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Journal

Investigative Ophthalmology & Visual Science, 43(4)

ISSN

0146-0404

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Publication Date

2002-04-01

Peer reviewed

Impact of Rigid Gas-Permeable Contact Lens Extended Wear on Corneal Epithelial Barrier Function

Meng C. Lin,¹ Andrew D. Graham,¹ Robert E. Fusaro,² and Kenneth A. Polse¹

PURPOSE. To measure the effect of hypoxia and eye closure on epithelial permeability to fluorescein (P_{dc}) during rigid lens extended wear (EW).

METHODS. Central corneal thickness (CT) and P_{dc} were measured in 42 subjects with an optical pachometer and automated scanning fluorophotometer, respectively. All subjects had been successfully wearing rigid gas-permeable (RGP) lenses on a 6-night EW regimen, and each individual was randomized to wear either medium- or high-oxygen-permeable (Dk) RGP lenses (two types of siloxane-fluorocarbon polymer lenses with Dk of 49 and 92). CT and P_{dc} measurements were performed at an afternoon visit (baseline) and were repeated in the morning after 8 hours of overnight wear. Subjects slept with a patch over the right eye. The patch was not removed until immediately before the morning measurement.

RESULTS. The mean overnight swelling response for subjects in the medium-Dk group was greater than that in the high-Dk group. Results of a paired *t*-test indicate that the eye wearing the medium-Dk lens with a patch overnight had a significant increase in epithelial permeability. Results of mixed-effect models suggest that eye closure and lens-induced hypoxia are significant factors in altering P_{dc} .

CONCLUSIONS. The results indicate that corneal epithelial permeability increases with hypoxic dose and that epithelial barrier function is impaired by overnight rigid lens wear. (*Invest Ophthalmol Vis Sci.* 2002;43:1019-1024)

Contact lens extended wear (EW) creates a stressful environment (e.g., chronic pressure, mechanical stress, and lens-induced hypoxia) for the cornea and has been associated with many serious ocular complications. Several studies have shown an association between ocular surface disorders in contact lens wearers and microbial keratitis that could cause blindness.¹⁻³ Therefore, understanding the mechanisms that lead to alterations in the corneal epithelium may be important in minimizing the incidence of such vision-threatening complications. Although most clinicians and researchers believe that alterations in the corneal epithelium may be related to contact lens-induced hypoxia, there has been very little clinical evidence to substantiate a direct link between corneal hypoxia and epithelial barrier function.

To explore the effects of contact lens wear on the corneal epithelium, our Berkeley research group developed a method of assessing epithelial barrier function by measuring the per-

meability of the epithelium to fluorescein (P_{dc}).⁴ We have found that when a standard disposable soft contact lens is worn with the eyes closed for as little as 1 hour, there is an increase in epithelial permeability of approximately 40%,⁵ and when the same lenses are worn overnight for 2 weeks, the P_{dc} increases 99%.⁶ There is, however, no association between increased P_{dc} and either wearing a contact lens that causes corneal hypoxia with the eyes open⁷ or exposing the cornea to hypoxia without contact lens wear.⁸ These studies suggest that decreased barrier function occurs when the corneal epithelium is exposed to a hypoxic environment, the presence of a contact lens, and eye closure.

Although changes in epithelial integrity are associated with contact-lens-induced hypoxia and eye closure for soft contact lenses, it is not known whether this relationship holds for other lens types (e.g., rigid) that perform differently on the eye. In addition, although epithelial permeability has been shown to increase under the hypoxic conditions of closed-eye lens wear, it is not known whether this relationship is hypoxia dose dependent. In this study, we investigated these questions by measuring P_{dc} before and after overnight wear on subjects in extended wear (EW) using rigid gas-permeable (RGP) lenses with a range of oxygen transmissibilities (Dk/t).

METHODS

Subject Recruitment

Forty-two experienced rigid-lens wearers (53% men and 47% women) aged 21 to 42 years (mean \pm SD, 24 ± 4.8 years) were recruited from the Berkeley Contact Lens Extended Wear Study (CLEWS). All subjects entering CLEWS had no prior overnight lens wear experience and minimal or no history of soft lens day wear. The CLEWS clinical trial protocol required that all subjects first adapt to day wear and then extended wear involving high oxygen-permeable (Dk) RGP contact lenses. After successful extended wear adaptation, subjects were randomized to either medium- or high-Dk lenses. With the exception of Dk, the randomized lenses were made with identical parameters to the adaptation lenses. After randomization, subjects reported for quarterly visits over a 12-month follow-up period at which both clinical and laboratory assessments were performed. Subject eligibility criteria for CLEWS have been described in detail elsewhere.⁹

Subjects recruited for the P_{dc} study had worn the assigned study lenses for 6-nights/wk extended wear for a minimum of 1 month, with subjects in both Dk groups having up to 12 months of EW experience. Ten subjects (five in the medium-Dk group and five in the high-Dk group) were asked to participate in the P_{dc} study after completing CLEWS and were therefore required to resume full-time EW for 1 month before P_{dc} assessment. Informed consent was obtained from all study participants after a full description of the measurement procedures. This research project adhered to the tenets of the Declaration of Helsinki, and the research protocol was approved by the institutional review board (Committee for Protection of Human Subjects, University of California, Berkeley).

Contact Lens Materials

The medium- and high-Dk contact lenses used in this study were made from a siloxane-fluorocarbon polymer (paflucocon B and D; Paragon

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Supported by National Eye Institute Grant R01-EY-07728.

Submitted for publication June 5, 2001; revised November 27, 2001; accepted December 11, 2001.

Commercial relationships policy: N.

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TABLE 1. Lens Oxygen Transmissibility Stratified by Oxygen Permeability Group

Study Group	Eye	n	Mean	Minimum	Maximum
Medium Dk	R	19	28.2	23.7	37.5
	L	19	28.0	22.5	37.5
High Dk	R	17	52.7	46.0	57.5
	L	17	53.3	43.8	57.5

Units of Dk/t are $10^{-9} \times (\text{cm/mL} \cdot \text{O}_2)/(\text{sec/mL} \cdot \text{mm Hg})$.

Vision Sciences, Mesa, AZ). Before dispensing, lens parameters including base curve radius, diameter, power, and central thickness were verified using standard verification instruments. The central Dk/t of four randomly selected lenses from each lens group was determined using Fatt's polarographic technique.¹⁰ For the study lenses of the 42 subjects, the average central lens thickness was 0.16 and 0.18 mm, which correspond to the average Dk/t of 28×10^{-9} and 53×10^{-9} ($\text{cm/mL} \cdot \text{O}_2)/(\text{sec/mL} \cdot \text{mm Hg})$ for the medium- and high-Dk lenses, respectively. For both lens materials, the average overall lens diameter was 9.2 mm. Lenses were fitted to achieve alignment. The details of the lens fitting criteria have been reported elsewhere.⁹

Instrumentation and Procedures

A Haag-Streit optical pachometer and an automated scanning fluorophotometer (Fluorotron Master; OcuMetrics, Mountain View, CA) were used to measure corneal thickness and epithelial permeability, respectively. The calibration and measurement techniques of both instruments have been described previously.^{4,11}

The experimental procedure required an afternoon (PM, baseline) visit and a morning (AM) visit after 8 hours of overnight wear. Subjects were asked to report to our laboratory for the PM visit a minimum of 4 hours after awakening, so that we could obtain afternoon baseline values for corneal thickness (CT) and P_{dc} . Before the CT measurements, the lens in the right eye was gently removed with a suction cup, and 20 replicate CT readings were taken and averaged. After repeating this procedure for the left eye, the background stromal fluorescence of both eyes was measured. Then $2 \mu\text{L}$ 0.35% NaF dye was instilled in the right eye and the eye was immediately scanned, followed by dye instillation and scanning of the left eye. Thereafter, a series of scans was made every 2 minutes, alternating between eyes, over a period of 20 minutes. At the end of this period, the eyes were thoroughly rinsed, and the stromal fluorescence of both eyes was measured again. The details of estimating P_{dc} from the fluorescence readings have been described elsewhere.⁴

At the PM visit, subjects were instructed to patch their right eyes immediately before sleep the night before the AM visit, and they were required to return to the laboratory within 2 hours of awakening the next morning with the patch in place. Subjects were first trained in the laboratory in patching procedures to ensure that the eye would remain completely closed during sleep, but without excessive pressure that could compress the lens on the cornea and cause adherence. After demonstrating the correct patching technique, subjects were dispensed gauze and surgical tape, along with written instructions to be reviewed that night, at the time of patching. Immediately after removal of the patch and lenses at the AM visit, CT and P_{dc} measurements were repeated according to the same procedures as described for the PM visit.

At the completion of both the PM and AM permeability measurements, a masked observer performed a detailed slit lamp examination using both white light and cobalt blue light with a yellow filter. The presence of corneal staining with fluorescein was graded on a 1 to 4 scale, where punctate staining of fewer than five points was grade 1; 5 to 10 points as grade 2; 11 to 25 points as grade 3; and more than 26 points as grade 4. Subjects exhibiting more than five punctate stains in the central cornea were excluded from the analysis to avoid an overestimate of the P_{dc} .

Statistical Methods

Epithelial permeability was transformed by natural logarithm to stabilize the variance and better approximate normality. We examined the effects of hypoxia and overnight RGP wear on the log permeability, $\ln(P_{dc})$, using mixed-effects analysis of variance models, implemented on computer (Proc Mixed; SAS, Cary, NC).¹² Among the various models explored were fixed effects for hypoxic dose, morning versus afternoon measurement (Visit), patched versus unpatched eyes, and length of time the eyes were open before P_{dc} measurements (TOpen). Hypoxic dose was characterized by medium-versus high-Dk lens group (DKGroup) or by the lens-specific oxygen transmissibility (Dk/t). A random effect for right or left eye was specified, with a compound symmetric covariance structure that assumes a common covariance in the repeat measurements on each subject (two eyes \times two visits) and independence between subjects. We also assessed the impact of other variables, including age, gender, ethnicity, contact lens history, and corneal thickness.

RESULTS

Descriptive

Thirty-six myopic subjects successfully completed the study, 19 wearing the medium-Dk (mean [95% CI] lens power, -3.50 D [$-2.50, -4.25$]), and 17 wearing the high-Dk lenses (mean, -2.75 D [$-2.00, -3.50$]). Previous investigations have determined that the accuracy and precision of the P_{dc} measurement technique, although inadequate for individual P_{dc} assessment, make it appropriate for group studies.⁴ Several sources of variability may contribute to error in the estimation of P_{dc} , including the presence of corneal staining, reflex tearing, and differences in the alignment of the subject between individual scans within a measurement session or between sessions. Of 42 subjects initially measured, four were not included in the analysis because central corneal staining was observed after the permeability assessment. Their inclusion could have resulted in an overestimate of the P_{dc} . Two subjects were excluded because of negative estimates of their P_{dc} , which were most likely caused by slight differences in the alignment of the subject between the background and postrinse fluorescence readings. If the subjects were unable to maintain a consistent alignment, the variation in measurement angles between the background scans and the postrinse scans could have resulted in lower mean postrinse stromal fluorescence compared with mean background fluorescence. This could have caused an erroneous negative estimate of the permeability, which is impossible by definition. The remaining 36 subjects included in

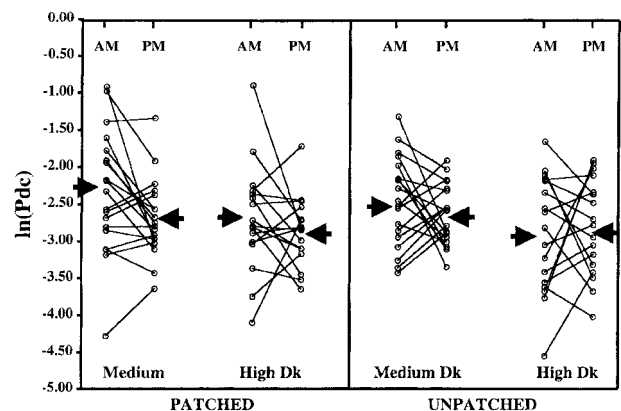


FIGURE 1. Readings for $\ln(P_{dc})$, in units of $\ln(\text{nanometers per second})$, taken at the baseline PM and overnight AM visits, in both the medium- and high-Dk lens groups. Arrows: mean $\ln(P_{dc})$.

TABLE 2. Mean Change in Natural Log Permeability between Morning (AM) and Baseline (PM) Visits

Lens Group/Eye	Mean Change (AM-PM) in $\ln(P_{dc})$	95% CI
Medium Dk/right	0.372	0.040, 0.700
Medium Dk/left	0.182	-0.170, 0.535
High Dk/right	0.179	-0.209, 0.575
High Dk/left	-0.095	-0.589, 0.400

the analysis showed no evidence of central corneal staining or lens adhesion and reported no experience of ocular discomfort on awakening.

Table 1 presents the mean, minimum, and maximum lens Dk/t in both eyes of the medium- and high-Dk subjects. On average, the groups differed by approximately 25 Dk/t units, and there was no overlap between groups, confirming that they received distinctly different hypoxic doses. The mean \pm SE overnight swelling response for subjects in the medium-Dk group was greater for both patched ($5.8\% \pm 0.8\%$) and unpatched eyes ($4.6\% \pm 0.8\%$), compared with the high-Dk group ($4.5\% \pm 0.7\%$ and $2.6\% \pm 0.6\%$ for the patched and unpatched eyes, respectively). As expected, the mean percentage of corneal swelling was greater in the patched eyes in both groups because of corneal deswelling (i.e., recovery) in the unpatched eyes, which were open, on average, for up to 90 minutes before the AM pachometry measurements. The separate Dk/t distributions and overnight corneal swelling results confirm that each group received a different hypoxic dose, resulting in correspondingly different physiological reactions and thereby providing the experimental conditions necessary to explore the effects of hypoxic dose on epithelial barrier function.

Figure 1 shows the PM versus AM $\ln(P_{dc})$ in all 36 subjects, stratified by eye and Dk group. In the medium-Dk lens group, the average $\ln(P_{dc})$ was greater in the morning (mean \pm SE, -2.34 ± 0.19) than at the afternoon baseline (-2.71 ± 0.12) in the patched eye, corresponding to an increase in P_{dc} after overnight lens wear. The same pattern was observed in the unpatched eye, with a greater $\ln(P_{dc})$ in the morning (-2.46 ± 0.14) than at the afternoon baseline (-2.64 ± 0.09), reflecting a somewhat smaller overnight increase in P_{dc} . In the high-Dk lens group, the patched eyes also exhibited a small increase in P_{dc} with overnight lens wear (-2.70 ± 0.18 vs. -2.88 ± 0.11 for the AM and PM $\ln(P_{dc})$, respectively), whereas no such increase in P_{dc} was found in the unpatched eyes (-2.91 ± 0.19 vs. -2.81 ± 0.16).

Table 2 shows the overnight change in $\ln(P_{dc})$ from baseline at the PM visit to the AM visit after 8 hours of eye closure. Results of a paired *t*-test indicate that the eye wearing the medium-Dk lens with a patch overnight had a significant increase ($P = 0.03$) in P_{dc} . By contrast, the unpatched eyes in the medium-Dk lens group, as well as both patched and unpatched eyes in the high-Dk group, did not have significant increases in

P_{dc} from their PM baseline values after 8 hours of overnight lens wear. The patched eyes in the medium-Dk group, which displayed the most significant overnight increase in P_{dc} , had the greatest hypoxic exposure and the least recovery time before P_{dc} measurements. The unpatched eyes in the medium-Dk group received the same lens-induced hypoxic dose but had some time to recover toward baseline P_{dc} before measurement, and therefore displayed a somewhat smaller overnight increase. A similar small increase was observed for the patched eyes of the high-Dk group, which had less hypoxic exposure but no recovery time before P_{dc} measurement. The unpatched eyes of the high-Dk group, which had the smaller dose of hypoxia and the most time to recover before P_{dc} measurements, did not display an overnight increase in P_{dc} . These results suggest that changes in epithelial barrier function during overnight wear could be hypoxia dose dependent.

Hypoxia Dose and Eye Closure

To perform a rigorous test of the relationship suggested by the above results, and to assess simultaneously the effects of hypoxia, eye closure, and other demographic variables on P_{dc} , we compared a variety of mixed-effects analysis of variance models. The first set of models shown in Table 3 allowed us to examine the difference in $\ln(P_{dc})$ between PM and AM visits and the effect of hypoxia dose (DkGroup or Dk/t). There was evidence of an overnight increase in P_{dc} ($P = 0.07$) along with significantly greater permeability overall in the medium-Dk group ($P = 0.05$). When hypoxia dose was represented by the lens-specific Dk/t in place of the Dk group categorization, the increase in permeability with hypoxic dose was also significant ($P = 0.02$). Models including an interaction term also showed significant effects of hypoxia dose and AM versus PM visit, with some possibility of an interaction between Visit and DkGroup ($P = 0.08$) or Dk/t ($P = 0.10$). If there is such an interaction, it suggests that the magnitude of the overnight change in P_{dc} depends on the level of hypoxic exposure. This possibility is investigated further in a later section.

The next set of models shown in Table 4 use the DkGroup or Dk/t variable for hypoxia dose as described earlier, but represent the effect of eye closure as the time the eyes were open before the P_{dc} measurements (TOpen), rather than PM versus AM visit. A simple indicator of PM versus AM visit treats both eyes of each subject equivalently when, in fact, the unpatched eye was open, up to 90 minutes longer than the patched eye in the morning and may have partially recovered toward baseline before AM P_{dc} measurements. In contrast, the length of time an eye was open before measurement identifies whether it was measured at the PM or AM visit, as well as whether the eye was patched at the morning measurement, thereby capturing both effects in a single variable. In addition, the average length of time the eyes were open before the AM measurement was slightly greater for the medium-Dk group, so a potential bias can be avoided by using the TOpen variable in place of PM versus AM visit.

TABLE 3. Models Using DkGroup or Dk/t with Visit, with and without Interactions

Model	Log Permeability	P			
		DkGroup	Dk/t	Visit	Interaction
1	$\ln(P_{dc}) = -2.91 + 0.29 \times \text{DkGroup} + 0.17 \times \text{Visit}$	0.05		0.07	
2	$\ln(P_{dc}) = -2.84 + [\text{DkGroup} \times (0.17 + 0.28 \times \text{Visit})]$	0.05		0.08	
3	$\ln(P_{dc}) = -2.24 - 0.01 \times \text{Dk/t} + 0.17 \times \text{Visit}$		0.02	0.07	
4	$\ln(P_{dc}) = -2.46 - 0.01 \times \text{Dk/t} + 0.61 \times \text{Visit} - 0.01 \times (\text{Dk/t} \times \text{Visit})$		0.02	0.03	0.10

The DkGroup and Visit parameters reflect the effects of medium Dk lenses and AM visit, respectively.

TABLE 4. Models Using DkGroup or Dk/t with TOpen, with and without Interactions

Model	Log Permeability	P			
		DkGroup	Dk/t	TOpen	Interaction
1	$\ln(P_{dc}) = -2.72 + 0.29 \times \text{DkGroup} - 0.0005 \times \text{TOpen}$ $\ln(P_{dc}) = -2.76 + 0.37 \times \text{DkGroup} - 0.0003 \times \text{TOpen} - 0.0004$ $\times (\text{DKGroup} \times \text{TOpen})$	0.05		0.07	
2		0.05		0.07	0.47
3	$\ln(P_{dc}) = -2.05 - 0.01 \times \text{Dk/t} - 0.0005 \times \text{TOpen}$		0.02	0.07	
4	$\ln(P_{dc}) = -1.19 - 0.02 \times \text{Dk/t} - 0.001 \times \text{TOpen} + 0.00002 \times (\text{Dk/t} \times \text{TOpen})$		0.02	0.16	0.37

The DkGroup parameter reflects the effect of medium Dk lenses. TOpen is the time in minutes that eyes were open before P_{dc} measurement.

The models shown in Table 4 confirm that hypoxia and eye closure have a significant impact on P_{dc} , but do not support the hypothesis that the magnitude of the overnight change in P_{dc} depends on the level of hypoxia. The $\ln(P_{dc})$ was significantly related to Dk/t ($P = 0.02$) and TOpen ($P = 0.06$) when considered as separate, additive effects; however, when an interaction term is included, it fails to achieve significance ($P = 0.37$) and reduces the precision of the TOpen estimate as well. That there was not a significant interaction term suggests that a greater overnight change in P_{dc} does not occur with greater hypoxia dose. Figure 2 shows the $\ln(P_{dc})$ predicted by the additive model for a range of TOpen. The parallel lines for Dk/t of 28 and 53 units (approximately the mean Dk/t of our medium- and high-Dk groups, respectively) indicate that the epithelium was significantly more permeable, on average, in subjects wearing lower Dk/t lenses and was more permeable after 8 hours of overnight wear for both levels of hypoxia.

Subject Characteristics

Various subject-level characteristics were added to our P_{dc} models to determine whether these factors could be related directly to P_{dc} or might have affected the relationship between P_{dc} and hypoxia or eye closure. Age, gender, prior history of daily lens wear, or ethnicity did not have an independent effect on P_{dc} or alter the estimates of the hypoxia or eye closure effects. Although the effect of ethnicity on P_{dc} did not achieve significance when all ethnic groups were included in the models, there was evidence that the Asian subjects had substantially different P_{dc} than the other groups. We therefore stratified our data based on two broad ethnic categories, Asians versus non-Asians. The Asian group (seven women, six men) included

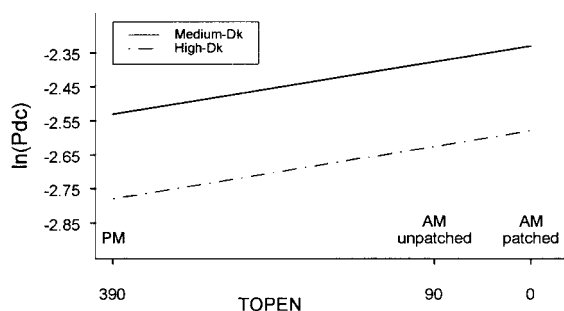


FIGURE 2. Model predictions using Dk/t and TOpen. The $\ln(P_{dc})$ is in units of $\ln(\text{nanometers per second})$. The parallel lines for medium- and high-Dk lens groups indicate that the epithelium was significantly more permeable, on average, in subjects wearing lower Dk/t lenses and was more permeable after overnight wear for both levels of Dk/t. Reference points are shown for the measurement of patched eyes immediately after eye opening in the AM (0 minutes), the maximum time that unpatched eyes were open before AM measurement (90 minutes), and the median time that eyes were open before PM measurements (390 minutes).

Chinese, Japanese, Korean, South Pacific Islander, and Taiwanese; the non-Asian category (10 women, 13 men) consisted of all other ethnic groups. We found, based on this ethnic stratification, that our Asian compared with non-Asian subjects, tended to be younger (23.8 ± 0.5 years vs. 27.0 ± 0.6 years, $P = 0.0004$) and have flatter central corneal curvature in both horizontal (42.66 ± 0.14 D vs. 43.74 ± 0.14 D, $P < 0.0001$) and vertical (43.77 ± 0.19 D vs. 44.28 ± 0.15 D, $P = 0.0378$) meridians, higher corneal toricity (1.11 ± 0.58 D vs. 0.58 ± 0.44 D, $P < 0.0001$), and higher contact lens power (-3.80 ± 0.26 D vs. -2.11 ± 0.13 D, $P < 0.0001$). The data in the parentheses are expressed as the mean \pm SE.

To carefully assess the difference in epithelial permeability between Asians and non-Asians, we used a model taking into account all variables (ethnicity, age, gender, corneal curvatures, TOpen, lens power, lens Dk/t, lens base curve radius (BCR), and months of EW), to avoid any possible bias from confounding variables. After excluding the insignificant variables, we devised the models that are shown in Table 5, which suggest that epithelial permeability is dependent mostly on ethnicity, TOpen, and Dk/t, whereas all other variables do not play a significant role in changing P_{dc} . The first model showed a greater P_{dc} in Asians than non-Asians, with marginal significance ($P = 0.07$). This simple additive (i.e., noninteraction) model is illustrated in Figure 3, which shows parallel lines for the overnight change in $\ln(P_{dc})$ for two levels of Dk/t, both of which were shifted upward by a constant amount for the Asian subgroups. We then fitted a series of models permitting differences in the slopes of the lines (i.e., interactions) for different levels of hypoxia or Asian versus non-Asian ethnicity. Although several different models were considered, the second model shown in Table 5, which permits the slopes of the overnight P_{dc} change to differ for Asians and non-Asians, provided the best fit to the data. This model reveals significant effects for hypoxia dose ($P = 0.02$), the time the eyes were open before measurement ($P = 0.02$), Asian ethnicity ($P = 0.01$), and the interaction between ethnicity and TOpen ($P = 0.04$). Figure 4 depicts this model graphically, showing that within each ethnic category there was greater permeability with greater hypoxic dose, on average, and an overnight increase in P_{dc} for both levels of Dk/t, but that both the overall average P_{dc} and the magnitude of the overnight increase in P_{dc} were much greater among the Asian subgroups.

DISCUSSION

This study has shown that during RGP contact lens wear, there is a reduction in epithelial barrier function that is directly related to hypoxia exposure at the corneal surface and that the permeability of the epithelium is significantly increased after wearing lenses overnight. Subjects wearing lenses with lower Dk/t had greater P_{dc} , on average, at both the afternoon and morning visits. In addition, P_{dc} was significantly greater after 8 hours of closed-eye wear for both medium- and high-Dk/t

TABLE 5. Models Using Dk/t with TOpen and NAsian, One Additive and One with a One-Way Interaction between NAsian and TOpen

Model	Log Permeability	P			
		Dk/t	TOpen	NAsian	Interaction
1	$\ln(P_{dc}) = -1.91 - 0.01 \times Dk/t - 0.0004 \times TOpen - 0.27 \times NAsian$ $\ln(P_{dc}) = -1.75 - 0.01 \times Dk/t - 0.001 \times TOpen - 0.50 \times NAsian$	0.02	0.08	0.07	
2	$+ 0.0001 \times (TOpen \times NAsian)$	0.02	0.02	0.01	0.04

The non-Asian (NAsian) parameter reflects the effect of non-Asian compared to Asian ethnicity (i.e., NAsian = 1 if non-Asian, 0 if Asian).

lenses. These results extend the findings of our previous soft lens studies to rigid contact lens wear and confirm that the combination of corneal hypoxia, the presence of a contact lens, and eye closure can result in disruption of the epithelial cell layer and impairment of epithelial barrier function.

Although P_{dc} was found to be greater with a higher hypoxic dose and greater after overnight wear, our results suggest that the magnitude of the overnight change in P_{dc} is not dependent on the level of oxygen available. Subjects wearing medium-Dk lenses had, on average, higher P_{dc} than those wearing high-Dk lenses at both afternoon and morning visits; however, the amount of overnight increase in P_{dc} was roughly the same in both lens groups. This finding may be partly a result of a higher baseline P_{dc} , on average, for our medium-Dk subjects, and further study is needed to determine whether the overnight increase in P_{dc} would be the same for medium- and high-Dk lenses among neophyte lens wearers with no baseline difference in P_{dc} between lens groups.

The greater P_{dc} observed at the afternoon baseline visit for our medium-Dk subjects is of potential clinical interest. Because all subjects had worn lenses on a full-time overnight basis for at least 30 days before P_{dc} measurements, the difference in baseline P_{dc} between the Dk groups suggests that individuals wearing lower Dk lenses may have reduced epithelial barrier function throughout the day and not just for a short period after overnight wear. This elevation in daytime P_{dc} could be explained by the cumulative effects of continuous exposure to a greater hypoxia dose in subjects wearing medium-Dk lenses. Several studies have shown that contact lens-induced hypoxia can have a substantial impact on the morphology and physiology of corneal epithelial cells. For example, low oxygen-permeable lenses (rigid or soft) can inhibit cell mitosis,¹⁵ reduce cell desquamation rate,¹⁴ enlarge superficial epithelial cells,¹⁵ and increase bacterial binding.¹⁶ Such hypoxia-driven alterations in the epithelial cell layer could explain the persistence of an elevated P_{dc} and impaired barrier function during the day in our medium-Dk group.

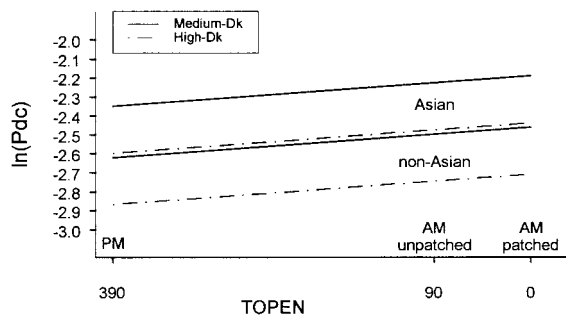


FIGURE 3. Additive model predictions for Asians versus non-Asians using Dk/t and TOpen. The $\ln(P_{dc})$ is in units of $\ln(\text{nanometers per second})$. The *parallel lines* for the overnight change in $\ln(P_{dc})$ in the medium- and high-Dk lens groups were shifted upward by a constant amount in Asian subjects (*top two lines*), reflecting greater P_{dc} . Reference points are as in Figure 2.

In addition to our findings that contact lens-induced hypoxia and eye closure affect P_{dc} , we also found that Asian eyes are more susceptible to changes in epithelial barrier function than are non-Asian eyes. This higher level of susceptibility to changes in epithelial permeability is apparently not due to the differences in age, corneal curvature, and lens power. In searching for other clues to account for the differences in P_{dc} between the two groups, we note that earlier studies have reported that both vertical palpebral aperture size¹⁷ and orbital fat content differ between Asian and non-Asians.^{18,19} Both parameters could affect the physical contact lens-corneal fitting relationship. For example, the narrow palpebral aperture size and lid tightness associated with Asian eyes may produce excessive lens-corneal apical pressure leading to greater epithelial trauma (increased P_{dc}) in the Asian compared with the non-Asian eye. The difference in P_{dc} is in agreement with a report that shows that lens-induced epithelial trauma, based on the presence of superficial punctate keratitis, is more common in Asian than in non-Asian eyes.²⁰ These findings may be partly explained if one could demonstrate that Asian eyes have greater epithelial fragility; however, to our knowledge there is no published work that has examined differences in epithelial fragility between Asians and non-Asians. Further studies are needed to better understand the complex set of factors that may make the Asian eye more prone to altered epithelial response during contact lens wear.

We found that changes in P_{dc} associated with RGPEW was substantially lower than in subjects wearing soft EW contact lenses.⁶ For example, we have previously shown that subjects wearing soft lenses had a 99% increase in P_{dc} after 2-week overnight wear.⁶ In the present study, subjects wearing rigid lenses showed an average increase of 20% in P_{dc} . We also observed that after overnight RGP wear, the unpatched eye had less change in P_{dc} than the patched eye. This is in contrast to our recent P_{dc} measurements for overnight soft lens wear in which the unpatched eye had an increased permeability compared with the patched eye.¹³ Because the RGP and soft lens P_{dc} studies used similar experimental protocols, the differ-

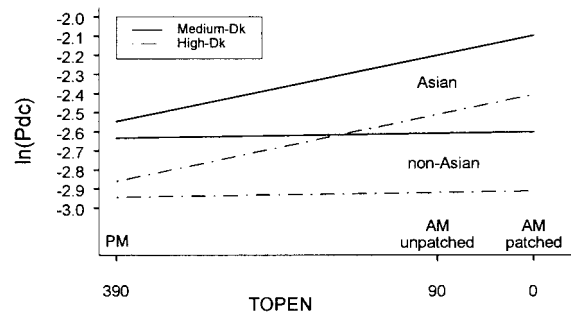


FIGURE 4. Interaction model predictions for Asians versus non-Asians using Dk/t and TOpen. The $\ln(P_{dc})$ is in units of $\ln(\text{nanometers per second})$. Both the overall average P_{dc} and the magnitude of the overnight increase in P_{dc} were greater in the Asian group (*two lines with steeper slopes*). Reference points are as in Figure 2.

ences in P_{dc} may be due to lens performance. For example, during sleep, trapped debris and other metabolic byproducts build up under the lens and are removed by tear exchange. Soft lenses have a much lower tear exchange rate than rigid lenses,^{22,23} and it is possible that the relatively long retention time of trapped debris under the soft lens after sleep may lead to epithelial trauma (e.g., increased P_{dc}) and make the cornea more susceptible to contact lens associated complications such as microbial keratitis.

In conclusion, we have shown in the present study that for rigid contact lenses, a greater dose of hypoxia is associated with increased permeability of the corneal epithelium, and that epithelial barrier function is impaired after overnight, closed-eye contact lens wear. Further, we have shown that both the overall hypoxic effect on permeability and the overnight difference in P_{dc} appear to be more pronounced among Asian subjects. In summary, our findings suggest that if contact lenses are to be worn on an overnight basis, lenses with the highest oxygen transmissibility and fastest rate of tear exchange are preferred, to minimize disruption of the corneal epithelial cell layer and maintain an adequate barrier to infection at the ocular surface.

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