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Authors
Lin, Meng C
Polse, Kenneth A

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Hypoxia, Overnight Wear, and Tear Stagnation Effects on the Corneal Epithelium: Data and Proposed Model

Meng C. Lin, O.D., Ph.D. and Kenneth A. Polse, O.D., M.S.

Purpose. To explore the possible mechanisms that may lead to overnight contact lens–associated corneal morbidity by examining data from several corneal epithelial permeability experiments obtained under different environmental and lens fitting paradigms. **Methods.** Epithelial permeability was assessed by using fluorometry to determine the fluorescein penetration rate from the tear film into the corneal stroma. Changes in this rate provide an index of the corneal epithelial status; increased permeability leads to decreased barrier function. **Results.** Hypoxia and tear stagnation during overnight lens wear play a significant role in altering the corneal epithelial barrier function ($P<0.05$). However, eliminating lens-induced hypoxia alone does not ameliorate changes in epithelial status ($P<0.05$). **Conclusions.** Based on data from these experiments, it is suggested that hypoxia and tear stagnation should be eliminated to minimize alteration of the corneal epithelium associated with overnight contact lens wear.
Key Words: Barrier function—Contact lenses—Cornea—Epithelium—Hypoxia.

When continuous-wear silicone hydrogel lenses first became available, it was widely believed that most of the serious clinical events associated with extended-wear soft lenses would be eliminated because of the high oxygen transmissibility (Dk/t) of the silicone materials.[1,2] Unfortunately, this has not been the case, and several recent studies have shown that the incidence rates of the more worrisome clinical events (e.g., infection and inflammation) are similar to those observed with extended-wear conventional soft contact lenses.[1,2] It now seems clear that to avoid many of the complications associated with continuous wear, not only must hypoxia be eliminated, but it also may be necessary to consider how other factors related to lens–eye interactions could affect corneal status. Such factors include lens performance (e.g., lens movement, position, and pressure exerted on the ocular surface), lens surface properties, prelens and postlens tear film thickness, and the rate of postlens tear flushing. A more complete understanding of the corneal response that may result from these lens–eye interactions could provide additional information to develop new lens designs and materials, which may reduce corneal morbidity associated with overnight wear. To evaluate the effects of lens performance on corneal integrity, a sensitive measurement to quantify changes in corneal status is needed.

One strategy that the authors' research team has used to quantify the subclinical effects (i.e., not observed with a standard biomicroscopic examination) of contact lenses on the corneal status is to estimate the epithelial barrier function by measuring the penetration rate of sodium fluorescein through the cornea.[3,4] The rate of fluorescein dye penetration is termed *epithelial permeability* (P_{dc}), which is inversely related to the epithelial barrier function.

This method was adopted because the tight junctions in the corneal epithelium normally restrict the amount and flow rate of fluorescein from the tears into the cornea; therefore, changes in the fluorescein penetration rate provide an index of altered epithelial barrier function. The permeability measurement is made by applying a specified volume and concentration of dye to the tears and metering the fluorescent light intensity as it changes from the tears to the stroma. An increased uptake in fluorescein dye (i.e., increased permeability) is a reflection of disrupted tight junctions in the epithelium (i.e., reduced epithelial barrier function). The permeability measurement can detect subclinical changes in the epithelium and therefore provides a highly sensitive index to monitor subtle changes in corneal status.

This report summarizes data from several corneal epithelial permeability experiments obtained under different environmental and lens fitting paradigms. Based on these data, a model is proposed to show how the corneal epithelium is affected by contact lens wear.

MATERIALS AND METHODS

Study Procedures

One-Hour Closed-Eye Experiments With Soft Lenses

One eye of each subject was randomly allocated to soft lens wear, and the other eye wore no lens and served as a control. After lens insertion, the eyes were closed for 1 hour. After the 1-hour closed-eye period, permeability measurements and slitlamp assessment were performed.

One-Hour Open-Eye Goggle Experiments With Soft Lenses

Subjects wore airtight goggles in which a mixture of humidified 95% nitrogen and 5% carbon dioxide (anoxia) was passed across the cornea for 1 hour in both eyes. The control eye did not wear a lens, and the test eye wore soft lenses. After 1 hour, permeability measurements and slitlamp assessment were performed to determine the effects of different soft lenses on the corneal epithelium.

From the School of Optometry, University of California, Berkeley, CA.
Address correspondence and reprint requests to Dr. M.C. Lin, 360 Minor Hall, MC 2020, School of Optometry, University of California, Berkeley, CA 94720-2020; e-mail: mlin@berkeley.edu
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TABLE 1. *Values of Natural Logarithm of Epithelial Permeability in 1-Hour Studies*

Study paradigm	No.	Test eye (mean ln[P_{dc}] ± standard error, nm/sec	Control eye (mean ln[P_{dc}] ± standard error, nm/sec)	*P* value (*t* test)
Closed eyes				
Low-Dk/t soft contact lens in test eye and no lens in control eye	32	–2.35 ± 0.02	–2.69 ± 0.03	0.016
High-Dk/t soft contact lens in test eye and no lens in control eye	32	–2.88 ± 0.10	–2.68 ± 0.09	0.055
Open eyes				
No lenses in either eye	35	–2.70 ± 0.10 (hypoxia)	–2.51 ± 0.09 (normoxia)	0.270
Etafilcon A lens in test eye and no lens in control eye	28	–2.65 ± 0.09 (hypoxia)	–2.74 ± 0.00 (hypoxia)	0.454
Lotrafilcon A lens in test and no lens in control eye	32	–2.57 ± 0.08 (hypoxia)	–2.71 ± 0.09 (hypoxia)	0.121

One-Hour Open-Eye Goggle Experiments Without Lenses

Subjects wore airtight goggles in which a mixture of humidified 95% nitrogen and 5% carbon dioxide (anoxia) was passed across the cornea in one eye, and the fellow eye was exposed to air (normoxia) and served as the control. After 1 hour, permeability measurements and slitlamp assessment were performed to determine whether hypoxia alone would induce changes in the corneal epithelium.

Extended- and Continuous-Wear Experiments

All studies described later, except the 1-hour studies. used similar protocols in which afternoon and morning P_{dc} was measured. Afternoon permeability measurements were taken a minimum of 4 hours after awakening, whereas morning P_{dc} was obtained within 2 hours. All research participants were instructed to patch one eye before sleep the night before their morning visits to allow for the assessment of the P_{dc} measurement immediately after eye opening, whereas the unpatched eye had been open for no more than 2 hours. On completion of each set of P_{dc} measurements, corneal staining was graded according to a scale from 0 to 4, whereby 0 is no observable staining; 1 is no more than 5 punctate staining; 2 is no more than 10 punctate staining; 3 is no more than 25 punctate staining; and 4 is more than 25 punctate staining. Only corneas that would be considered normal (e.g., less than grade 1) by standard clinical slitlamp examination were used in the P_{dc} analysis. Therefore, the P_{dc} data provided in this article represent conservative estimates of changes in the epithelial barrier function.

Instrumentation

An automated scanning fluorometer (Fluorotron Master; Ocumetrics, Mountain View, CA) was used to obtain the permeability measurements. This instrument passes a 100-nm bandwidth of blue light from the tears to the anterior chamber in 5 to 8 seconds. Measurements are repeated during a 20-minute testing period to generate a single profile of the combined tear film and corneal fluorescence. The area under this fluorescence profile is proportional to the fluorescein mass encountered along the scan path. The repeatability of this method was evaluated, and a reliable group mean index was found for detecting a 25% difference in barrier function with 95% confidence and 80% power when groups of 32 or more subjects are used. Details of the experimental methods, instrumentation, and calculation of P_{dc} values have been described previously.[4]

Data Analysis

For all experiments, the raw P_{dc} values were transformed on a natural logarithmic (ln) scale to approximate normal distribution for direct pair comparison (Student's *t* test) between test groups or between fellow eyes. Therefore, the more negative the value of $\ln(P_{dc})$ is, the less permeable the corneal epithelium (i.e., less compromised corneal epithelial barrier function). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Effects of Ocular Environments With and Without Lens Wear on P_{dc}: A Series of 1-Hour Studies

A series of 1-hour studies was conducted to investigate the effect of open eyes versus closed eyes on P_{dc} with or without soft contact lens wear under different hypoxic conditions. Table 1 lists the values of $\ln(P_{dc})$ and the number of subjects whose data were analyzed in the various studies.[5–7] These include the changes in P_{dc} after 1-hour closed- and open-eye paradigms in which the level of hypoxia was varied by using lenses with varying Dk/t levels or goggles in which the partial pressure of O_2 was controlled with a mixture of nitrogen and carbon dioxide. Figure 1 provides a summary of the changes listed in Table 1 and changes after 6 to 8 hours of sleep without contact lens wear. Six to 8 hours of closed-eye wear without contact lenses did not alter the P_{dc}.[4] One-hour eye closure with lenses with a high Dk/t did not decrease

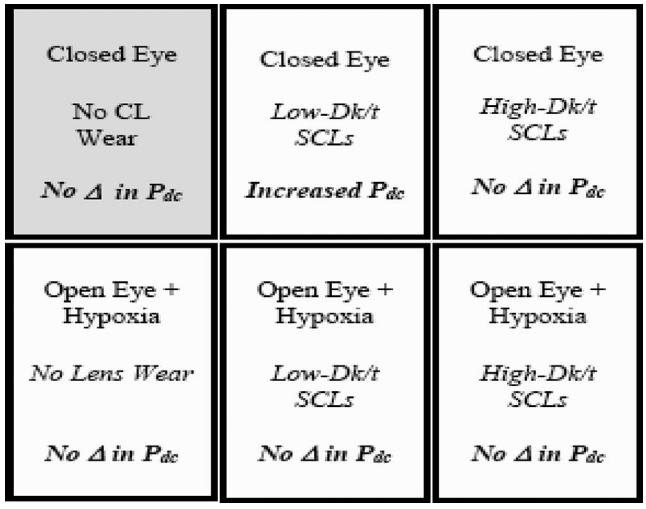

FIG. 1. Results of studies on corneal epithelial permeability (P_{dc}) using fluorometry. The nonshaded upper boxes summarize P_{dc} results after 1 hour of eye closure with lens wear. The shaded box summarizes results from normal 6 to 8 hours of eye closure without contact lenses. The lower boxes show P_{dc} results with and without lenses in the open-eye hypoxic environment for 1 hour. Δ = change.

TABLE 2. *Values of Natural Logarithm of Epithelial Permeability (Mean ln[P_{dc}] ± Standard Error, nm/sec) for Subjects Who Wore High- or Low-Dk/t Soft Lenses After 8 Hours of Overnight Wear*

	Patched	Unpatched
Balafilcon A (n = 33)		
Baseline afternoon visit	–2.99 ± 0.09	–2.86 ± 0.09
Overnight morning visit	–2.71 ± 0.10	–2.44 ± 0.10
	P=0.031	P=0.005
Etafilcon A (n = 35)		
Baseline afternoon visit	–2.92 ± 0.09	–2.78 ± 0.09
Overnight morning visit	–2.53 ± 0.10	–2.27 ± 0.11
	P=0.005	P=0.001

the epithelial barrier function. However, with as little as 1 hour of eye closure with low-Dk/t lenses, there was a significant decrease in the epithelial barrier function. In contrast to the 1-hour open-eye experiments, wearing contact lenses or a short-term hypoxic exposure without lens wear had no impact on P_{dc}.

These results suggest that short-term (i.e., 1 hour) contact lens wear in the open-eye condition does not alter P_{dc}, whereas contact lens–induced hypoxia during eye closure lowers the epithelial barrier function. This article later examines the effects of longer periods of contact wear on P_{dc}.

The Effects of Contact Lens–Induced Hypoxia on Epithelial Permeability During Extended Wear

Tables 2 and 3 summarize the effects of contact lens–induced corneal hypoxia while wearing a soft lens for 8 hours overnight or a gas-permeable lens for 6 days of extended wear.[8,9] Table 2 shows the changes in P_{dc} after 1 night of closed-eye lens wear for 68 subjects randomized to low-Dk/t (etafilcon A) or high-Dk/t (balafilcon A) lenses. The low-Dk/t lenses showed a greater change in P_{dc}, with increases of 47% and 66%, compared to 32% and 52% in the high-Dk/t lens group for the patched and unpatched eyes, respectively. The change in P_{dc} was substantially greater for the unpatched (open for approximately 2 hours) than for the patched eye for both groups. However, the changes were consistently greater in the low-Dk/t group.

To further explore different levels of hypoxia on epithelial permeability, an additional set of measurements was completed with gas-permeable lenses (siloxane–fluorocarbon polymer lenses with an oxygen permeability of 49 and 92) made with different lens thicknesses, which resulted in a distribution of Dk/t from 20 to 60.[9] In this study, 36 subjects wore low- or medium-Dk/t lenses in a 6-night extended-wear protocol. Permeability measurements were obtained after a minimum of 1 month of extended wear.

TABLE 3. *Values of Natural Logarithm of Epithelial Permeability (Mean ln[P_{dc}] ± Standard Error, nm/sec) for Subjects Who Wore Medium- or High-Dk/t Gas-Permeable Lenses After a Minimum of 1 Month of 6 Nights of Extended Wear*

	Patched	Unpatched
Low-Dk/t (n = 19)		
Baseline afternoon visit	–2.71 ± 0.12	–2.64 ± 0.09
Overnight morning visit	–2.34 ± 0.19	–2.46 ± 0.14
	P=0.030	P=0.292
Medium-Dk/t (n = 17)		
Baseline afternoon visit	–2.88 ± 0.11	–2.81 ± 0.16
Overnight morning visit	–2.70 ± 0.18	–2.91 ± 0.19
	P=0.353	P=0.692

Table 3 shows the mean change in ln(P_{dc}) at the afternoon and morning visits for the patched and unpatched eyes.

The patched eye wearing the low-Dk/t lens had a modest increase (P=0.03) in P_{dc}. In contrast, the unpatched eyes in the low-Dk/t lens group and the patched and unpatched eyes in the medium-Dk/t group did not have significant increases. Although the unpatched eyes in the low-Dk/t group received the same hypoxic dose as the patched eyes during sleep, after 2 hours of open-eye wear, the unpatched eye had nearly recovered to the baseline value. For the medium-Dk/t group, there was no significant difference between P_{dc} for either eye. These results suggest that contact lens–induced hypoxia has a modest effect on P_{dc}.

To further explore the relationship between hypoxia and the P_{dc} response, a multivariable analysis was performed to examine the difference in ln(P_{dc}) between afternoon and morning visits for all gas-permeable lenses with Dk/t values ranging from 20 to 60. Several models suggested that the magnitude of the change in P_{dc} depends on the level of hypoxic exposure.[9]

The results from the soft and rigid lens studies indicate that the epithelial barrier function is altered during overnight lens wear and that the greater the contact lens–induced hypoxia is, the greater the change in P_{dc}. These data also show that hypoxia alone cannot account for all the change in the epithelial barrier function; therefore, there must be additional factors. From the patched and unpatched P_{dc} data, it was inferred that insufficient tear flow after eye opening can contribute to the observed changes in the epithelial barrier function. The next series of experiments examined the effects of low and high tear flow without hypoxia to evaluate the relative contributions of hypoxia and tear flow on epithelial permeability.

The Effects of Contact Lens Wear Without Lens-Induced Hypoxia on Epithelial Permeability During Continuous Wear

This study examined changes in P_{dc} by using lenses that essentially eliminate hypoxia but have low or high tear flushing rates.[10] Both study lenses had high-Dk/t values (lotrafilcon A, Dk/t of 140; tisilfocon A, Dk/t of 175) but substantially different tear flushing rates (lotrafilcon A, 21 minutes; tisilfocon A, 5 minutes).[11–13] Subjects were randomized to gas-permeable or silicone hydrogel lenses and adapted to 7-day extended wear. After the adaptation, subjects entered a washout period by discontinuing lens wear for 30 days on average. At the end of the washout period, baseline P_{dc} measurements (i.e., afternoon and morning readings) were obtained. After these measurements, subjects wore their assigned lenses for 30 days of continuous wear. After this 30-day continuous-wear period, P_{dc} measurements (i.e., afternoon and morning readings) were repeated.

Table 4 shows the changes in P_{dc} from the afternoon reading to the morning reading after 30 days of continuous wear for lotrafilcon A and tisilfocon lenses. For the lotrafilcon A group, changes in P_{dc} were small (4%) and not statistically significant for the patched eye. For the fellow eye, however, there was a substantial and statistically significant reduction (60%) in the epithelial barrier function. For the gas-permeable lens group, there was a significant reduction in P_{dc} for the patched eye, but there were no P_{dc} differences between the baseline reading and that after 30 days of continuous wear for the open (unpatched) eye.

TABLE 4. *Values of Natural Logarithm of Epithelial Permeability (Mean ln[P_{dc}] ± Standard Error, nm/sec) for Subjects Who Wore Lotrafilcon A Silicone Hydrogel or Tisilfocon A Gas-Permeable Lenses After 30 Days of Continuous Wear*

	Patched	Unpatched
Lotrafilcon A (n = 37)		
Baseline afternoon visit	–2.26 ± 0.10	–2.36 ± 0.11
Post–30-day morning visit	–2.22 ± 0.15	–1.89 ± 0.13
	P=0.833	P=0.004
Tisilfocon A (n = 27)		
Baseline afternoon visit	–2.36 ± 0.13	–2.30 ± 0.11
Post–30-day morning visit	–1.99 ± 0.09	–2.21 ± 0.13
	P=0.022	P=0.614

DISCUSSION

The results from these corneal epithelial permeability studies provide some clues about the mechanisms that may lead to corneal morbidity associated with contact lens wear. The data suggest that hypoxia without contact lens wear during open- and closed-eye conditions has little impact on the corneal epithelial barrier function. However, the combined effect of lens-induced hypoxia and overnight contact lens wear increases the rate of fluorescein penetration into the cornea. In addition to the effects of corneal hypoxia, it appears that overnight soft lens wear with high or low oxygen-permeable lenses results in a significant increase in epithelial permeability. These results provide evidence that there must be at least one factor other than hypoxia contributing to the changes in epithelial status after overnight lens wear.

It is hypothesized that one of these factors is linked to the rate of tear flushing from under the lens to outside the lens after the eye is opened. To test this hypothesis, epithelial permeability rates were compared before and after 30 days of continuous wear on subjects who wore lenses that did not cause corneal hypoxia but had substantially different tear flushing rates. For the silicone hydrogel lenses, which have a low tear flushing rate, after overnight wear, the open eye showed a substantial decrease in the epithelial barrier function. However, after overnight gas-permeable lens wear, the open eye showed complete recovery (i.e., normal epithelial barrier function).

Based on these results, it is suggested that altered barrier function associated with contact lens overnight lens wear must result, in part, from mechanical agitation of the debris (e.g., inflammatory cells and metabolic byproducts) that accumulates during sleep. This can be explained from the soft and gas-permeable lens P_{dc} results. For the eyes wearing the soft lenses, the debris is sandwiched between the lens and cornea and unable to be removed efficiently after eye opening. Because the lens is stationary when the eye is closed (during sleep and with the patch), the epithelium is sequestered, and no change in the epithelial barrier function was observed. Once the eyes are open and blinking resumes, the soft lens begins to move and the trapped debris, which cannot be removed quickly, is mechanically agitated against the epithelium and leads to lowered barrier function. For gas-permeable lenses, however, once the eye is open, the trapped debris is quickly removed, and the epithelium recovers to baseline levels.

What is the role of contact lens–induced corneal hypoxia? The current results show that the epithelium is affected by contact lens–induced corneal hypoxia and that the magnitude of the effect is dose-dependent. However, normoxia alone does not eliminate overnight contact lens–induced morbidity, so it appears that the hypoxic effect may not be as critical to epithelial status as previously thought. For example, epithelial recovery is complete within 2 hours of eye opening with low-Dk/t lenses that have adequate tear flushing (e.g., gas-permeable materials). This finding suggests that although contact lens–induced overnight hypoxia can cause increased epithelial permeability, the cornea is able to recover from such effects if the normal ocular surface (i.e., precorneal tear film) can be quickly restored after eye opening. The implications from these results suggest the factors that control postlens tear flow dynamics must be more completely understood to develop lenses that will avoid ocular morbidity associated with overnight wear.

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