Sympathetic Swelling Response of the Control Eye to Soft Lenses in the Other Eye

Desmond Fonn,1 Rénéé du Toit,1 Trefford L. Simpson,1 José A. Vega,1 Ping Situ,1 and Robin L. Chalmers2

PURPOSE. To compare central corneal swelling and light scatter after 8 hours of sleep in eyes wearing high- and low-Dk hydrogel lenses and to the contralateral control eyes.

METHODS. Twenty neophyte subjects wore a Lotrafilcon A (Dk, 140; Ciba Vision, Duluth GA) silicone hydrogel lens and an Etafilcon A (Dk, 18; Acuvue; Vistakon, Jacksonville, FL) 58% water content hydrogel lens of similar center thickness in random order in the right eye only, for overnight 8-hour periods. The contralateral nonwearing left eyes served as controls. Central corneal thickness was measured using an optical pachometer and light scatter using a Van den Berg stray-light meter before lens insertion, after lens removal on waking, and every 20 minutes for the next 3 hours.

RESULTS. Central corneal swelling induced by the Etafilcon A lens on eye opening was significantly higher than with the Lotrafilcon A lens (8.66% ± 2.84% versus 2.71% ± 1.91%; P < 0.00001). Light scatter induced by the Etafilcon A lens on eye opening was significantly higher than with the Lotrafilcon A lens (46.09 ± 5.62 versus 42.78 ± 6.07 Van den Berg units, P = 0.0078). The swelling of the control eyes paired with the Etafilcon A lens-wearing eyes was also slightly but significantly higher than that of the control eyes paired with the Lotrafilcon A lens-wearing eyes (2.34% ± 1.26% versus 1.44% ± 0.91%; P = 0.0002). Light-scatter measurements were not significantly different between control sets of eyes but showed the same trend.

CONCLUSIONS. In neophyte subjects, corneal swelling of the contralateral control eyes appears to be influenced by the swelling of the fellow lens-wearing eyes—that is, the swelling of the contralateral control eye was significantly lower when there was less swelling of the fellow eye wearing the high-Dk lens. Although there was no statistically significant difference in light-scatter measurements between the control sets of eyes, a trend similar to the corneal swelling results was observed, which could be used to support the suggestion that this may be a sympathetic physiological response rather than an unusual sampling coincidence. (Invest Ophthalmol Vis Sci. 1999;40: 3116–3121)

Corneal hydration control is dependent on sufficient oxygen reaching the epithelial surface when a contact lens is worn. This is even more critical when contact lenses are worn during sleep because of the reduced oxygen tension under the closed lid.1 Holden and Mertz2 showed that the oxygen transmissibility of a hydrogel lens has to be an average of 87.0 ± 3.3 × 10−9 (centimeters × milliliters O2)/ (seconds × milliliters × millimeters of mercury) during sleep (closed eye) for zero lens-induced edema. Currently marketed hydrogel lenses fall short of this criterion, but in spite of this, millions of patients wear these relatively low-transmissibility lenses on an extended-wear basis.3 This shortfall in transmissibility may be linked to the significantly higher incidence of ulcerative keratitis with extended wear than with daily wear.4–8 It has been suggested that the cause of extended-wear–induced infection is chronic hypoxia that renders the corneal epithelium less viable and more susceptible to surface binding of the pathogens,9 of which Pseudomonas aeruginosa appears to be the most frequent.10,11

To demonstrate the effect of low-transmissibility lenses, various researchers12–14 have measured corneal swelling in response to wearing Etafilcon A lenses (Acuvue; Vistakon, Jacksonville, FL; Dk/T = 28 × 10−9) overnight (while sleeping) and have found that corneal thickness increased by approximately 10%. This corneal swelling result is substantially greater than the average overnight swelling response of 3% to 4% when no lenses are worn.15,15–17 Light scatter is another technique to measure the corneal effects of contact lens wear.18–20 This method, originally described by Van den Berg21 employs a stray-light meter and is an indirect index of corneal edema. The instrument measures the forward light scatter produced by the edematous cornea. Traditionally, experiments to measure the corneal swelling effects of hydrogel lenses have been conducted using one eye of the subject to wear the test lens and the contralateral eye (no lens wear) as the control.2,13,16,17,22

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TABLE 1. Subjects’ Biometric Data

<table>
<thead>
<tr>
<th>Eyes</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (hor) D</td>
<td>42.98 ± 1.29</td>
<td>43.07 ± 1.30</td>
</tr>
<tr>
<td>K (ver) D</td>
<td>43.56 ± 1.35</td>
<td>43.85 ± 1.48</td>
</tr>
<tr>
<td>Rx (sph) D</td>
<td>−1.36 ± 1.25</td>
<td>−1.30 ± 1.36</td>
</tr>
<tr>
<td>Rx (cyl) D</td>
<td>−0.59 ± 0.30</td>
<td>−0.73 ± 0.70</td>
</tr>
<tr>
<td>Central corneal thickness (mm)</td>
<td>0.54 ± 0.02</td>
<td>0.54 ± 0.02</td>
</tr>
</tbody>
</table>

K, curvature; hor, horizontal; ver, vertical; Rx, prescription; sph, sphere; cyl, cylinder.

The construction of this experimental design is the potential of a sympathetic effect on the control eye, but in previous hydrogel experiments this phenomenon has not been evident. In a study by Harris and Mandell, three subjects wore a polymethylmethacrylate lens on one eye only, and they found that the contralateral nonwearing eyes swelled by approximately 3%. This was an open-eye experiment and presumably was in response to reflex lacrimation that is common in unadapted rigid lens wearers.

The recent development of an experimental high permeability hydrogel lens (Dk > 140 × 10⁻¹¹) enabled us to conduct a study to determine the level of corneal swelling and light scatter it produces during sleep. We compared this with the overnight swelling response and light scatter of an approved extended-wear 58% ionic hydrogel lens conducted on another night and to the contralateral (control) non-lens-wearing eye in 20 neophyte subjects.

METHODS

Subjects

Twenty subjects (10 men and 10 women, age 26.8 ± 7.5 years) with no history of contact lens wear or any current ocular or systemic disease were recruited for this study. After ethics approval from the Office of Human Research and Animal Care at the University of Waterloo, informed consent was obtained from each subject, and all subjects were treated in accordance with the tenets of the Declaration of Helsinki. The relevant ocular biometric information is recorded in Table 1.

Lenses

The specifications of the lenses used to induce corneal swelling in this study are provided in Table 2. The difference in oxygen transmissibility (Dk/T) of these lenses would predictably produce different levels of hypoxia and thus degrees of corneal swelling.

TABLE 2. Nominal Contact Lens Parameters

<table>
<thead>
<tr>
<th>Lenses</th>
<th>Water Content (%)</th>
<th>BVP (D)</th>
<th>Diameter (mm)</th>
<th>Dk Value</th>
<th>Base Curves (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotrafilcon A</td>
<td>24</td>
<td>−3.00</td>
<td>14.0</td>
<td>140 × 10⁻¹¹</td>
<td>8.8</td>
</tr>
<tr>
<td>Etafilcon A</td>
<td>58</td>
<td>−3.00</td>
<td>14.0</td>
<td>18.0 × 10⁻¹¹</td>
<td>8.8</td>
</tr>
</tbody>
</table>

BVP, back vertex power; Dk value, oxygen transmission per unit thickness.

Lotrafilcon A (Ciba Vision, Duluth GA) is an experimental silicone-hydrogel contact lens that has been developed for up to 30 nights’ extended wear. The inclusion of siloxane in the Lotrafilcon A material results in a highly permeable moiety. Etafilcon A is a hydrogel lens with a much lower permeability value that has been approved in the United States for 7-day extended wear.

Procedure

A double-masked randomized study was conducted that ensured that half the subjects would wear the Etafilcon A lens first and the other half would wear the Lotrafilcon A lens first. The subjects participated in two overnight test sessions. They wore each of the contact lenses on one eye only, for a period of 9 hours from 10 PM until 7 AM the following morning. The subjects slept during this period from 11 PM. Prolonged eye closure (sleep) maximizes corneal swelling with contact lenses because of reduced oxygen tension (hypoxia) under the lens. In each case the naked contralateral eye was used as the control.

Central corneal thickness and light scatter were measured at approximately 4 PM (baseline) before lens insertion that night and then immediately after lens removal at 7 AM when the subject was awakened the following morning. Central corneal thickness and light-scatter measurements were repeated every 20 minutes thereafter for 3 hours. Central corneal swelling was measured with a modified optical pachometer on a biomicroscope (Carl Zeiss, Thornwood, NY), which was interfaced with a computer. The pachymeter design was similar to that described previously. Each pachymetry measurement included seven readings. The computer was programmed to remove the high and low readings, and the mean and SD of each measurement set was then recorded. A typical measurement produced a SD of ±5.0 μm.

Forward light scatter was measured with the Van den Berg stray-light meter (Medical Physics and Informatics, Amsterdam, The Netherlands). This instrument uses the psychophysical method of direct compensation. A full explanation of the stray-light measurement procedure has been described previously. Briefly, subjects view a dark disc surrounded by an annulus of flickering LEDs. Although no light emanates from the dark central field when the subject is initially viewing it, this area appears to flicker because of intraocular light scatter. By adjusting the amount of counterphase light, the flicker in the central field appears to cease. This amount of counterphase light is used to measure the scattered light. Forward light scatter can be measured at visual angles of 3.5°, 10°, and 28°. Only 3.5° was used in this study because of time constraints, and light scatter is more likely to be affected by epithelial than stromal corneal edema. The mean of three readings for each eye was calculated.

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TABLE 3. Overnight Corneal Swelling Induced by Contact Lens Wear and 8 Hours of Eye Closure in Neophyte Subjects

<table>
<thead>
<tr>
<th></th>
<th>Lotrafilcon A (n = 20)</th>
<th>Control* (n = 20)</th>
<th>Etafilcon A (n = 20)</th>
<th>Control† (n = 20)</th>
<th>No Lens Wear‡ (n = 13)</th>
<th>No Lens Wear§ (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overnight swelling (%)</td>
<td>2.71 ± 1.91</td>
<td>1.44 ± 0.91</td>
<td>8.66 ± 2.84</td>
<td>2.34 ± 1.26</td>
<td>2.65 ± 1.49</td>
<td>2.33 ± 1.57</td>
</tr>
<tr>
<td>Range (%)</td>
<td>0.75–9.11</td>
<td>0.43–4.61</td>
<td>4.58–14.8</td>
<td>0.56–6.16</td>
<td>0.17–4.75</td>
<td>0.51–6.62</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
* The contralateral left eye (control) response on the night that the Lotrafilcon A lens was worn.
† The contralateral left eye (control) response on the night that the Etafilcon A lens was worn.
‡ The right eye response (previously lens-wearing eyes * and †) when no lens was worn.
§ The left eye on the night when no lens was worn on the right eye contralateral (control). This was the eye that served as the control in the first two experimental procedures.

Biomicroscopy was performed by a different observer to assess the cornea for the presence of corneal striae. This procedure was repeated every 20 minutes after pachometry and before light-scatter measurements for approximately 2 hours or until the striae had disappeared.

After the lenses were inserted, they were allowed to settle before sleep. The lens and the postlens tear film were examined to ensure the lens was fitting correctly and symmetrically covered the cornea and that no postlens tear film debris was present. The subjects then slept in the Center for Contact Lens Research laboratories and remained in this area throughout each experiment.

After the lens-wearing experiments were completed, we were able to recruit 13 of the subjects to return for an additional night of experimentation to measure the overnight corneal swelling response of both eyes with no lens wear.

**Data Analysis**

Repeated measures analysis of variance was performed on corneal swelling and light-scatter outcome variables. The effects of measurement time (baseline, eye opening, 20 minutes, and so on), lens material (Lotrafilcon A versus Etafilcon A) and eye (control versus experimental) were examined. The planned pairwise comparisons of the corneal swelling and light-scatter variables were performed using paired t-tests. Comparisons were made between the responses of the two lens materials, between the lens-wearing eyes versus their controls, and between the two control sets of eyes. The significance level for these was set at 0.05.

**RESULTS**

**Contact Lens–Induced Overnight Corneal Swelling**

The corneal swelling results induced by the contact lenses with 8 hours of eye closure (sleep) are shown in Table 3. The three-hour deswelling profiles after lens removal and the respective control eye (no lens wear) deswelling functions are shown in Figures 1, 2, and 3. Zero on the abscissa represents baseline corneal thickness. The overall analysis showed that there were differences in average swelling that depended on material type (F = 52.6; P < 0.0001), control versus experimental eyes (F = 67.1; P < 0.0001) and time after eye opening (F = 183.7; P < 0.0001). The most salient interaction was the one showing that the effect of lens material depended on time after eye opening (F = 35.3; P < 0.0001).

The Lotrafilcon A lens induced significantly less corneal swelling than the Etafilcon A lens (paired t-test; P = 0.0000). The deswelling, as shown in Figure 1, was much quicker for the Lotrafilcon A–induced corneal swelling (100 minutes) than for that induced by Etafilcon A, which took approximately 180 minutes.

The Etafilcon A lens-wearing eyes swollen an average of 8.66% ± 2.84%, which was significantly more than control eyes (2.34% ± 1.26%) without lenses in the same test session (paired t-test; P < 0.0000). The deswelling profile (Fig. 2) of the control eye recovered commensurately with the initial swelling. The Lotrafilcon A lens-wearing eyes swollen an average of 2.71% ± 1.91%, which was significantly more than the control eyes (1.44% ± 0.91%) without lenses in the same test session (paired t-test; P = 0.0006).

**Measures of Control Eye Overnight Corneal Swelling**

The contralateral eye of each subject was used as the control (no lens wear). The contralateral closed eye swelling results at three sessions are shown in Table 3 in columns 2, 4, and 6. Figure 4 is a comparison of the deswelling curves of the control eyes when they were measured for the respective hydrogel lenses. There is a clear separation of the curves. The control
eyes swelled significantly more when the Etafilcon A lenses were worn in the other eye than when the Lotrafilcon A lenses were worn (paired t-test; \( P < 0.0002 \)). Figure 5 shows the individuals’ control eye swelling responses. Except for four cases in which the differences were very small, the data plots of the other 16 subjects show that the control eye swelled more when the Etafilcon A lens was worn in the other eye. This indicates the possibility of a sympathetic effect.

It was for this reason that we recalled 13 subjects to have them sleep in the laboratory without wearing lenses to remeasure the swelling effects of eye closure with no contralateral lens. The consequence was a swelling effect of 2.33\% \pm 1.57\%.

The difference between this value, however, and the swelling in the control eye (1.38\% \pm 0.58\%) were not statistically significant for the same 13 subjects when wearing the Lotrafilcon A lens in the other eye (paired t-test; \( P > 0.05 \)).

**Light Scatter**

The overall analysis of average light scatter showed that there were no differences that depended on material type (\( F = 0.4; P = 0.5 \)); there were differences between control and experimental eyes (\( F = 6.8 P = 0.017 \)) and time after eye opening (\( F = 18.9; P < 0.0001 \)). Most important, however, there was an interaction showing that there was a difference in light scatter for the different lens materials that depended on time after eye opening (\( F = 2.125; P < 0.05 \)). The results are presented in Figure 6. In a comparison of the two experimental eyes, Etafilcon A eyes exhibited more light scatter than the Lotrafilcon A eyes at lens removal and 20 minutes and 40 minutes after removal (paired t-tests \( P = 0.0078, P = 0.0143, \) and \( P = 0.0223 \), respectively). Interestingly, the same trend as corneal swelling was seen, with the Etafilcon A controls showing more light scatter than the Lotrafilcon A controls at lens removal and up to 60 minutes (paired t-test; \( P = 0.24 \)).

**DISCUSSION**

The anticipation of a hydrogel contact lens that delivers sufficient O2 to the cornea according to the criterion of Holden and
Mertz,2 which was documented 15 years ago, appears to have been realized. This prototype silicone hydrogel is one of two materials that are currently under investigation.30,31 The nominal (Dk/T = 175 × 10⁻⁹) transmissibility of this lens is greater than 87 × 10⁻⁹, which was the predicted lens value that would not produce any more edema when worn than eye closure alone. Although the difference between the Lotrafilcon A–induced swelling (2.71% ± 1.91%) and that of the control (1.44% ± 0.91%) was statistically significant, this difference is probably clinically insignificant. However, the difference in Lotrafilcon A–induced overnight swelling was significantly less than the Etafilcon A–induced overnight swelling of 8.66% ± 2.84% and most certainly is of clinical importance.

Our results of Etafilcon A lens-induced overnight swelling and no-lens-wear overnight corneal swelling appear to be consistently lower by 1% to 1.5% than previously published reports.12–17,22 Figures 1 through 4 all show deswelling beyond baseline by approximately 1%, where baseline is the zero ordinate value on each graph. This phenomenon has been documented previously.32,33 and it may be physiological. Another plausible explanation is that the baseline measurements at 4 PM were not the minimum corneal thickness values. This is difficult to rationalize, because the corneal thickness measurements (deswelling) were completed at approximately 10 AM, and the baseline measurements were recorded the previous day at 4 PM. Therefore, if anything, the 10 AM thicknesses should have been more than baseline. The 1% corneal thickness difference between baseline and the 180-minute measurement after lens removal would account for the difference between our swelling results and the others that were previously mentioned. Diurnal variation suggests that corneas are thinnest in the evening.34 although there is more recent evidence that shows that 4 PM measurements are the same as those at 10 PM.35

The choice of experimental design for this study was a practical and accepted method.2,26,29 The alternative to using the subjects’ contralateral eye as a control would have been to use a separate control group, thus having to double the sample size. If this latter design were chosen, it would not have revealed the serendipitous apparent yoked (sympathetic) response of the contralateral eyes. The Lotrafilcon A lens appeared to be associated with commensurately less swelling of the control eye than the Etafilcon A lens, and the difference was statistically significant. Although we do not propose a mechanism, the fact that 16 of the 20 subjects exhibited this phenomenon would suggest this to be physiologically rather than a coincidental statistical aberration. The light-scatter scores in the control eyes showed the same trend as the corneal swelling—that is, light scatter was slightly lower in the control eye when it was paired with the Lotrafilcon A than with the Etafilcon A lens. The fact that different investigators using different instruments and techniques measured a similar response pattern lends further support to the idea of an apparent sympathetic swelling effect.

However interpretation of the corneal swelling effects of the contralateral eye is confounded by the corneal swelling results when no lenses were worn on either eye. In this case the left eye swelled 2.33% ± 1.57% (Table 3) compared with the contralateral control of 2.34% ± 1.26% when the Etafilcon A lens (low Dk) was worn on the other eye (right). Unfortunately, only 13 of the 20 subjects returned for the non-lens-wear experiment. If the suggested sympathetic effect is real, we expect that the high-Dk lens is responsible for affecting a lower swelling response of 1.44% in the contralateral eye. The presence of silicone in the high-Dk hydrogel lens may suppress corneal swelling in the lens-wearing eye17,32 and thus affect the contralateral eye.

Another observation of contralateral corneal swelling while wearing a rigid contact lens on the other eye was by Harris.25 The response was presumed to be due to an osmolarity effect as a result of lacrimation. Further support for our suggestion of a sympathetic effect has been shown by Druaix et al.36 in a study in which excimer laser photoablation induced an increase in the hyaluronan content of treated and untreated contralateral rabbit corneas. Therefore, when the epithelium is disrupted because of hypoxia or mechanical irritation by a contact lens, it is conceivable that the production of matrix material such as hyaluronan induces swelling in the contralateral eye. However, it is unlikely that the edema produced by a hydrogel lens is attributable to mechanical irritation, especially during sleep when presumably very little lens and lid movement occurs.

The forward light-scatter plots in Figure 6 show that the measures had returned to baseline approximately 60 minutes after lens removal and eye opening, with Etafilcon A–induced scatter lasting somewhat longer. Because the forward light-scatter technique used in this experiment was presumed to essentially measure epithelial effects by using a 3.5° angle, it appears that stromal edema may have been partially responsible for the scatter because the epithelium usually regains its transparency well within an hour.37

The sample size of 20 was chosen to ensure that the study would have sufficient power to yield a statistically significant difference if corneal swelling were a few percentage points. This was in fact the case because there was even a difference in swelling between the control eyes at different sessions. However, when the non-lens-wear experiment was repeated, we were able to recruit only 13 subjects. In comparing the overnight swelling results for these 13 subjects, when no lens was worn in the other eye, the control eyes (left) swelled 2.33% ± 1.57% compared with 1.44% ± 0.91% when the Lotrafilcon A lens was worn in the other eye. The difference between these two responses was not statistically significant, showing the value of a larger sample size. Perhaps more im-

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**Figure 6.** Forward light-scatter measurements (mean ± SEM) before wearing and after contact lens removal after 8 hours of sleep. The plots include the lens-wearing eyes with error bars and their respective controls without error bars.
important, however, in using large sample sizes is the wide range of individual swelling results displayed in Table 3. This shows that corneas in some subjects swelled substantially even with a highly permeable hydrogel lens, indicating a range of oxygen demand in human subjects.

There are a number of interesting observations to be made about this study. The first is that the low-swelling contralateral eye seems to have been affected by the swelling response of the eye wearing the high-Dk lens. It is clear that further work will have to be conducted to corroborate this hypothesis. If this finding were true, the paradigm of using the contralateral eye as a control would be inappropriate. The second observation is that we now have a hydrogel contact lens that induces only slightly, but significantly more, corneal swelling than the nonwearing control eye. This would suggest that the transmissibility of the hydrogel lens has to be slightly higher than 175 × 10⁻⁹ or that the swelling of the control eye using this paradigm was an inappropriate comparison.

References