Factors Predicting the Ocular Surface Response to Desiccating Environmental Stress

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PURPOSE. To identify factors predicting the ocular surface response to experimental desiccating stress.

METHODS. The ocular surfaces of both eyes of 15 normal and 10 dry eye subjects wearing goggles were exposed to a controlled desiccating environment (15%–25% relative humidity and 2–5 L/min airflow) for 90 minutes. Eye irritation symptoms, blink rate, tear meniscus dimensions, noninvasive (RBUT) and invasive tear break-up time, and corneal fluorescein and conjunctival lissamine green-dye staining were recorded before and after desiccating stress. Pre- and postexposure measurements were compared, and Pearson correlations between clinical parameters before and after desiccating stress were calculated.

RESULTS. Corneal and conjunctival dye staining significantly increased in all subjects following 90-minute exposure to desiccating environment, and the magnitude of change was similar in normal and dry eye subjects; except superior cornea staining was greater in dry eye. Irritation severity in the desiccating environment was associated with baseline dye staining, baseline tear meniscus height, and blink rate after 45 minutes. Desiccation-induced change in corneal fluorescein staining was inversely correlated to baseline tear meniscus width, whereas change in total ocular surface dye staining was inversely correlated to baseline dye staining, RBUT, and tear meniscus height and width. Blink rate from 30 to 90 minutes in desiccating environment was higher in the dry eye than normal group. Blink rate significantly correlated to baseline corneal fluorescein staining and environmental-induced change in corneal fluorescein staining.

CONCLUSIONS. Ocular surface dye staining increases in response to desiccating stress. Baseline ocular surface dye staining, tear meniscus height, and blink rate predict severity of ocular surface dye staining following exposure to a desiccating environment.

Keywords: dry eye, cornea, tears

Tear dysfunction is one of the most common eye diseases with reported prevalence ranging from 2% to 14.4%.^{1–5} Patients with tear dysfunction typically complain of eye irritation symptoms, such as foreign body sensation, burning, and dryness. These symptoms are often reported to worsen in a low humidity airplane cabin environment or during exposure to an air draft from an automobile air conditioner vent. Indeed, some patients with mild-to-moderate dry eye only experience eye irritation when they are exposed to adverse environmental conditions. Exposure to a low humidity environment has been found to increase tear evaporation rate.⁶ Mice exposed to low humidity environmental conditions for days have been found to develop ocular surface epithelial disease, including altered corneal epithelial barrier function.^{7–9}

Demonstrating the clinical efficacy of therapeutic agents for dry eye has proven to be challenging because therapeutic effects must overcome environmentally induced day-to-day and seasonal fluctuations of eye discomfort symptoms and ocular surface signs. Furthermore, there may be wide variation in ambient environmental conditions between geographically distinct testing sites in multicenter clinical trials.

The adverse environmental chamber (AEC) is one approach to standardize environmental conditions in clinical trials and identify patients who develop worsening irritation symptoms and/or ocular surface signs in response to desiccating environmental conditions.¹⁰ Studies evaluating the effects of an AEC on the ocular surface have found trends toward increased severity of discomfort symptoms after exposure to the adverse environment for 90 to 120 minutes as well as statistically significant differences in sign and symptom response in contact lens wearers or between an anti-inflammatory therapy and its vehicle.^{11,12} An AEC was also used to screen for responders in a dry eye clinical trial.¹³ However, AECs are expensive to build and maintain and permit subject evaluation only at sites where the chambers are located. These factors may limit the ability to utilize environmental chambers as a means to recruit subjects or identify responders in multicenter clinical trials. Furthermore, chambers subject not only the eyes but also the entire body to the adverse environment. To provide a cost-effective alternative to the AEC, we designed an environmentally controlled goggle system to

FIGURE 1. Rendition of modified laboratory goggles used to create a drafty low humidity environment around the eye. Ambient air was pumped continuously at a flow rate of 3 L/min through a conditioning system and into the goggles such that the air surrounding the eye and adnexa maintained a relative humidity of 15% to 25% (mean, 21%). Small vents on the top surface of the goggles prevented pressure buildup. Relative humidity (humidity sensor), temperature (thermistor), and airflow were measured by sensors in the goggles and recorded in real time in an electronic database.

deliver a constant flow of dehumidified air while monitoring blink rate.

The purpose of this study was to evaluate the effects of a 90-minute exposure of the ocular surface to desiccating environmental stress in a cohort of normal subjects and dry eye patients, using our environmentally controlled goggles, on conventional efficacy parameters used in Food and Drug Administration (FDA) clinical trials, including eye irritation symptoms, tear break-up time, and ocular surface dye staining. Blink rate was also assessed as a reflexive measure of ocular surface discomfort.

METHODS

The Baylor College of Medicine Institutional Review Board approved this study. All subjects were treated in accordance with the Declaration of Helsinki. Twenty-five subjects were

recruited to participate after informed consent. Subjects were classified as having dry eye if they fulfilled at least two of the following criteria: eye irritation symptom severity score ≥ 8 (sum of visual analog scale and questionnaire), ocular surface dye staining (mean total conjunctival lissamine green staining ≥ 3 plus mean total corneal fluorescein staining ≥ 2), tear break-up time ≤ 6 seconds. Patients were diagnosed with Sjögren syndrome aqueous tear deficiency based on published criteria.¹⁴

Experimental Desiccating Environment

Subjects wearing a pair of modified laboratory goggles in which a desiccating environment was created watched a movie for 90 minutes on a video monitor positioned 1 m away (Fig. 1). A 90-minute test period was chosen because this interval has been used in previously published FDA clinical trials that utilized a controlled adverse environmental chamber and because increases in total corneal and conjunctival staining were observed in an a pilot study of 10 subjects (five normal and five dry eye).^{12,13} Ambient air was pumped continuously at a flow rate of 2 to 5 L/min through a conditioning system into the goggles such that the air surrounding the eye and adnexa maintained a relative humidity of 15% to 25% (mean, 21%) throughout the test period. Small vents in the goggles prevented pressure buildup for maximum comfort. Relative humidity, temperature, and airflow were measured every 10 seconds over the test period by sensors in the goggles and were recorded in an electronic database. A representative graph of humidity and airflow during the evaluation is presented in Figure 2.

Blink Measurement

Blink rate was monitored by electromyography (EMG) using BIOPAC EL504 electrodes (Vermed, Bellow Falls, VT) embedded in the padded superior rim of the goggles. Each blink was translated into a direct current signal and shown as a real-time waveform in LabVIEW (National Instruments, Austin, TX). A blink threshold specific to each subject was determined visually and set by the device operator prior to each trial such that blink readings were accurate within $\pm 5\%$.

FIGURE 2. Graph of percentage relative humidity and airflow (L/min) measurements taken every 10 seconds over the 90-minute test period from a representative subject.

TABLE 1. Subject Demographic Data

	Age, mean $\pm$ SD	Sex (F/M)
Normal ($n = 15$)	31.4 $\pm$ 17.8	6/9 (0.667)
Dry eye ($n = 10$)	53.7 $\pm$ 14.0	9/1 (9.000)

Ocular Surface and Tear Evaluations

All subjects underwent a comprehensive subjective and objective examination described below to classify subjects as normal or dry eye before exposure to the desiccating environment. Severity of eye irritation symptoms was measured with a questionnaire adapted from the Ocular Surface Disease Index (OSDI)¹⁵ containing five questions that recorded frequency of photophobia, gritty/sandy, burning/stinging, blurred vision, and fluctuation of vision symptoms, plus a 5-unit visual analog scale measuring the severity of irritation. The sum score of these instruments ranged from 0 to 30.

Fluorescein tear break-up time (TBUT), corneal fluorescein staining, and conjunctival lissamine green staining were performed as previously described.¹⁶ Ocular surface dye staining was graded in real time and in digital images captured with the Eyecap digital imaging system (Haig Streit, Mason, OH). Noninvasive tear break-up time (RBUT) was measured with the Tear Stability Analysis System (Tomey, Phoenix, AZ) as previously described.¹⁷

Tear meniscus height and width were measured noninvasively by anterior segment optical coherence tomography (OptoVue, RTVue, Fremont, CA) as previously reported.¹⁸

Statistical Analyses

Sample size calculations were performed using StatMate (GraphPad, La Jolla, CA) using results from a pilot trial of 10 subjects (five normal and five dry eye). A sample size of 25 subjects was calculated to have 90% power of detecting a significant difference ($\alpha = 0.05$) in total corneal staining before and after low humidity environmental challenge. The data were analyzed using GraphPad Prism (GraphPad). Normality of the data was determined with the D'Agostino and Pearson Omnibus normality test. Differences in mean values between groups were evaluated with the Student's *t*-test. Pearson correlation coefficients between parameters were calculated.

A *P* value of ≤ 0.05 was considered to be statistically significant.

RESULTS

Twenty-five subjects were recruited, 15 with no signs or symptoms of dry eye and 10 fulfilling the diagnostic criteria for dry eye. All of the dry eye subjects had aqueous tear deficiency (a tear meniscus height ≤ 205 μ m) and four had Sjögren syndrome. Demographic data are provided in Table 1.

Baseline Tear and Ocular Surface Parameters

Statistically significant differences in baseline tear and ocular surface values were found between normal and dry eye subjects (Table 2). On average, dry eye subjects had increased baseline irritation symptom scores, decreased TBUT, decreased tear meniscus height and width, increased corneal and conjunctival staining in every individual area, and increased total (corneal + conjunctival) staining compared with normal subjects.

Tear and Ocular Surface Response to the Desiccating Environment

The subjective and objective responses of all subjects to a controlled desiccating environment delivered in goggles for 90 minutes were measured and are summarized in Table 3. All subjects, except for one with severe dry eye, tolerated the goggles well. The patient who did not tolerate the goggles requested to stop after 45 minutes owing to irritation. When all subjects (normal and dry eye) were combined, the inferior cornea, all areas of the conjunctiva, and total ocular surface showed significant increases in staining compared with baseline after exposure to the desiccating environment. Figure 3 shows the magnitude of change in dye staining in each region of the cornea and conjunctiva.

Change from baseline values for both the normal and dry eye groups and comparative differences in change between the two groups were calculated for all tear and ocular surface parameters and are presented in Table 4. No significant change from baseline was found in either group for irritation symptoms, RBUT, tear meniscus height or width, staining in the nasal cornea, temporal cornea, central cornea or superior

TABLE 2. Tear and Ocular Surface Parameters at Baseline

Parameter	All, $n = 25$	Normal, $n = 15$	Dry Eye, $n = 10$	NL vs. DE
	Mean $\pm$ SEM (SD)	Mean $\pm$ SEM (SD)	Mean $\pm$ SEM (SD)	<i>P</i> Value
Irritation symptoms	9.12 $\pm$ 0.89 (4.43)	7.20 $\pm$ 0.71 (2.731)	12.00 $\pm$ 1.59 (5.033)	<0.01
TBUT	7.36 $\pm$ 0.92 (4.59)	9.41 $\pm$ 1.25 (4.85)	4.28 $\pm$ 0.45 (1.43)	<0.01
RBUT	144.9 $\pm$ 45.71 (219.2)	84.68 $\pm$ 49.13 (183.8)	238.5 $\pm$ 82.33 (247.0)	0.10
Tear meniscus height	208.4 $\pm$ 107.5 (21.51)	267.8 $\pm$ 21.85 (84.64)	119.2 $\pm$ 22.28 (70.44)	0.0001
Tear meniscus width	158.9 $\pm$ 20.94 (104.7)	217.9 $\pm$ 21.92 (84.91)	70.30 $\pm$ 18.71 (59.17)	<0.0001
Cornea staining inferior	1.82 $\pm$ 0.37 (1.87)	0.60 $\pm$ 0.13 (0.51)	3.65 $\pm$ 0.52 (0.17)	<0.0001
Cornea staining nasal	1.42 $\pm$ 0.40 (1.98)	0.13 $\pm$ 0.06 (0.2289)	3.35 $\pm$ 0.59 (1.87)	<0.0001
Cornea staining temporal	1.04 $\pm$ 0.37 (1.83)	0.00 $\pm$ 0.00 (0.00)	2.60 $\pm$ 0.66 (2.09)	<0.0001
Cornea staining central	1.04 $\pm$ 0.35 (1.74)	0.03 $\pm$ 0.033 (0.13)	2.55 $\pm$ 0.62 (1.96)	<0.0001
Cornea staining superior	0.62 $\pm$ 0.24 (1.184)	0.00 $\pm$ 0.00 (0.00)	1.55 $\pm$ 0.46 (1.46)	0.0004
Cornea staining total	5.98 $\pm$ 1.63 (8.12)	0.83 $\pm$ 0.17 (0.65)	13.70 $\pm$ 2.5 (8.06)	<0.0001
Conjunctiva staining nasal	2.40 $\pm$ 0.41 (2.06)	1.07 $\pm$ 0.30 (1.16)	4.40 $\pm$ 0.43 (1.35)	<0.0001
Conjunctiva staining temporal	1.88 $\pm$ 0.43 (2.16)	0.37 $\pm$ 0.23 (0.90)	4.15 $\pm$ 0.40 (1.270)	<0.0001
Conjunctiva staining total	4.28 $\pm$ 0.82 (4.09)	1.43 $\pm$ 0.47 (1.81)	8.55 $\pm$ 0.76 (2.41)	<0.0001
Total ocular surface staining	10.26 $\pm$ 2.38 (11.91)	2.27 $\pm$ 0.56 (2.19)	22.25 $\pm$ 3.23 (10.22)	<0.0001

NL, normal; DE, dry eye.

TABLE 3. Change From Baseline—All Subjects

Parameter	All Subjects (<i>n</i> = 25)		
	Pre Mean ± SEM (SD)	Post Mean ± SEM (SD)	<i>P</i> Value
Irritation symptoms	9.0 ± 0.91 (4.48)	8.93 ± 0.86 (4.2)	0.92
TBUT	7.35 ± 0.91 (4.67)	7.29 ± 1.04 (5.22)	0.86
RBUT	141.8 ± 43.87 (214.9)	91.49 ± 24.98 (122.4)	0.19
Tear meniscus height	208.4 ± 21.51 (107.5)	253.1 ± 34.89 (44.72)	0.12
Tear meniscus width	158.9 ± 20.94 (104.7)	184.9 ± 27.30 (136.5)	0.2778
Cornea staining inferior	1.82 ± 0.37 (1.87)	2.68 ± 0.47 (2.35)	0.0003
Cornea staining nasal	1.42 ± 0.40 (1.98)	1.44 ± 0.40 (2.00)	0.91
Cornea staining temporal	1.04 ± 0.37 (1.83)	1.60 ± 0.63 (3.13)	0.14
Cornea staining central	1.04 ± 0.35 (1.74)	1.28 ± 0.44 (2.20)	0.26
Cornea staining superior	0.62 ± 0.24 (1.18)	0.82 ± 0.29 (1.4)	0.12
Cornea staining total	5.98 ± 1.63 (8.12)	7.56 ± 1.95 (9.75)	0.017
Conjunctiva staining nasal	2.40 ± 0.41 (2.06)	3.38 ± 0.41 (2.03)	<0.0001
Conjunctiva staining temporal	1.88 ± 0.43 (2.16)	2.16 ± 0.45 (2.23)	0.01
Conjunctiva staining total	4.28 ± 0.82 (4.09)	5.54 ± 0.81 (4.01)	<0.0001
Total ocular surface staining	10.26 ± 2.38 (11.91)	13.88 ± 3.05 (15.24)	0.0007

Pre indicates values before desiccating environmental challenge with goggles. Post indicates values after desiccating environmental challenge with goggles.

cornea, and staining in the temporal conjunctiva. TBUT significantly decreased only in the dry eye group, while total cornea staining increased only in the normal group. Significant increases in inferior cornea staining, nasal conjunctiva staining, and total conjunctiva staining were observed in both normal and dry eye groups. Change from baseline in superior corneal staining was the only sign that showed a significant difference between groups.

Parameters Predicting Ocular Surface Response to the Desiccating Environment

Irritation severity scores after 45 or 90 minutes of low humidity exposure were significantly correlated ($P \leq 0.05$) with the severity of baseline corneal ($r^2 = 0.39$ and 0.39 , respectively) and ocular surface ($r^2 = 0.44$ and 0.43 , respectively) dye staining, baseline tear meniscus height ($r^2 = -0.47$ at 45 minutes) and blink rate ($r^2 = 0.72$ and 0.47 , respectively). Correlations were performed between baseline measurements and change from baseline for all objective parameters (Table 5). Baseline cornea, conjunctiva, and total staining were found to be significantly correlated with baseline tear meniscus height and width and with baseline TBUT. Significant correlations were found between baseline cornea, conjunctiva, and total staining and the change in total staining. Baseline tear meniscus height and baseline RBUT were also significantly correlated with the change in total ocular surface staining. Baseline tear meniscus width was noted to correlate with change in corneal staining. These findings indicate that the severity of baseline corneal dye staining, tear meniscus height, and RBUT predict the ocular surface response to a desiccating environment, with baseline corneal fluorescein staining having the strongest correlation ($r^2 = 0.40$).

Blink Rate Measurements

There was a numerical, but not significant, increase in blink rate during the 90-minute exposure to the desiccating environment. Compared with the normal group, blink rate was statistically greater in the dry eye group at all time points after 15 minutes (Fig. 4). Correlations were performed between blink rate at baseline and change from baseline measurements (Table 6). Blink rate at all time points after 15 minutes was positively correlated with the severity of cornea

staining or total cornea and conjunctival staining and negatively correlated with TBUT and tear meniscus width at baseline. Blink rate at one or more time points correlated with the change in corneal and total ocular surface staining.

DISCUSSION

This study used novel climate-controlled goggles to subject the ocular surface to a regulated drafty low humidity environment. The effects of this environmental challenge were evaluated on normal and dry eye subjects. The study was powered to detect differences in corneal fluorescein staining before and after the environmental challenge. Ocular surface disease, measured by increased inferior and total corneal and nasal and temporal bulbar conjunctival dye staining significantly increased in all subjects following 90-minute exposure to the desiccating environment. Of interest, the magnitude of change was similar in normal and dry eye subjects, except for the superior cornea where greater staining developed in subjects with dry eye. Although dry eye subjects complained of more eye irritation before the challenge, there was no change in mean irritation symptoms in the dry eye or control groups during the 90-minute test period. These findings indicate that even a normal ocular surface is susceptible to developing ocular surface disease in response to low humidity environmental challenge. They also indicate that irritation symptoms don't always accompany development of ocular surface epithelial disease in this type of environmental challenge. It is possible that

FIGURE 3. Percentage change from baseline in severity of fluorescein staining in five zones on the cornea and lissamine green staining in nasal and temporal bulbar conjunctiva.

TABLE 4. Change From Baseline—Normal and Dry Eye Subjects

Parameter	Normal (<i>n</i> = 15)				Dry Eye (<i>n</i> = 10)				NL vs. DE	
	Pre Mean ± SEM (SD)	Post Mean ± SEM (SD)	<i>P</i> Value		Pre Mean ± SEM (SD)	Post Mean ± SEM (SD)	<i>P</i> Value		<i>P</i> Value	
Irritation symptoms	7.20 ± 0.71 (2.7)	7.28 ± 0.59 (2.30)	0.93		12.00 ± 1.59 (5.03)	12.00 ± 1.63 (5.16)	1.00		0.96	
TBUT	9.40 ± 1.25 (4.83)	9.79 ± 1.39 (5.38)	0.46		4.28 ± 0.45 (1.43)	3.53 ± 0.38 (1.20)	<0.01		0.23	
RBUT	83.80 ± 45.75 (177.2)	40.28 ± 12.68 (49.10)	0.36		238.5 ± 82.33 (247.0)	176.9 ± 53.47 (160.4)	0.40		0.82	
Tear meniscus height	267.8 ± 21.85 (84.64)	319.9 ± 47.81 (185.2)	0.27		119.2 ± 22.28 (70.44)	152.9 ± 30.36 (96.01)	0.06		0.66	
Tear meniscus width	217.9 ± 21.92 (84.91)	243.5 ± 36.92 (143.0)	0.52		70.30 ± 18.71 (59.17)	97.05 ± 18.92 (59.83)	0.11		0.78	
Cornea staining inferior	0.60 ± 0.13 (0.51)	1.37 ± 0.35 (1.37)	0.01		3.650 ± 0.52 (1.65)	4.65 ± 0.68 (2.16)	0.01		0.59	
Cornea staining nasal	0.13 ± 0.06 (0.23)	0.27 ± 0.21 (0.80)	0.47		3.35 ± 0.59 (1.87)	3.20 ± 0.62 (1.98)	0.68		0.44	
Cornea staining temporal	0.00 ± 0.000 (0.00)	0.00 ± 0.00 (0.00)	0.33		2.60 ± 0.66 (2.09)	4.00 ± 1.24 (3.92)	0.15		0.06	
Cornea staining central	0.03 ± 0.03 (0.14)	0.00 ± 0.00 (0.00)	0.33		2.55 ± 0.62 (1.96)	3.20 ± 0.78 (2.46)	0.23		0.11	
Cornea staining superior	0.00 ± 0.00	0.00 ± 0.00	0.33		1.55 ± 0.46 (1.46)	2.05 ± 0.52 (1.66)	0.12		0.04	
Cornea staining total	0.83 ± 0.17 (0.65)	1.63 ± 0.46 (1.78)	0.03		13.70 ± 2.55 (8.06)	16.45 ± 3.19 (10.09)	0.08		0.12	
Conjunctiva staining nasal	1.07 ± 0.30 (1.16)	2.30 ± 0.45 (1.74)	0.0008		4.40 ± 0.43 (1.35)	5.00 ± 0.38 (1.2)	0.003		0.10	
Conjunctiva staining temporal	0.37 ± 0.23 (0.90)	0.60 ± 0.24 (0.91)	0.07		4.15 ± 0.40 (1.27)	4.50 ± 0.42 (1.33)	0.09		0.60	
Conjunctiva staining total	1.43 ± 0.47 (1.81)	2.90 ± 0.62 (2.40)	0.0009		8.55 ± 0.76 (2.41)	9.50 ± 0.74 (2.3)	0.0025		0.20	
Total ocular surface staining	2.27 ± 0.56 (2.19)	4.53 ± 0.98 (3.81)	0.002		22.25 ± 3.23 (10.22)	25.95 ± 3.81 (12.05)	0.02		0.08

FIGURE 4. Blink rate. Lines show the mean ± SD of blink rate in the normal control and dry eye groups. Asterisks indicate significant differences between the groups ($P < 0.05$).

induction of reflex tearing, indicated by an increase in inferior tear meniscus height may have prevented some of the irritation.

A previous study that evaluated the effects of a 2-hour exposure to a controlled low humidity environment in an AEC reported that contact lens-wearing subjects experienced worsening eye discomfort while wearing their lenses, but not without them.¹¹ Noninvasive tear break-up time decreased both with and without lenses, and conjunctival dye staining increased without lenses. The environmentally controlled goggles used in the current study appeared to have caused greater magnitude of ocular surface disease than was observed in this AEC study, and they appear to be an effective and more economical alternative method for presenting a low-humidity environmental challenge directly to the ocular surface, without exposing the entire body to desiccating stress.

Because dry eye includes a spectrum of diseases resulting from perturbations of tear production, tear stability and/or tear spread, we performed correlation analyses to determine if certain factors predicted greater ocular surface dye staining and eye irritation in response to the desiccating environmental challenge. Baseline dye-staining scores and tear meniscus parameters, as well as increased blink rate at 60 and 90 minutes of adverse environmental exposure, correlated with greater change in total ocular surface staining. With regard to eye irritation, baseline corneal and total staining and tear meniscus height and blink rate at 45 minutes were associated with worse symptoms. The ability to predict which factors increase susceptibility to respond to a low-humidity environmental challenge may aid in screening subjects with environmentally modifiable disease to participate in dry eye therapeutic trials.

The association between decreased tear meniscus and desiccation-induced worsening of signs and symptoms suggests that patients with compromise of the integrated lacrimal functional unit (LFU) are more susceptible to adverse environmental challenge. The LFU regulates tear secretion onto the ocular surface in response to environmental conditions. Tear dysfunction develops when the integrated LFU can no longer respond to an adverse environmental challenge because of disease or dysfunction of one or more of its components.¹ A number of ocular and systemic conditions have been identified that affect reflex tearing by the LFU, including Sjögren syndrome, use of systemic anticholinergic medications, and autonomic and sensory neuropathies.^{19,20} Indeed the severity of ocular surface disease was found to be worse in Sjögren syndrome, a condition where the ability to reflex tear is lost early in the course of the disease.²¹ Only four subjects with Sjögren syndrome were evaluated in this pilot study, therefore it is not possible to determine if the ocular

TABLE 5. Correlations Between Baseline Objective Measurements and Change From Baseline

	Baseline Total Staining	Baseline Corneal Staining	Baseline Conj Staining	Change Total Staining	Change Corneal Staining	Change Conj Staining	Baseline TBUT	Change TBUT	Baseline RBUT	Change RBUT	Baseline Tear Men Ht	Change Tear Men Ht	Baseline Tear Men Wd	Change Tear Men Wd
Baseline total staining		$P < 0.0001$ $r^2 = 0.97$	$P < 0.0001$ $r^2 = 0.90$	$P = 0.001$ $r^2 = 0.37$	$P = 0.05$ $r^2 = 0.16$	$P = NS$ $r^2 = 0.02$	$P = 0.002$ $r^2 = 0.35$	$P = NS$ $r^2 = 0.05$	$P = 0.01$ $r^2 = 0.25$	$P = NS$ $r^2 = 0.01$	$P < 0.0001$ $r^2 = 0.54$	$P = NS$ $r^2 = 0.03$	$P < 0.0001$ $r^2 = 0.58$	$P = 0.0NS$ $r^2 = 0.01$
Baseline corneal staining			$P < 0.0001$ $r^2 = 0.79$	$P < 0.001$ $r^2 = 0.40$	$P = NS$ $r^2 = 0.15$	$P = NS$ $r^2 = 0.02$	$P = 0.004$ $r^2 = 0.30$	$P = NS$ $r^2 = 0.03$	$P = 0.006$ $r^2 = 0.30$	$P = NS$ $r^2 = 0.03$	$P < 0.0001$ $r^2 = 0.52$	$P = NS$ $r^2 = 0.02$	$P < 0.0001$ $r^2 = 0.52$	$P = NS$ $r^2 = 0.01$
Baseline conj staining				$P = 0.008$ $r^2 = 0.27$	$P = 0.05$ $r^2 = 0.16$	$P = NS$ $r^2 = 0.03$	$P < 0.001$ $r^2 = 0.38$	$P = NS$ $r^2 = 0.08$	$P = NS$ $r^2 = 0.14$	$P = NS$ $r^2 = 0.001$	$P < 0.0001$ $r^2 = 0.50$	$P < 0.05$ $r^2 = 0.05$	$P < 0.0001$ $r^2 = 0.62$	$P = NS$ $r^2 = 0.01$
Change total staining					$P < 0.001$ $r^2 = 0.67$	$P = NS$ $r^2 = 0.03$	$P = NS$ $r^2 = 0.14$	$P = NS$ $r^2 = 0.004$	$P = 0.01$ $r^2 = 0.24$	$P = NS$ $r^2 = 0.05$	$P = 0.01$ $r^2 = 0.25$	$P = NS$ $r^2 = 0.08$	$P = 0.005$ $r^2 = 0.30$	$P = NS$ $r^2 = 0.01$
Change corneal staining						$P = NS$ $r^2 = 0.002$	$P = NS$ $r^2 = 0.12$	$P = NS$ $r^2 = 0.02$	$P = NS$ $r^2 = 0.05$	$P = NS$ $r^2 = 0.002$	$P = NS$ $r^2 = 0.1$	$P = NS$ $r^2 = 0.03$	$P = 0.03$ $r^2 = 0.19$	$P = NS$ $r^2 = 0.01$
Change conj staining							$P = NS$ $r^2 = 0.02$	$P = NS$ $r^2 = 0.004$	$P = NS$ $r^2 = 0.03$	$P = NS$ $r^2 = 0.07$	$P = NS$ $r^2 = 0.001$	$P = 0.06$ $r^2 = 0.01$	$P = NS$ $r^2 = 0.01$	$P = NS$ $r^2 = 0.001$
Baseline TBUT								$P = NS$ $r^2 = 0.05$	$P = NS$ $r^2 = 0.004$	$P = NS$ $r^2 = 0.03$	$P = NS$ $r^2 = 0.09$	$P < 0.01$ $r^2 = 0.27$	$P = 0.02$ $r^2 = 0.20$	$P = NS$ $r^2 = 0.09$
Change TBUT									$P = NS$ $r^2 = 0.007$	$P = NS$ $r^2 = 0.01$	$P = NS$ $r^2 = 0.03$	$P = NS$ $r^2 = 0.05$	$P = NS$ $r^2 = 0.11$	$P = NS$ $r^2 = 0.03$
Baseline RBUT										$P < 0.001$ $r^2 = 0.68$	$P = 0.008$ $r^2 = 0.28$	$P = NS$ $r^2 = 0.001$	$P = 0.04$ $r^2 = 0.2$	$P = NS$ $r^2 = 0.004$
Change RBUT											$P = NS$ $r^2 = 0.12$	$P = NS$ $r^2 = 0.01$	$P = NS$ $r^2 = 0.02$	$P = NS$ $r^2 = 0.03$
Baseline tear men height												$P = NS$ $r^2 = 0.001$	$P < 0.0001$ $r^2 = 0.57$	$P = NS$ $r^2 = 0.01$
Change tear men height												$P = NS$ $r^2 = 0.001$	$P = NS$ $r^2 = 0.51$	$P < 0.001$ $r^2 = 0.51$
Baseline tear men width													$P = NS$ $r^2 = 0.01$	$P = NS$ $r^2 = 0.03$
Change tear men width														

Tear Men Ht, tear meniscus height; Tear Men Wd, tear meniscus width; NS, nonsignificant.

TABLE 6. Correlations Between Blink Rate With Baseline Parameters and Response to Desiccating Environment

	Baseline Total Staining		Change Total Staining		Baseline Conj Staining		Change Conj Staining		Baseline Corneal Staining		Change Corneal Staining		Baseline TBUT		Change TBUT		Baseline RBUT		Change RBUT		Baseline Tear Men Ht		Change Tear Men Ht		Baseline Tear Men Wd		Change Tear Men Wd	
	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²	P	r ²
BR at 15 min	P = NS	r ² = 0.1	P = 0.002	r ² = 0.36	P = NS	r ² = 0.05	P = NS	r ² = 0.32	P = NS	r ² = 0.04	P = NS	r ² = 0.02	P = 0.02	r ² = 0.22	P = NS	r ² = 0.01	P = NS	r ² = 0.001	P = NS	r ² = 0.02	P = NS	r ² = 0.07	P = NS	r ² = 0.01	P = NS	r ² = 0.08	P = NS	r ² = 0.08
BR at 30 min	P = 0.004	r ² = 0.42	P = 0.004	r ² = 0.41	P = 0.005	r ² = 0.40	P = NS	r ² = 0.16	P = 0.01	r ² = 0.34	P = NS	r ² = 0.004	P = 0.03	r ² = 0.26	P = NS	r ² = 0.03	P = NS	r ² = 0.03	P = NS	r ² = 0.02	P = NS	r ² = 0.05	P = NS	r ² = 0.28	P = NS	r ² = 0.01	P = NS	r ² = 0.01
BR at 45 min	P = 0.001	r ² = 0.42	P = 0.001	r ² = 0.40	P = 0.002	r ² = 0.36	P = NS	r ² = 0.11	P = NS	r ² = 0.13	P = NS	r ² = 0.05	P = 0.02	r ² = 0.21	P = NS	r ² = 0.03	P = NS	r ² = 0.02	P = NS	r ² = 0.02	P = NS	r ² = 0.01	P = NS	r ² = 0.02	P = NS	r ² = 0.02	P = NS	r ² = 0.02
BR at 60 min	P = 0.007	r ² = 0.34	P = 0.01	r ² = 0.36	P = 0.006	r ² = 0.41	P = NS	r ² = 0.03	P = 0.01	r ² = 0.36	P = NS	r ² = 0.005	P = 0.005	r ² = 0.42	P = NS	r ² = 0.03	P = NS	r ² = 0.04	P = NS	r ² = 0.13	P = NS	r ² = 0.15	P = NS	r ² = 0.33	P = NS	r ² = 0.05	P = NS	r ² = 0.05
BR at 75 min	P = 0.01	r ² = 0.34	P = 0.03	r ² = 0.28	P = 0.003	r ² = 0.45	P = NS	r ² = 0.11	P = NS	r ² = 0.16	P = NS	r ² = 0.01	P < 0.01	r ² = 0.4	P = NS	r ² = 0.04	P = NS	r ² = 0.16	P = NS	r ² = 0.09	P = NS	r ² = 0.17	P = NS	r ² = 0.30	P = NS	r ² = 0.03	P = NS	r ² = 0.03
BR at 90 min	P = 0.002	r ² = 0.38	P = 0.005	r ² = 0.33	P = 0.001	r ² = 0.44	P = NS	r ² = 0.040	P = NS	r ² = 0.15	P = NS	r ² = 0.003	P = 0.002	r ² = 0.39	P = NS	r ² = 0.02	P = NS	r ² = 0.13	P = NS	r ² = 0.07	P = NS	r ² = 0.12	P = NS	r ² = 0.21	P = NS	r ² = 0.05	P = NS	r ² = 0.05

BR, blink rate; conj, conjunctiva; NS, nonsignificant.

surface in patients with this condition is more susceptible to ocular surface disease than that of patients with preserved reflex tearing.

Our environmentally controlled goggles contain a blink sensor that records blink impulses in real time. This objective method has advantages over measuring blink rate visually during the trial or in video recordings. We observed an increase in blink rate in both groups, and this was significantly greater in the dry eye group. The increase in blink rate during the challenge suggests that dry eye subjects were more sensitive to the adverse environment. Blink rate may prove to be a good noninvasive objective measure of dry eye-induced sensory reflex stimulation that is not dependent on the ability of a questionnaire to adequately capture the subjective response to the challenge.

The goggles may prove to be a useful tool to evaluate the efficacy of therapies administered before the environmental challenge to blunt the ocular surface response to short-term desiccation in patients with tear dysfunction. Comparing the severity of parameters before and after the environmental challenge could potentially reduce some of the pitfalls of conventional environmental studies that must demonstrate efficacy greater than the day-to-day and seasonal variations in the signs and symptoms that occur during clinical trials spanning many months. While this study was designed and powered to evaluate the effects of short-term desiccating stress on corneal fluorescein staining, the conventional efficacy parameter in FDA clinical trials, these environmentally controlled goggles might also be valuable in studying the effects of short-term exposure to a desiccating environment on expression of stress-related genes by ocular surface cells.

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