Critical Contact Lens Oxygen Transmissibility and Tear Lens Oxygen Tension to Preclude Corneal Neovascularization

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Objective: The purpose of this study is to determine the peripheral oxygen transmissibility (pDk/t) and respective central oxygen transmissibility (cDk/t) in soft contact lenses (SCLs) which might preclude SCL-driven corneal neovascularization (NV) in healthy myopic SCL users.

Methods: Twenty subjectively successful SCL-wearing patients who presented with asymptomatic but active peripheral corneal NV (not ghost vessels) were recruited as study patients. Twenty-one patients who did not have NV were similarly recruited as controls. Demographic data were collected. Corneal NV was documented and photographed. Current habitual SCLs were collected and thicknesses measured to allow for the calculation of both pDk/t and cDk/t and estimation of local tear oxygen tensions.

Results: No statistical differences between study and control groups in patient age, refraction, or the numbers of years, days per week, or hours per day patients reported SCL wear were identified. Statistically significant differences were found between the two groups for both pDk/t (P = 0.006) and cDk/t (P = 0.004): mean (±SD) pDk/t was 38.0 ± 23.5 and 19.2 ± 17.7 Fatt units for control and study corneas, respectively. Mean cDk/t were 80.0 ± 54.4 and 36.8 ± 33.1 Fatt units for control and study corneas, respectively. Peripheral tear oxygen tension that “protected” corneas from vascular filling was over 84 mm Hg.

Conclusion: Maintaining a pDk/t above 30 to 40 Fatt units with daily wear SCLs should protect most normal corneas from NV as a complication of SCL wear.

Keywords: Oxygen transmissibility—Contact lens—Corneal neovascularization—Silicone—hydroxyethylmethacrylate.

Healthy corneas are transparent to light in part because blood vessels are excluded in what has been described as “lymphangiogenic privilege.” Growth of blood vessels into the cornea, also called corneal neovascularization (NV), is always a pathological finding and is the result of a diseased state or other corneal insult. It is probably the result of the liberation of vasoproliferative cytokines (e.g., vascular endothelial growth factor) from stressed cells that overwhelm anti-angiogenic factors.2-6

Initially NV is peripheral, subjectively silent, and usually slow in progression, only becoming symptomatic when disturbing vision. When caused by contact lens (CLs) wear, NV is usually superficial (e.g., a pannus) in the upper and middle third of the stroma but rarely can be found deeper in the stroma.7-11 Corneal NV can also eventually cause both stromal opacification and intracorneal hemorrhage.12,13 When the stimulus to corneal NV is removed, vessels lose their blood column but remain as clear tubules in the tissue, although often difficult to clinically visualize. These have been termed “ghost” vessels14,15 which refill with blood when the stimulus is reintroduced.

Prevalence of NV among CL wearers has been estimated between <1% and 34%, with a lower prevalence in those who wear rigid gas permeable (GP) as opposed to hydrogel or soft contact lens (SCLs) CLs.9,16-18 Nomura et al.,18 for example, recently noted a prevalence of NV in 30% of hydrogel wearers and 7% in rigid GP lens wearers. There seems to be an increased NV risk for patients who are highly myopic,19,20 have severe dry eyes,21 or have ocular surface disease (e.g., idiopathic or associated with other inflammatory/immune diseases),22 such as rosacea23 and Stevens–Johnson syndrome.24 Deep stromal NV may be associated with active or healed infections, corneal grafts, and keratoconus.10,25 Neovascularization is also more prevalent in those who sleep with CLs (e.g., extended wear), wear hydrogel CLs made from “low” oxygen permeable (DK) plastics,26 and in those who use aphakic or therapeutic CLs.27,28 Keech et al.,29 in particular, noted that 18% of extended SCL wearers and 11% of daily wear hydrogel CL wearers show some degree of corneal NV. It is of concern that eyes with corneal NV may be more susceptible to future inflammatory events compared with eyes without corneal NV.30,31

Both Duffin et al.32 and Chan and Weissman14 showed that the pannus associated with CL wear can be related to CL-driven hypoxia. Further demonstrating the role of corneal oxygenation in the genesis of corneal NV, Dumbleton et al.26 showed no change in NV during 9 months of observation of patients using CLs for extended wear who wore high oxygen transmissibility (DK/t) silicone hydrogel SCLs, compared with NV progression in patients who similarly wore traditional hydroxyethylmethacrylate (HEMA) low DK/t SCLs.

Although critical oxygen metrics have been quantized in the literature for several corneal and conjunctival functions (such as corneal swelling and limbal injection),35-37 a value has not been proposed for corneal NV. The purpose of this proposed research is to begin to quantify a minimal SCL peripheral oxygen transmissibility (pDk/t) that would preclude corneal NV in otherwise healthy myopic corneas.

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METHODS

This study was performed in compliance with the Declaration of Helsinki and approved by the University of California, Los Angeles (UCLA) Arthur Ashe Student Health and Wellness Center and the UCLA Institutional Review Board. Informed consent was provided to all subjects before any data acquisition.

Between July 2015 and February 2016, patients with myopia who wore their habitual SCLs into their comprehensive eye examinations at the UCLA Arthur Ashe Student Health and Wellness Center in Los Angeles were recruited. The study group consisted of a cohort of 20 patients with myopia who all showed active corneal NV in one or both eyes but were otherwise healthy. A cohort of 21 subjects recruited from the same clinic but not diagnosed with corneal NV served as a control group. We recruited two groups of a target size of 20 patients each because previous statistical sample size and power calculation evaluations of earlier data suggested that two groups (n = 15) each would be appropriate for this study. Only one eye per patient was studied. If both eyes demonstrated corneal NV and qualified for the study, the one eye studied was randomly chosen for evaluation by coin toss.

In our study, NV was defined as superficial or deep corneal blood vessels that extended 0.5 mm or more into the cornea beyond the normal limbal vascular arcade and showed a blood column (as opposed to “ghost” vessels). Such active corneal NV was diagnosed clinically with slit-lamp biomicroscopy, using both direct focal and retro illumination.

Inclusion criteria included subjectively successful daily wear spherical SCL wear on the eyes of essentially healthy normal patients with myopia. Subject patients were excluded if they presented with a history of any eye trauma, disease (e.g., keratoconus), eye surgery (e.g., corneal transplants or laser-assisted in situ keratomileusis) or if they reported any systemic disease (e.g., diabetes) that might increase the risk of eye issues, especially corneal NV. Exclusion factors also included patients who were younger than 18 years, had not worn SCLs for more than 6 months, and any patient who self-reported any sleeping with their CLs (extended wear). Extended wear was defined in this study as sleeping in CLs overnight (greater than 6 hr at a stent) at least once a week routinely for at least 6 months preceding their UCLA Arthur Ashe eye examination.

Demographic data collected for each patient included age, sex, average CL wear time, CL wear frequency, frequency of CL replacement, age of current CLs, CL care solutions used, years of wearing CLs, brand of current CL, horizontal visible iris diameter (VID), vertical VID, and a professional assessment of the fit of the CL on the eye. Peripheral corneal NV (our “subject group”) was photodocumented (Fig. 1).

During the examinations, each patient was refitted in new CLs, or given new SCLs of the previous prescription if their prescription was not being changed. With the patients permission, their old CLs were donated to the study and stored at the time of eye examination in a new clean case with fresh preserved multipurpose CL solution (Optifree Puremoist; Alcon, Fort Worth, TX). Each case was labeled with a code, so that patient data integrity could be maintained without use of personal identifiers.

Central and peripheral thicknesses of the SCLs were later measured to permit quantification of local Dk/t units. Measurement occurred no more than a few weeks after clinical evaluation. All CLs to be measured were noted to be well hydrated in clear-appearing solution at the time of measurement.

Peripheral Dk/t and central oxygen transmissibility (cDk/t) of each SCL were determined in the following manner. After each SCL was removed from its container, the center and location over the patient’s VID were identified by carefully centering the SCLs on a custom-made prescored (at various diameters in millimeters) metal hemisphere. Any excess fluid was blotted with lint-free tissue, and marks were made with an extra-fine point permanent marker at both the SCL center and in the lens periphery. The lens periphery mark was recorded at the horizontal and/or vertical VID for each subject. We approximated that this is where the SCL overlies previously recorded peripheral corneal NV. Each SCL was then replaced in its case to rehydrate for at least a minute. The SCL was then removed again from its storage container and gently reblotted with lint-free tissue before CL thicknesses were measured at both the central and peripheral locations with an electrical thickness gauge. Five individual readings were taken at each location for each SCL. No differences were found between these measurements; however, there was no need to average, and only the first measurement value was recorded.

The nominal Fatt Dk units (units of oxygen permeability [Dk] are ×10−11 [cm2/s]/mL O2/mL mm Hg), whereas units of CL oxygen transmissibility [Dk/t] are ×10−9 [cm/s]/mL O2/mL mm Hg, but both will be reported here as “Fatt Dk units” and “Fatt Dk/t units” respectively, for simplicity of the SCL materials supplied by the CL manufacturers in the literature allowed for calculation of local Fatt Dk/t units at each SCL center and periphery. Using each calculated Dk/t value, local pO2 values in the tear layer between the lens and the cornea were then calculated using the Brennan spreadsheet method. Parametric statistics was used to evaluate our results.

RESULTS

Analysis of our data shows that both study (subject) and control groups are demographically homogenous. Subjects are similar in age, sex, and refractive prescription (Table 1).

There were statistically significant differences (Student t test), however, in both SCL pDk/t and cDk/t Fatt units and between our

FIG. 1. Clinical photograph of observed filled corneal NV (see arrow) seen in our subject group. In this instance, the patient presented wearing a 58% water nonsilicone hydrogel CL. CL, contact lens; NV, neovascularization.
subject and control groups. Mean±SD pDk/t was 38.0±23.5 Fatt Dk/t units for the control and 19.2±17.7 Fatt units for the study group CLs (P=0.006, with power of 0.84). Similarly, mean±SD cDk/t was 80.0±54.4 Fatt Dk/t units for the control CLs and 36.8±33.1 Fatt units for those CLs whose corneas showed NV (P=0.004 with power of 0.93) (Table 2).

Using stepwise regression analysis, the observed variations in both SCL peripheral and central oxygen transmissibility values were solely captured by the group variable. No other collected confounding factors, such as subject age, number of hours subjects reported wearing their SCLs per day, number of times that they wore CLs per week, or the number of years that the subjects reported having worn CLs, could statistically explain the variation of the oxygen transmissibility values.

The Brennan spreadsheet method calculated mean±SD peripheral tear oxygen tension of 46±30 mm Hg for the eyes that showed actively “filled” corneal vessels (our “study” cohort). Predicted mean±SD peripheral tear layer oxygen tension was 84±39 mm Hg for corneas that showed no NV.

### DISCUSSION

The critical oxygen tension at the anterior corneal surface to preclude corneal swelling (stromal edema) was initially proposed at 11 to 19 mm Hg. Over time, this metric increased closer to 100 mm Hg or greater for both stromal edema and other corneal/conjunctival physiological functions. Hypoxic corneal stromal edema, however, is most likely mediated by enhanced lactate production through increased anaerobic glycolysis and not by liberation of secondary vasoproliferative or inflammatory cytokines, as suggested for NV.

Figure 2 presents our data in a Box plot for both central and peripheral oxygen transmissibility values. Box edges represent the 25th and 75th percentiles. Whiskers are the extreme parameters, and asterisks are outliers. Corneal neovascularization (study subject group) is significantly associated with lower Dk/t SCLs in both groupings. Dk/t, oxygen transmissibility; SCL, soft contact lens.

Previous authors have proposed different critical Dk/t thresholds for peripheral corneal oxygen requirements during open-eye SCL wear. These can be divided into those proposed for precluding corneal edema (swelling) and those for precluding limbal vessel injection, which, as discussed above, most likely follow different metabolic pathways. Alvord et al., for example, using finite element modeling, suggested that the peripheral cornea is hypoxic when SCLs ≤100 Fatt Dk/t units are worn, but Brennan suggested this value should be revised to ≤30 Fatt Dk/t units if a proper anterior chamber oxygen pressure is used in the calculation. Morgan et al. also found that peripheral corneal swelling was avoided during wear of SCLs ≥30 Fatt Dk/t units.

More similar to our work, but still not quite the same (as we studied, not limbal or conjunctival but corneal NV), Papas suggested that 125 Fatt Dk/t units were needed to avoid limbal vascular filling (“redness”). Maldonado-Codina et al. similarly found that limbal and conjunctival injection developed during lower Dk/t hydrogel SCL wear (several optical powers) could be avoided with higher Dk/t silicone SCLs.

Although different endpoints and methodologies are used, our results seem to be more consistent with the threshold pDk/t proposed by both Brennan and Morgan et al. for corneal swelling.
We clinically note that two of our subjects (the outliers seen in Fig. 2) presented with active NV, as opposed to ghost vessels, while wearing higher Dk silicone SCLs. We suspect that previous eye examinations had resulted in the diagnosis of NV and we suspect the treatment was refitting into higher Dk silicone SCLs. Providing patients with higher Dk silicone SCLs undoubtedly provides corneas more oxygen—but perhaps not enough to preclude corneal vessel blood filling in all cases (including our two outliers). Sweeney,51 for example, found low levels of corneal edema continuing with a small population of patients wearing silicone SCLs. This suggested to her that such patients have a higher oxygen demand, perhaps from a high refractive error and/or extended wear. Corneal oxygen influx also is known to have a wide range.52,53

As also supported by Figure 2, there is a large range of tolerance for the stimulation of active NV. Clinically, we have seen some patients who do not develop NV even with years of extended wear using traditional HEMA (nonsilicone) SCLs. And then there are those patients who, after months of use of new silicone SCLs, continue to show active NV with blood columns rather than ghost vessels (as noted in our subject outliers). Such variability can be caused by many factors. Smith et al.,54 for example, showed that corneal relief from hypoxia is not linearly related with Dk/t.

Nomura et al.18 reported a correlation between the amount of CL wear in numbers of times CLs are worn per week and an increased likelihood of developing NV and with more severe NV. Although we did not quantify the severity of NV in our patients, our study surprisingly did not find any correlation with NV and the number of hours subjects reported wearing their SCLs per day, nor with the number of times that they wore CLs per week, nor with the number of years that the subjects reported having worn CLs. This lack of correlation may be attributed to our small sample size.

Our study’s limitations also include self-reported data. This includes the number of hours per day our subjects wore CLs, number of years of CL wear, and their denials of extended wear. We also do not know the complete preceding CL histories of our patients, including the years of silicone versus traditional HEMA (nonsilicone) SCLs wear. We acknowledge that the silicone SCL wearers who present with active corneal NV may be those who would be most sensitive to NV than others. And, as it is difficult to accurately measure the length of corneal NV in vivo, we did not attempt to correlate such growth with SCL Dk/t here.

Theory suggests that the thickest portion of the CL will create the greatest local hypoxic effect to the immediate underlying corneal tissue.53,55,56 We, therefore, suspect that pDk/t is probably the most important factor driving NV. Unfortunately, CL manufacturers currently only provide information of cDk/t (and usually of only a −3.00 diopter sphere optically powered CL) in their literature as the indicator of oxygen transmission through an entire range of CLs of various optical powers and peripheral thicknesses. A few (if any) clinicians measure, and no manufacturers provide, values for the thickest portion of the CL—the “local Dk/t” of any given CL parameter. We, therefore, provide cDk/t information in this study to assist the practicing clinician who wishes to use the results of our research. We acknowledge, however, that values of cDk/t are not consistently associated with any specific pDk/t values, even if Dk is constant, due to variance in optical powers.

Given the relatively high Dk/t values of most silicone hydrogel materials, we suspect minimal if any corneal NV should develop for the most patients who use silicone SCLs solely for daily wear. Although prevalence of silicone SCL use is high, constituting 66% for their participation in data collection.

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REFERENCES