regularity can be measured objectively, under such circumstances the subjective symptoms of the patients also diminish. The perfect artificial tear can be selected easily and individually using this method.

5. The reproducibilty of the keratometric values significantly worsened 60 seconds postblink ($p=0.007$ and $p=0.038$). The standard deviation of the values exceeded 0.5 diopter. The SRI and the SAI remained reproducible between two blinks. Similarly to the previous results this also proved that the topographic image should not be captured when a long time has elapsed after the blink (appr. 30 seconds). Although we still did not know when the ocular surface is the most regular and the most representative. To investigate this the alterations must be analyzed in a more detailed format.

6. With our newly-developed high-speed videotopograph the alterations induced by the tear-film can be accurately followed from the moment of the opening of the eye. According to the literature the rapid movement of the tear-film after the blink takes appr. 1 second and the stable tear layer develops in less than 2 seconds. Our examinations showed that longer time is needed to attain the most regular ocular

surface, which we named first in the world tear-film build up time (3-10 seconds in heathy subjects). At later times the SRI increases, the ocular surface regularity worsens. The tear-film is thinning and finally breaks up, indicated by the significant increase of the SRI. Thus topographic tear-film break-up time could also determined. Our method views the analysis of tear-film stability from another aspect. The fluorescein tear-film break up time used in practice is based on the phenomenon of dry spot formation. This is a specific sign, considering the break-up mechanism. However corneal topographic indices gained with videotopography rather refer to the regularity of the entire ocular surface. Both the SRI and the SAI bring us closer to the optical consequences caused by the changes of the tear-film. It is evident that an irregular surface provides worse optical quality, but the appearance of one dry spot alone may not influence the optical quality of the eye significantly.

The planning of laser-assisted refractive surgical procedures performed on the cornea rely partly on the data provided by the corneal topograph. To achieve the best postoperative visual function it would be advisory to find the ideal time point after blinking individually, when the ocular surface is the most regular. Initially the tear-film is irregular, build-up takes a few seconds, later reproducibility worsens. Therefore our proposal is to obtain videokeratographic images 4-9 seconds after the blink.

7. The tear-film was less regular in dry eye patients than in healthy subjects. After the instillation of artificial tears the tear-film became more regular and the dynamics became similar to the healthy tear-film dynamics.

8. In everyday life incomplete blinks occur frequently, tear-film dynamics is not different under such circumstances than after complete blink. The ocular surface overally was more regular after complete blinking, but the mean build-up and break-up time showed no difference. We concluded that the alterations of the tear-film occur similarly to our study conditions in everyday life in the interblink period.

9. Significant quantitative differences were found in the cornea of dry eye patients

compared with healthy subjects. Superficial and intermediate epithelial cell density was smaller than in healthy subjects ($p<0.01$), which is possibly caused by the enlargement of those cells due to metabolic dysfunction. Intermediate cell density has not been reported in previous investigations. The epithelium and the cornea was thinner in lagophthalmos induced dry eye, than in healthy subjects and other dry eye groups. The number of beadlike formations per mm along the subbasal nerves was significantly higher in lagophthalmos patients compared with the normal group ($p<0.05$). Epithelial and corneal thickness showed significant negative correlation with LIPCOF ($R=-0.50$, $P<0.01$ and $R=-0.64$, $P<0.0001$) and staining ($R=-0.52$, $P<0.01$ and $R=-0.57$, $P<0.001$). The thickness of the epithelium showed significant positive correlation with the total corneal thickness ($R=0.56$; $P<0.01$). Multiple regression analysis showed that LIPCOFs, adjusted for age and the result of other dry eye tests correlated strongly with epithelial thickness at the lower periphery ($R^2=0.25$, $P<0.05$), corneal thickness at the centre ($R^2=0.23$, $P<0.05$) and corneal thickness at the lower periphery ($R^2=0.39$, $P<0.001$).

In a few patients with dysthyroid ophthalmopathy, we found Fuchs-like disorders at the layer of the endothelium, in none of the other groups of subjects did we find similar alterations.

According to our results the most severe corneal symptoms in dry eye can be found in lagophthalmos at the lower paralimbal region. The progress of the condition is well indicated by the presence of LIPCOFs which are detectable during the biomicroscopic examination of the anterior segment.

New results

1 Due to the alterations of the preocular tear-film corneal topography is changing between two successive blinks. SRI, SAI and PVA were found suitable parameters for the assessment of this process.

2 Color-coded topographic maps of the ocular surface were earlier considered an unchanging quality of the individual eye. We found that the pattern is often altered in the interblink interval.

3 The reproducibility of keratometric values worsens significantly with time between two successive blinks.

4 The dynamics of the tear-film was described in healthy and dry eyes, and furthermore the effect of an artificial tear drop using high-speed videotopography.

5 We defined the tear-film build-up time first in the literature. This stands for the time needed to attain the most regular ocular surface after the blink.

6 We determined the non-invasive tear-film break-up time with high-speed videotopography. This presents the stability of the tear-film from a different aspect than the traditional tear-film break-up time.

7 Recommendation was presented for the optimal execution of cornea topographic measurements. According to our suggestion the 4-9 seconds interval after the blink is best for capturing images.

8 After incomplete blinks – common in everyday life – tear-film dynamics is similar to that after the complete blink. Therefore we concluded that our study conditions resemble the true circumstances.

9 Significant signs were found at the epithelium and the subbasal nerves of the cornea in dry eye; the epithelial and corneal thickness was smaller than in the normal control group. These findings correlate strongly with the clinical severity of the disease.

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