In Vivo Corneal Oxygen Uptake During Soft-Contact-Lens Wear

Sho C. Takatori,[1] Percy Lazon de la Jara,[2,3] Brien Holden,[2–4] Klaus Ehrmann,[2,3] Arthur Ho,[2–4] and Clayton J. Radke[1,5]

[1]Department of Chemical and Biomolecular Engineering, University of California, Berkeley, Berkeley, California
[2]Brien Holden Vision Institute, Sydney, New South Wales, Australia
[3]School of Optometry & Vision Science, University of New South Wales, Sydney, New South Wales, Australia
[4]Vision Cooperative Centre, Sydney, New South Wales, Australia
[5]Vision Science Group, University of California, Berkeley, Berkeley, California

Correspondence: Clayton J. Radke, Department of Chemical and Biomolecular Engineering, University of California, 101E Gilman, Berkeley, CA 94720-1462; radke@berkeley.edu.

Submitted: October 18, 2012
Accepted: March 31, 2013

Citation: Takatori SC, Lazon de la Jara P, Holden B, Ehrmann K, Ho A, Radke CJ. In vivo corneal oxygen uptake during soft-contact-lens wear. *Invest Ophthalmol Vis Sci*. 2013;54:3472–3478. DOI:10.1167/iovs.12-11169

Purpose. We develop a new method to compute in situ corneal oxygen uptake during soft-contact-lens (SCL) wear using a micro-polarographic Clark electrode.

Methods. After steady SCL wear and subsequent removal, a membrane-covered polarographic microelectrode is immediately placed onto the cornea. The resulting polarographic signal is related to the steady-state corneal oxygen uptake rate during soft-contact-lens wear. We devise a new analysis to quantify oxygen uptake into the cornea during lens wear. The proposed procedure is applied to new polarographic data for 10 human subjects with 12 different commercial lenses during open eye. We compare our results with recent theory.

Results. Average corneal oxygen uptake rates at open eye during SCL wear for 10 subjects wearing 12 different commercial lenses vary from 2 to 10 μL(STP)/cm^2/h. High oxygen permeability lenses have uptake rates of ~10 μL(STP)/cm^2/h, in close agreement with our previously obtained no-lens human uptake rates of 9 to 13 μL(STP)/cm^2/h at open eye.[40] Application of the classical data-interpretation procedure to our experimental data gives corneal-uptake results that are approximately three to five times smaller than those obtained with our new interpretation scheme.

Conclusions. We provide a simple and reliable tool to quantify corneal-oxygen-uptake rates during in vivo soft-contact-lens wear. Comparison of our newly measured in vivo oxygen uptakes to model prediction for SCLs of varying oxygen transmissibility is in good agreement with available theory.

Keywords: corneal-oxygen uptake, soft contact lens, polarographic oxygen sensor, long-time analysis, corneal oxygenation

The human cornea is nourished and supplied anteriorly with oxygen by the environment. Contact lenses with low oxygen transmissibility (i.e., $D_L k_L/L_L$, where $D_L k_L$ is the lens oxygen permeability and L_L is the lens thickness) impede environmental oxygen supply[1–3] and may cause corneal edema, acidosis, and various adverse events associated with oxygen deficiency.[4–6] Quantifying the critical oxygen demand of the human cornea has, thus, received decades of attention and some debate.[7–27] Most efforts focus on mathematical modeling,[1–3,7,24,28–32] but—with some exceptions[1–3]—do not incorporate the metabolic processes of the human cornea. Consequently, in vivo experimental methods to ascertain the corneal oxygen uptake have received attention,[33–36] most notably the polarographic oxygen sensor (POS) of Fatt et al.[37–39] Unfortunately, the classical analysis of POS data has recently come into question.[40]

The POS technique employs a Clark oxygen microelectrode[41,42] to quantify atmospheric oxygen flux into the human cornea with and without soft-contact-lens (SCL) wear.[14,35–39,43–62] Briefly, the membrane-covered Clark microelectrode is emplaced either directly onto the cornea or on a worn contact lens. The resulting instrument signal is converted into oxygen partial pressure at the anterior corneal or lens surface.[14,35–39,41–62] Rasson and Fatt[37,39] developed an interpretation scheme for soft contact lens wear, but incorrectly neglected limiting current[63–65] at the cathode and assumed that oxygen initially in the protective membrane diffused into the lens with no oxygen flux into the cathode. Thus, traditional interpretation of POS data[37–39] that relates the initial slope of a semilogarithmic graph of measured partial pressure versus time to the steady-state oxygen flux into the cornea prior to microelectrode placement[38,50,51,54,58–60] is inadequate. Consequently, we devised a new procedure to quantify in vivo corneal oxygen uptake without SCL wear.[40]

Here we extend that previous development without SCL wear[40] to quantify corneal oxygen uptake during SCL wear. The presence of a SCL demands a slightly more involved mathematical description, but the calculation of oxygen uptake remains straightforward and consistent with previous modeling efforts. The proposed interpretation scheme is applied to newly measured POS data for 10 human subjects with 12 different commercial SCLs under open-eye conditions. Our simple, yet rigorous, procedure provides a reliable tool for in vivo

Table 1. Contact Lens Parameters

Contact Lens Name	Oxygen Diffusivity, D_L, 10^{-7} cm²/s*	Oxygen Partition Coefficient, k_L, 10^{-3} mL O_2 (STP)/mL mm Hg	Oxygen Permeability, $D_L k_L$, Barrer†	Lens Thickness, L_L, μm
Acuvue 2	3.2	0.88	28	74 (−3.00 D)
Focus Night & Day	8.4	1.67	140	93 (−3.00 DS), 137 (+6.00 DS)
O_2 Optix	5.8	1.9	110	88 (−3.00 DS), 108 (+6.00 DS)
PureVision	6.0	1.52	91	120 (−3.00 DS), 126 (+6.00 DS)
Acuvue Oasys	4.5	2.29	103	78 (−3.00 DS)
Acuvue Advance	4.2	1.43	60	92 (−3.00 DS), 129 (+6.00 DS)
Acuvue Moist	3.2‡	0.88	28	84 (−3.00 D)
CibaSoft	0.7§	1.14	8	125 (+6.00 DS)

* Diffusivity values obtained from Chhabra et al.[66] unless otherwise stated.
† 1 Barrer = 10^{-11} (cm²/s)(mL O_2 [STP])/(mL mm Hg).
‡ Estimated from the oxygen diffusivity and partition coefficient in Acuvue 2, a similar material.
§ Estimated from the oxygen diffusivity and partition coefficient in Biomedics 38, a similar material.

assessment of oxygen uptake for both previous data in the literature and for those newly obtained.

Methods

Experiment

A Clark-type micro-polarographic oxygen sensor (POS; Radiometer E5047/0 and Radiometer Amplifier PHM 73; Radiometer, Copenhagen, Denmark) linked to a personal computer was used to quantify the corneal-oxygen-uptake rate of 10 subjects. The supplied probe was equipped with a 30-μm diameter platinum cathode and an 18-μm thick polymer membrane. The sensor was calibrated in distilled/deionized water (Milli-Q; Millipore Corp., Billerica, MA) at 36°C saturated with air (155 mm Hg O_2) and with pure nitrogen (0 mm Hg O_2) to convert probe readings to oxygen tension. The probe was routinely immersed in a nitrogen-saturated aqueous solution to ensure proper calibration throughout the experiment. The sensor protective membrane was saturated initially with oxygen at 155 mm Hg for all measurements.

Ten nonhabitual contact-lens wearers were enrolled in a prospective, nondispensing, randomized, open label clinical study. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. A total of 12 commercial SCLs were tested on each subject on different days but under the same conditions: five silicone hydrogel lenses (–3.00 DS and +6.00 DS Focus NIGHT & DAY [CIBA Vision, Duluth, GA]; O2Optix [CIBA Vision]; PureVision [Bausch & Lomb, Rochester, NY]; Acuvue Advance [Vistakon, Jacksonville, FL]; and –3.00DS Acuvue OASYS [Vistakon]), and three conventional hydrogels (+6.00 D CibaSoft [CIBA Vision]; –3.00D Acuvue Moist [Vistakon]; and –3.00 D Acuvue 2 [Vistakon]). Table 1 lists the central 8-mm harmonic mean thicknesses, nominal oxygen permeabilities, oxygen diffusivities, and partition coefficients of each SCL.

The same 10 human subjects examined in the nonlens wear study were assessed for their nascent corneal oxygen uptake as reported previously.[40] In separate settings, a SCL was worn in one eye under open-eye conditions. After 45 minutes of wear, the lens was slid off the cornea, and the POS was immediately applied perpendicularly onto the center of the cornea. Anterior corneal oxygen tension was then measured with subjects fixated straight ahead at a target 3 m away. Transient oxygen tensions were measured in both eyes of every subject: once for the eye with the SCL and once for the eye without the SCL. The lens-wearing eye and the order of measurements were assigned randomly. Each SCL experiment lasted approximately 1 hour. Measured oxygen-tension decline curves were analyzed as described below to ascertain the steady-state oxygen flux into the cornea before the POS was applied.

The goal of the POS clinical study was to ascertain environmental oxygen uptake (i.e., oxygen flux) into human corneas during contact-lens wear, $J_o(0)$, and to compare those values with the previously determined values without contact lens wear, $J_o^*(0)$, on the same subjects. Units chosen for oxygen uptake are μL O_2(STP)/cm²/h.

Oxygen Transport

Because the measured data correspond to the Clark microelectrode applied directly onto the cornea after lens removal, we extend our no-lens analysis[40] with a minor change in the initial steady-state oxygen profile in the cornea. Figure 1 shows expected transient oxygen partial-pressure profiles upon placing the Clark electrode probe onto the bare cornea immediately after SCL wear. Since the lens is absent, only the probe resting against the cornea is depicted. As in the no-lens analysis,[40] we adopt a one-dimensional analysis and neglect axial diffusive resistance of the thin electrolyte film between the

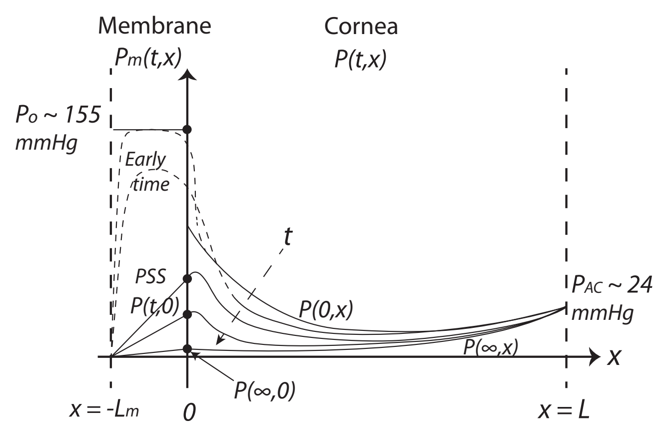

Figure 1. Illustration of transient oxygen tension profiles upon placing a POS onto the cornea after SCL wear and removal. *Solid curves* represent transient oxygen-tension profiles in the covering membrane, $P_m(t,x)$, of thickness, L_m, and in the cornea, $P(t,x)$, of thickness, L. The steady-state oxygen profile before microelectrode emplacement is demarked by $P(0,x)$. *Dashed curves* show the early time profiles before membrane pseudo-steady state (PSS) is established. *Filled circles* along the membrane/anterior corneal interface at $x = 0$ represent the measured POS data. The *dashed line with an arrow* denotes progression of time. Oxygen tension at the endothelium/anterior chamber interface, P_{AC}, may be lower than that with no contact lens wear,[70] but gives no change in our calculated results.

cathode and the covering membrane and that of the thin tear film between the covering membrane and the cornea. In Figure 1, $x = -L_m$ corresponds to the anterior membrane/electrode interface, $x = 0$ corresponds to the posterior membrane/anterior cornea interface, and $x = L$ specifies the posterior cornea/anterior chamber interface. Oxygen concentration at the electrode surface ($x = -L_m$) is zero because of the limiting-current condition.[40,66] Because the cathode surface consumes oxygen, a flux of oxygen is directed out of the membrane toward the electrode surface. This is illustrated in Figure 1 by the positive slope of all tension profiles at $x = -L_m$. This observation contrasts with that of Rasson and Fatt[37,39] who assumed that oxygen initially in the membrane was directed only into the SCL with no oxygen flux into the electrode. Figure 1 differs somewhat from the corresponding Figure 1 in Takatori et al.[40] in that the initial steady-state tension profile in the cornea, $P(0,x)$, reflects the cornea during contact-lens wear. For this reason, there is a discontinuity in the membrane tension at time zero between $P_m(0,x) = 155$ mm Hg and that at the corneal anterior surface, $P(0,0)$. This discontinuity begins to vanish immediately after probe emplacement.

Dashed profiles in Figure 1 correspond to very early time when the POS is first positioned onto the cornea following wear of the contact lens. In this time frame, oxygen is supplied from the membrane both to the cornea raising oxygen locally in the cornea and to the electrode where oxygen is reduced to hydroxide ions.[40] Here, the POS signal does not correspond to the oxygen tension at the membrane/cornea interface because the tension profile in the membrane is not linear. Oxygen tension is measured only after the membrane achieves pseudo-steady state, or for times exceeding L_m^2/D_m, where D_m is the oxygen diffusivity in the membrane. Once the profiles in the membrane become linear (solid lines in Fig. 1), the POS signal correctly reflects the oxygen tension at the corneal surface, shown as filled circles at $x = 0$ in Figure 1. For the POS used in our experiments, membrane pseudo-steady state is achieved in approximately 20 s.[40] Thus, beyond 20 s—depending on membrane material and thickness—oxygen-tension profiles in the membrane, $P_m(t,x)$, are linear starting from zero at membrane/electrode surface ($x = -L_m$). Eventually, the net flux of oxygen is directed into the membrane toward the microelectrode and is supplied by the cornea (see Fig. 1). The cornea then acts as a source of oxygen for the electrode.

A maximum tension appears in the cornea after membrane pseudo-steady state is established. Farther into the cornea (near $x = 0$), oxygen also diffuses into the cornea due to metabolic oxygen demand. The maximum in the corneal-tension profile moves inward in time, ultimately merging into a monotonic decline from the anterior chamber to the membrane. Finally, a terminal steady-state profile, labeled as $P(\infty,x)$ in Figure 1, is reached where the anterior chamber supplies oxygen to both the microelectrode and the cornea.

We seek the magnitude of $J_o(0)$, the flux of oxygen into the anterior cornea corresponding to that established during contact-lens wear before the microelectrode was emplaced. $J_o(0)$ is also equivalent to the steady oxygen flux through the SCL and into the cornea before probe insertion. Modeling efforts indicate that during contact-lens wear, the cornea also receives some oxygen from the anterior chamber.[1–3,67] $J_o(0)$, however, reflects only oxygen supply to the epithelium and to the anterior sections of the stroma. After membrane pseudo-steady state is achieved, the POS signal is linearly proportional to the oxygen tension at the corneal surface, $P(t,0)$.[37,40] As in our previous effort,[40] we relate $P(t,0)$ to the oxygen uptake into the cornea at $x = 0$.

Filled circles in Figure 1 at $x = 0$ illustrate how the measured oxygen tensions decline in time starting from $P_o = 155$ mm Hg (open eye) down to the final steady state of $P(\infty,0)$, a value much less than $P_{AC} = 24$ mm Hg (anterior chamber). A reactive-diffusion model is required to convert the measured transient decline of $P(t,0)$ to oxygen uptake of the cornea, $J_o(0)$. A brief summary of our interpretation scheme is outlined below.

Oxygen Uptake

Transient diffusion of oxygen through the cornea and the covering membrane to the POS electrode has been analyzed previously.[40] The distinction here is that the steady profile of oxygen in the cornea before POS placement (see curve $P(0,x)$ in Fig. 1) is that corresponding to SCL wear in the environment rather than to that of a bare cornea exposed to the environment. As shown in Appendix A, the oxygen-tension profile across an SCL is linear following Fick's second law. The tension profile of the contact lens–covered cornea also follows Fick's second law, but now including a first-order reactive loss of oxygen (see Equation 6 in Takatori et al.[40]). The resulting steady tension profiles in the SCL and in the cornea are given by Equations A1 and A2. The desired steady oxygen flux through the lens and into the cornea follows directly as described in Appendix A:

$$J_o(0) = \varphi\left[\frac{\cosh\varphi - P_{AC}/P_o}{\beta_L\varphi(\cosh\varphi) + \sinh\varphi}\right]Dk\frac{P_o}{L} \qquad (1)$$

where D is the average diffusivity of oxygen in the cornea; k is the average partition coefficient of oxygen in the cornea (i.e., the product Dk is the corneal oxygen permeability); and L is the average corneal thickness. D and k are taken here as characteristic of the stroma,[1–3,67] and are reported in Table 2 along with L, and membrane properties.[68,69] P_o (155 mm Hg) is the open-eye oxygen tension in the environment, and P_{AC} (24 mm Hg) is the oxygen tension at the anterior chamber. Oxygen tensions at the endothelium/anterior chamber interface may take on much lower values during contact-lens wear[70] than that listed in Figure 1 with no impact on our results. $\varphi^2 = k_1L^2/Dk$ is the square of the Thiele modulus[71] or the Damköhler number,[72] with k_1 the first-order rate constant or the zero-tension slope of the Monod rate expression for oxygen consumption.[40,67] The parameter $\beta_L = DkL_L/(D_Lk_LL)$ is the ratio of diffusion resistance of oxygen in the SCL to that in the cornea. Values for the SCL oxygen diffusivities, D_L, and partition coefficients, k_L, are from Chhabra et al.,[66] as listed in Table 2. Thus, the only unknown parameter in Equation 1 is the first-order metabolic consumption rate constant, k_1 (embedded in the Thiele modulus). Once k_1 is obtained for each subject with each lens, in vivo oxygen uptake by the cornea during contact-lens wear can be determined. Equation 1 applies also to no–contact lens wear. In the limit of zero lens thickness, it correctly reduces to the previous result that[40]

$$J_o^*(0) = \varphi\left[\frac{\cosh\varphi - P_{AC}/P_o}{\sinh\varphi}\right]Dk\frac{P_o}{L}. \qquad (2)$$

Comparison of Equations 1 and 2 shows that SCL wear reduces oxygen uptake into the cornea so that $J_o(0)/J_o^*(0) < 1$. High SCL oxygen transmissibility (i.e., a large value of D_Lk_L/L_L), reduces the parameter β_L toward zero resulting in unimpeded oxygen flow into the cornea.

To obtain the metabolic consumption rate constant k_1 for a particular subject, tension data from the POS must be analyzed. Because we slide off the SCL before measurement and consider only long-time data, the analysis is identical to that in our previous effort.[40] Measured transient tensions are graphed on a semilogarithmic scale versus time, such as shown in Figure 2. The experiment must be carried out long enough so that the graph becomes linear in time:

Table 2. Physical Parameters

Parameter (Units)	Value	Source
D_m (cm^2/s)*	2.44×10^{-7}	Kroschwitz & Seidel[68]; Jensen et al.[69]
D (cm^2/s)†	1.28×10^{-5}	Chhabra et al.[2]
k_m (mL[STP]/[mL mm Hg])	6.97×10^{-5}	Jauregui & Fatt[38]
k (mL[STP]/[mL mm Hg])	2.30×10^{-5}	Chhabra[66]
L_m (µm)	18	Radiometer
L (µm)	480	Chhabra et al.[2]

* Determined from measured oxygen permeability in the polymer membrane ($D_m k_m = 1.7$ Barrer[68,69]) after division by the partition coefficient $k_m = 6.97 \times 10^{-5}$ mL (STP)/(mL mm Hg).[38]

† Determined from oxygen permeability in the stroma ($Dk = 29.5$ Barrer[2]) after division by the partition coefficient $k = 2.3 \times 10^{-5}$ mL (STP)/(mL mm Hg).[66]

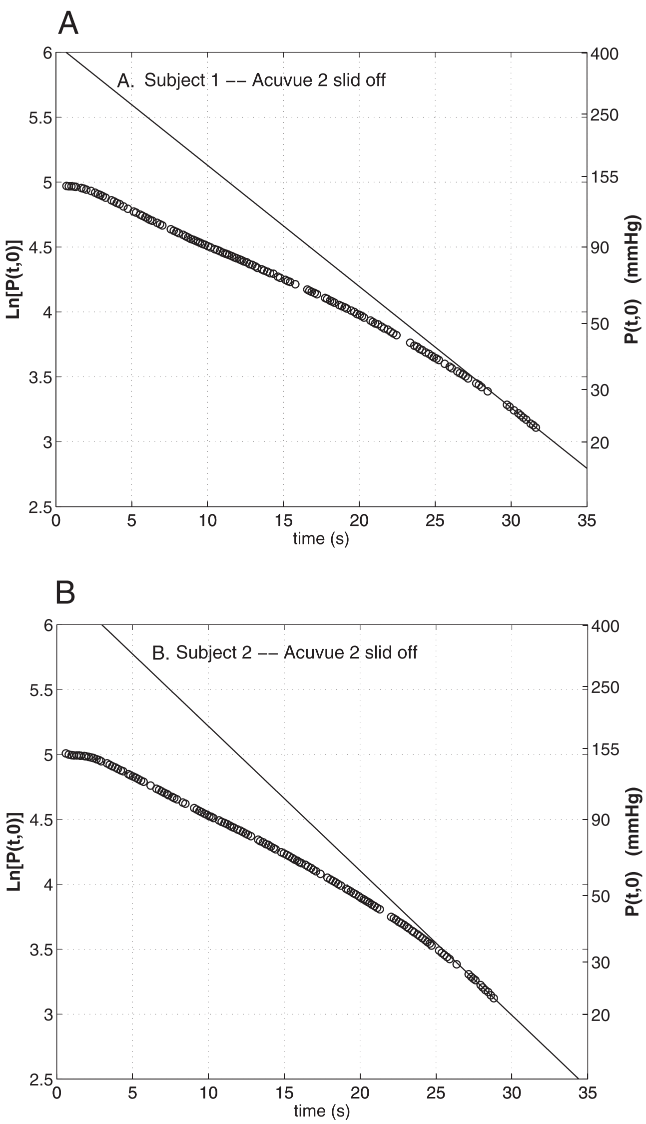

Figure 2. Measured open-eye POS tensions (*open circles*) reported as a semilogarithmic graph of $ln[P(t,0)]$ and $P(t,0)$ versus time immediately after removal of a –3.00 D Acuvue 2 lens. Least squares fit *straight lines* through the long-time linear regions of the data give the negative slope α_1. (**A**) Subject 1. (**B**) Subject 2. Oxygen tension is reported in mm Hg.

$$\ln P(t,0) = \ln A_1 - \alpha_1 t \tag{3}$$

with negative slope α_1, as illustrated by the solid line in Figure 2. With α_1 experimentally determined, the first-order metabolic rate constant follows as

$$k_1 k^{-1} = \alpha_1 - b_1^2 D/L^2 \tag{4}$$

where b_1 is established by trial and error from

$$\tan b_1 + \beta b_1 = 0 \tag{5}$$

and $\beta = DkL_m/(D_m k_m L)$ is the ratio of diffusion resistance in the membrane to that in the cornea. The specific POS used in this study is identical to that used previously so that the values of β (0.649) and b_1 (2.18) are available.[40] This exercise determines k_1 for the individual subject under study and, hence, ascertains oxygen uptake from Equation 1 (or Equation 2 in the case of no–contact lens wear). Calculation of corneal oxygen uptake from our experimental-POS tension data and Equation 1 prove insensitive to the exact choice of P_{AC}. Values of the posterior-endothelium oxygen tension as low as 5 mm Hg alter $J_o(0)$ by less than 1%. This result makes physical sense because almost all of the oxygen supply to the cornea originates at the anterior surface, not at the anterior chamber.

It is possible to place the POS directly onto the SCL without removing the lens and to perform the measurement. In this case, however, it takes longer both to reach a pseudo-steady state in the membrane and to obtain the long-time exponential phase of Equation 3 in the cornea. As importantly, a more involved analysis is required. For completeness, we record this analysis online in Supplementary Appendices B and C.

Results and Discussion

POS measurements for two human subjects wearing Acuvue 2 lenses are shown in Figure 2 following lens slide-off on semilogarithmic scales. Corresponding best eye-fit straight lines at later time are also shown in Figure 2. As demanded by Equation 3, semilogarithmic linear behavior emerges at later times. Table 3 presents our results during open eye for 12 SCLs averaged over a single measurement for each lens on each of 10 subjects. Average semilogarithmic slopes, α_1, with error limits at 95% confidence, calculated metabolic rate constants, expressed as k_1/k, and oxygen uptakes, $J_o(0)$ in µL(STP)/cm^2/h are summarized. Error limits for $J_o(0)$ reflect the 95% Student's *t*-test confidence limits in the measured slopes α_1.

Comparison of the oxygen-consumption rate constants, k_1 (i.e., reported as $k_1 k^{-1}$), in Table 3 and with those in Table 2 of our earlier work[40] show minor variations among subjects both with and without SCL wear. Further, k_1 values are very close in magnitude independent of whether or not a SCL is worn. Since oxygen-metabolism kinetics is a property of the human cornea

Table 3. Open-Eye Corneal Oxygen Uptake During SCL Wear*

Contact Lens	α_1, s^{-1}	k_1k^{-1}, s^{-1}	$J_o(0)$, $\mu L/cm^2/h$ SCL Slide-Off†
Acuvue 2, −3.00 D	0.09 ± 0.01	0.06 ± 0.01	7.2 ± 0.5
Focus Night & Day, −3.00 DS	0.09 ± 0.01	0.06 ± 0.01	10 ± 0.8
Focus Night & Day, +6.00 DS	0.09 ± 0.07	0.06 ± 0.01	9.1 ± 0.5
O_2 Optix, −3.00 DS	0.09 ± 0.01	0.06 ± 0.01	9.4 ± 1.0
O_2 Optix, +6.00 DS	0.09 ± 0.01	0.06 ± 0.01	9.2 ± 0.6
PureVision, −3.00 DS	0.09 ± 0.02	0.05 ± 0.02	8.3 ± 1.5
PureVision, +6.00 DS	0.08 ± 0.02	0.05 ± 0.02	7.8 ± 2
Acuvue Oasys, −3.00 DS	0.09 ± 0.01	0.06 ± 0.01	9.7 ± 0.5
Acuvue Advance, −3.00 DS	0.09 ± 0.01	0.06 ± 0.01	8.6 ± 0.4
Acuvue Advance, +6.00 DS	0.09 ± 0.01	0.06 ± 0.01	7.8 ± 0.8
Acuvue Moist, −3.00 D	0.09 ± 0.01	0.06 ± 0.01	6.9 ± 0.6
CibaSoft, +6.00 DS	0.12 ± 0.01	0.09 ± 0.01	2.8 ± 0.04

* All error estimates are based on 95% confidence in a Student's *t*-test.

† Calculated from Equation 1 using $P_o = 155$ mm Hg.

and not of the lens, this result strengthens the validity of our analysis.

Table 3 further reveals that thicker lenses of the same material result in lower uptake, as expected from the relative magnitudes of the driving force for oxygen diffusion and the resistance embodied in lens transmissibility. For identical lens materials, an increased thickness leads to an increased transport resistance and, accordingly, to lower oxygen uptake into the cornea. In Table 3, all thicker +6.00 DS lenses exhibit lower average oxygen flux than those for the corresponding thinner −3.00 DS lenses.

Anterior oxygen uptake rates in Table 3 vary from 2 to 10 $\mu L(STP)/cm^2/h$ at open eye. No-lens uptake rates are around 9 to 13 $\mu L(STP)/cm^2/h$ at open eye.[40] High oxygen permeability lenses in Table 3 evidence uptake rates of almost 10 $\mu L(STP)/cm^2/h$, approaching those of the no-lens situation. The traditional analysis of Fatt and coworkers[37–39] applied to our POS data in Table 3 results in corneal-oxygen uptake values that are 3 to 5 times smaller. Variability among the limited number of subjects and SCLs is not large for both interpretation schemes.

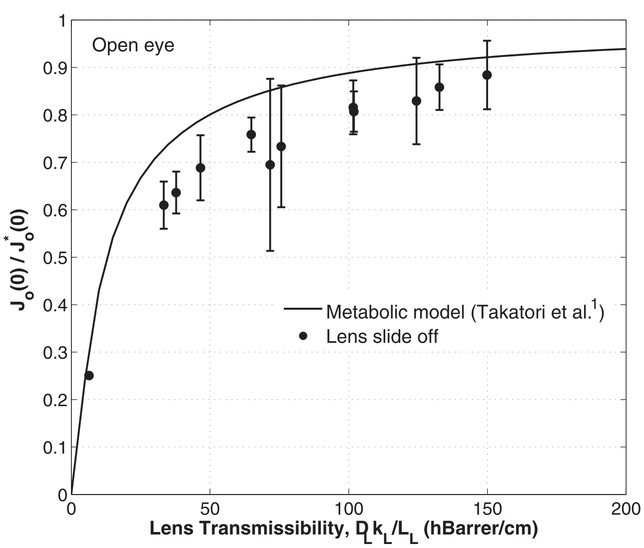

Figure 3. Fraction of oxygen uptake into the human cornea by SCL wear at open eye, $J_o(0)/J_o^*(0)$, as a function of lens transmissibility. *Filled circles* with maximum *error bars* represent measured values from the lens slide-off experiment. Each datum is an average value over 10 subjects. The no-lens wear (*baseline*) uptake was $J_o^*(0) = 11.3$ $\mu L/cm^2/h$, the average no-lens flux over the same 10 subjects.[40] The *solid line* corresponds to an available theoretical model[1] that asymptotes to unity at higher D_Lk_L/L_L (not shown in figure).

Although corneal oxygen uptake with SCL wear in Table 3 is lower than that without contact-lens wear reported in Table 2 of our earlier work,[40] the difference diminishes as lens transmissibility, D_Lk_L/L_L, increases. This point is emphasized in Figure 3 that graphs oxygen uptake into the cornea with lens wear, $J_o(0)$, relative to that without lens wear, $J_o^*(0)$, as a function of SCL transmissibility, D_Lk_L/L_L. Oxygen-uptake fraction is shown as filled circles with error bars. Each datum is an average of $J_o(0)$ over 10 subjects while the no-lens wear (baseline) oxygen flux was set at $J_o^*(0) = 11.3$ $\mu L/cm^2/h$, the average no-lens uptake over the same 10 subjects.[40] The solid line corresponds to an available model.[1] The two subject-specific parameters in the model,[1] the maximum Monod oxygen consumption rate and the oxygen permeability of the cornea, were established to yield $J_o^*(0) = 11.3$ $\mu L/cm^2/h$ during no-lens wear. Lens permeability in the model calculations[1] was then varied from 0 to 200 Barrer to produce the solid curve. Agreement between measured oxygen-uptake reduction due to SCL wear and that predicted is good showing the validity of the theoretical model and the validity of the POS measurement/interpretation procedure. Both theory and POS experiment reveal that full oxygenation of the human eye, 11.3 $\mu L/cm^2/h$ for the 10 subjects studied, is reached only asymptotically. That is, very high lens transmissibility is required before the lens no longer impedes oxygen transport. Conversely, 90% anterior corneal oxygenation is achieved with a lens transmissibility of 150 hBarrer/cm.

In vivo no-lens uptake rates using a POS with our proposed interpretation scheme are around 9 to 13 $\mu L(STP)/cm^2/h$ at open eye.[40] With SCL wear, corneal-oxygen flux falls to 2 to 10 $\mu L(STP)/cm^2/h$ depending on lens transmissibility. Thus, although our subject size is small, we experimentally verify that an SCL impedes oxygen diffusion into the cornea and by how much. Previous corneal oxygen uptakes based on the interpretation scheme of Fatt and coworkers[37–39] are inaccurate because the POS-covering membrane is assumed to be well mixed with no supply of oxygen to the Clark electrode.[73] Also, Figure 2 reveals that POS tensions do not initially decay linearly in time on a semilogarithmic graph, as assumed in the Fatt analysis.

Our new POS data for the effect of SCLs on human-corneal oxygenation confirms quantitatively the role of lens transmissibility in controlling the amount of oxygen the cornea receives. Agreement between theory and experiment is good.

This finding confirms the validity of the POS experimental data and protocol. Although POS measurements can be taken directly on the SCL during wear, we recommend lens removal because the analysis is straightforward and because pseudo-steady state is achieved quickly allowing subject comfort. We also recommend that the POS membrane not be saturated at environmental oxygen tension (i.e., 155 mm Hg) but closer to that of the steady value at the anterior cornea surface during SCL wear (i.e., at $P(0,0)$ in Fig. 1) since the time to achieve pseudo-steady state is reduced. An estimated value for $P(0,0)$ is available from Equation A2 in Appendix A.

We recommend adoption of our lens-slide-off POS experiment and analysis in future measurements of the effects of contact-lens wear on corneal oxygenation.

Acknowledgments

Disclosure: **S.C. Takatori**, None; **P. Lazon de la Jara**, Australian Government Cooperative Research Centre Program (F), Brien Holden Vision Institute (F, E); **B. Holden**, Australian Government Cooperative Research Centre Program (F), Brien Holden Vision Institute (F, E); **K. Ehrmann**, Australian Government Cooperative Research Centre Program (F), Brien Holden Vision Institute (F, E); **A. Ho**, Australian Government Cooperative Research Centre Program (F), Brien Holden Vision Institute (F, E); **C.J. Radke**, None

References

1. Takatori SC, Radke CJ. A quasi-2-dimensional model for respiration of the cornea with soft contact lens wear. *Cornea*. 2012;31:405–417.
2. Chhabra M, Prausnitz JM, Radke CJ. Modeling corneal metabolism and oxygen transport during contact lens wear. *Optom Vis Sci*. 2009;86:454–466.
3. Leung BK, Bonanno JA, Radke CJ. Oxygen-deficient metabolism and corneal edema. *Prog Retin Eye Res*. 2011;30:471–492.
4. Bruce AS, Brennan NA. Corneal pathophysiology with contact lens wear. *Surv Ophthalmol*. 1990;35:25–58.
5. Smelser GK, Chen DK. Physiological changes in cornea induced by contact lenses. *AMA Arch Ophthalmol*. 1955;53: 676–679.
6. Sweeney DF. Clinical signs of hypoxia with high-Dk soft lens extended wear: is the cornea convinced? *Eye Contact Lens*. 2003;29:S22–S25. discussion (suppl 26)-29, S192–S194.
7. Brennan NA. Beyond flux: total corneal oxygen consumption as an index of corneal oxygenation during contact lens wear. *Optom Vis Sci*. 2005;82:467–472.
8. Brennan NA, Efron N, Weissman BA, Harris MG. Clinical application of the oxygen transmissibility of powered contact lenses. *CLAO J*. 1991;17:169–172.
9. Efron N, Brennan NA. In search of the critical oxygen requirement of the cornea. *Contax*. 1987;2:5–11.
10. Efron N, Fitzgerald JP. Distribution of oxygen across the surface of the human cornea during soft contact lens wear. *Optom Vis Sci*. 1996;73:659–665.
11. Fatt I, Neumann S. The average oxygen transmissibility of contact lenses: application of the concept to laboratory measurements, clinical performance and marketing. *Contact Lens J*. 1990;18:80–85.
12. Fatt I, Ruben CM. A new oxygen transmissibility concept for hydrogel contact lenses. *J Br Contact Lens Assoc*. 1993;16: 141–149.
13. Fatt I, Ruben CM. The point-to-point variation of oxygen delivery to a cornea covered by a hydrogel contact lens in the open eye. *Int Contact Lens Clin*. 1994;21:50–56.
14. Hill RM, Fatt I. Oxygen deprivation of the cornea by contact lenses and lid closure. *Am J Optom Arch Am Acad Optom*. 1964;41:678–687.
15. Hill RM, Fatt I. Oxygen measurements under a contact lens. *Am J Optom Arch Am Acad Optom*. 1964;41:382–387.
16. Holden BA, Mertz GW. Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. *Invest Ophthalmol Vis Sci*. 1984;25:1161–1167.
17. Huang P, Zwang-Weissman J, Weissman BA. Is contact lens "T" still important? *Cont Lens Anterior Eye*. 2004;27:9–14.
18. Morgan PB, Efron N. The oxygen performance of contemporary hydrogel contact lenses. *Cont Lens Anterior Eye*. 1998;21:3–6.
19. O'Neal MR, Polse KA, Fatt I. Oxygen permeability of selected GPH polymers and predictions of tear layer oxygen tension. *Int Contact Lens Clin*. 1983;10:256–266.
20. Compan V, Lopez-Alemany A, Riande E, Refojo MF. Biological oxygen apparent transmissibility of hydrogel contact lenses with and without organosilicon moieties. *Biomaterials*. 2004; 25:359–365.
21. Fatt I. Have we found the cornea's 'critical oxygen requirement'? *Optician*. 1987;194:17–21.
22. Fatt I. Is there a problem in EOP land? *Int Contact Lens Clin*. 1993;20:150–152.
23. Fatt I. New physiological paradigms to assess the effect of lens oxygen transmissibility on corneal health. *CLAO J*. 1996;22: 25–29.
24. Harvitt DM, Bonanno JA. Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. *Optom Vis Sci*. 1999;76: 712–719.
25. Mandell RB, Polse KA, Fatt I. Corneal swelling caused by contact lens wear. *Arch Ophthalmol*. 1970;83:3–9.
26. Polse KA, Mandell RB. Critical oxygen tension at the corneal surface. *Arch Ophthalmol*. 1970;84:505–508.
27. Weissman BA, Fazio DT. Human corneal oxygen flux under soft contact lenses. *Am J Optom Physiol Opt*. 1982;59:635–638.
28. Brennan NA. Corneal oxygenation during contact lens wear: comparison of diffusion and EOP-based flux models. *Clin Exp Optom*. 2005;88:103–108.
29. Fatt I. Steady-state distribution of oxygen and carbon dioxide in the in vivo cornea. II. The open eye in nitrogen and the covered eye. *Exp Eye Res*. 1968;7:413–430.
30. Fatt I, Bieber MT. The steady-state distribution of oxygen and carbon dioxide in the in vivo cornea. I. The open eye in air and the closed eye. *Exp Eye Res*. 1968;7:103–112.
31. Fatt I, Bieber MT, Pye SD. Steady state distribution of oxygen and carbon dioxide in the in vivo cornea of an eye covered by a gas-permeable contact lens. *Am J Optom Arch Am Acad Optom*. 1969;46:3–14.
32. Fatt I, Freeman RD, Lin D. Oxygen tension distributions in the cornea: a re-examination. *Exp Eye Res*. 1974;18:357–365.
33. Bonanno JA, Stickel T, Nguyen T, *et al*. Estimation of human corneal oxygen consumption by noninvasive measurement of tear oxygen tension while wearing hydrogel lenses. *Invest Ophthalmol Vis Sci*. 2002;43:371–376.
34. Harvitt DM, Bonanno JA. Direct noninvasive measurement of tear oxygen tension beneath gas-permeable contact lenses in rabbits. *Invest Ophthalmol Vis Sci*. 1996;37:1026–1036.
35. Hill RM, Fatt I. Oxygen uptake from a reservoir of limited volume by the human cornea in vivo. *Science*. 1963;142:1295–1297.
36. Hill RM, Fatt I. Oxygen depletion of a limited reservoir by human conjunctiva. *Nature*. 1963;200:1011–1012.
37. Fatt I. Measurement of oxygen flux into the cornea by pressing a sensor onto a soft contact lens on the eye. *Am J Optom Physiol Opt*. 1978;55:294–301.
38. Jauregui MJ, Fatt I. Estimation of oxygen tension under a contact lens. *Am J Optom Arch Am Acad Optom*. 1971;48: 210–218.

39. Rasson JE, Fatt I. Oxygen flux through a soft contact lens on the eye. *Am J Optom Physiol Opt*. 1982;59:203–212.
40. Takatori SC, Lazon de la Jara P, Holden B, et al. In vivo oxygen uptake into the human cornea. *Invest Ophthalmol Vis Sci*. 2012;53:6331–6337.
41. Clark LC, Sachs G. Bioelectrodes for tissue metabolism. *Annals New York Acad Sci*. 1968;148:133–153.
42. Clark LC Jr, Wolf R, Granger D, Taylor Z. Continuous recording of blood oxygen tensions by polarography. *J Appl Physiol*. 1953;6:189–193.
43. Farris RL, Takahashi GH, Donn A. Oxygen flux across the in vivo rabbit cornea. *Arch Ophthalmol*. 1965;74:679–682.
44. Fatt I. An ultramicro oxygen electrode. *J Appl Physiol*. 1964; 19:326–329.
45. Fatt I. The oxygen electrode: some special applications. *Annals New York Acad Sci*. 1968;148:81–92.
46. Fatt I, Helen RS. A multicathode polarographic oxygen sensor and its performance. *J Appl Physiol*. 1969;27:435–437.
47. Fink B, Hill RM. Corneal oxygen uptake: A review of polarographic techniques, applications, and variables. *Cont Lens Anterior Eye*. 2006;29:221–229.
48. Fink BA, Carney LG, Hill RM. Intra-subject variability of human corneal oxygen uptake. *Int Contact Lens Clinic*. 1990;17:224–227.
49. Fitzgerald JP, Efron N. Oxygen uptake profile of the human cornea. *Clin Exp Optom*. 1986;69:149–152.
50. Larke JR, Parrish ST, Wigham CG. Oxygen sensors for clinical use. *J Br Contact Lens Assoc*. 1980;3:70–74.
51. Larke JR, Parrish ST, Wigham CG. Apparent human corneal oxygen uptake rate. *Am J Optom Physiol Opt*. 1981;58:803–805.
52. Lazon de la Jara P, Holden BA, Terry R, La Hood D, Ehrmann K. Oxygen levels and oxygen flux with silicone hydrogel contact lenses under open and closed eye conditions. Poster presented at: the American Academy of Optometry (AAO) meeting; December 7–9, 2006; Denver, CO.
53. Augsburger AR, Hill RM. Corneal anesthetics and epithelial oxygen flux. *Arch Ophthalmol*. 1972;88:305–307.
54. Bentley CR, Larke JR. Apparent respiration rate of the human corneal epithelium with tetracaine HCl and benoxinate HCl. *Am J Optom Physiol Opt*. 1983;60:960–963.
55. Chi JM, Fink BA, Hill RM, Mitchell GL. Factors influencing the measurement of oxygen shortfall of the human cornea: sequencing of test conditions. *Cont Lens Anterior Eye*. 2007;30:17–21.
56. Holden BA, Polse KA, Fonn D, Mertz GW. Effects of cataract surgery on corneal function. *Invest Ophthalmol Vis Sci*. 1982; 22:343–350.
57. Holden BA, Sweeney DF, Vannas A, Nilsson KT, Efron N. Effects of long-term extended contact lens wear on the human cornea. *Invest Ophthalmol Vis Sci*. 1985;26:1489–1501.
58. Morris J, Ruben M. Clinical aspects of the measurement of oxygen flux into the cornea. *Br J Ophthalmol*. 1981;65:97–100.
59. Parrish ST, Larke JR. Apparent corneal oxygen uptake rate and debt in contact lens wearing subjects. *J Bri Contact Lens Assoc*. 1982;5:54–58.
60. Quinn TG, Schoessler JP. Human corneal epithelial oxygen demand–population characteristics. *Am J Optom Physiol Opt*. 1984;61:386–388.
61. Takahashi GH, Fatt I. The diffusion of oxygen in the cornea. *Exp Eye Res*. 1965;4:4–12.
62. Takahashi GH, Fatt I, Goldstick TK. Oxygen consumption rate of tissue measured by a micropolarographic method. *J Gen Physiol*. 1966;50:317–335.
63. Chhabra M, Prausnitz JM, Radke CJ. A single-lens polarographic measurement of oxygen permeability (Dk) for hypertransmissible soft contact lenses. *Biomaterials*. 2007;28: 4331–4342.
64. Mancy KH, Okun DA, Reilley CN. A galvanic cell oxygen analyzer. *J Electroanal Chem*. 1962;4:65–92.
65. Newman JS, Thomas-Alyea KE. *Electrochemical Systems*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2004:377–405.
66. Chhabra M, Prausnitz JM, Radke CJ. Polarographic method for measuring oxygen diffusivity and solubility in water-saturated polymer films: application to hypertransmissible soft contact lenses. *Ind Eng Chem Res*. 2008;47:3540–3550.
67. Chhabra M, Prausnitz JM, Radke CJ. Diffusion and Monod kinetics to determine in vivo human corneal oxygen-consumption rate during soft contact-lens wear. *J Biomed Mat Res B: Appl Biomat*. 2009;90B:202–209.
68. Kroschwitz JI, Seidel A. *Kirk-Othmer Encyclopedia of Chemical Technology*. 5th ed. Hoboken, NJ: Wiley-Interscience. 2004:381–382.
69. Jensen OJ, Jacobsen T, Thomsen K. Membrane-covered oxygen electrodes: I. Electrode dimensions and electrode sensitivity. *J Electroanal Chem Interf Electrochem*. 1978;87:203–211.
70. McLaren JW, Dinslage S, Dillon JP, *et al*. Measuring oxygen tension in the anterior chamber of rabbits. *Invest Ophthalmol Vis Sci*. 1998;39:1899–1909.
71. Fogler HS. Diffusion and reaction. In: Fogler HS. *Elements of Chemical Reaction Engineering*. 4th ed. Upper Saddle River, NJ: Prentice Hall; 2006:819–823.
72. Deen WM. Analysis of Transport Phenomena. 2nd ed. New York: Oxford University Press; 2012:56.
73. Takatori SC, Lazon de la Jara P, Holden B, et al. Author response: In vivo oxygen uptake into the human cornea. *Invest Ophthalmol Vis Sci*. 2012;53:6829.

Appendix A. Steady Tension Profile With SCL Wear

We desire in vivo oxygen uptake by the human cornea during SCL wear or the steady flux of oxygen through the lens and into the cornea just before POS placement onto the eye—i.e., $J_o(0)$. Solutions of the steady-state forms of Equation 6 in Takatori et al.[40] without the reaction term for the lens and with reactive loss for the cornea give the initial steady oxygen profiles

$$P_L(0,x) = P_{AC}\left[\frac{1-(P_o/P_{AC})\cosh\varphi}{\cosh\varphi+(\beta_L\varphi)^{-1}\sinh\varphi}\right]x/L_L + P_{AC}\left[\frac{1+(\beta_L\varphi)^{-1}(P_o/P_{AC})\sinh\varphi}{\cosh\varphi+(\beta_L\varphi)^{-1}\sinh\varphi}\right] \qquad (A1)$$

and

$$P(0,x) = P_{AC}\left[\frac{1+(\beta_L\varphi)^{-1}(P_o/P_{AC})\sinh\varphi}{cosh\varphi+(\beta_L\varphi)^{-1}\sinh\varphi}\right]\cosh(\varphi x/L) + P_{AC}\left[\frac{1-(P_o/P_{AC})\cosh\varphi}{(\beta_L\varphi)\cosh\varphi+\sinh\varphi}\right]\sinh(\varphi x/L) \qquad (A2)$$

where $P_L(0,x)$ and $P(0,x)$ are the steady-state profiles in the SCL and cornea, respectively, $\varphi^2 = k_I L^2/Dk$ is the square of the Thiele modulus, and $\beta_L = DkL_L/(D_Lk_LL)$ is the ratio of diffusion resistance in the SCL to that in the cornea.

Since oxygen flux at steady state is identical through the lens and into the cornea, we have that

$$J_o(0) = -Dk(\partial P(0,0)/\partial x) = J_o(-L_L) = -D_Lk_L(\partial P_L(0,0)/\partial x) \qquad (A3)$$

Thus, oxygen uptake follows immediately upon differentiation of Equations A1 or A2 as reported in Equation 1 of the text.

Investigative Ophthalmology & Visual Science