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Hypersensitivity to Cold Stimuli in Symptomatic Contact Lens Wearers

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Abstract

Purpose—To examine the cooling thresholds and the estimated sensation magnitude at stimulus detection in controls and symptomatic and asymptomatic contact lens (CL) wearers, in order to determine whether detection thresholds depend on the presence of symptoms of dryness and discomfort.

Methods—49 adapted CL wearers and 15 non-lens wearing controls had room temperature pneumatic thresholds measured using a custom Belmonte esthesiometer, during Visits 1 and 2 (Baseline CL), Visit 3 (2 weeks no CL wear) and Visit 4 (2 weeks after resuming CL wear). CL wearers were subdivided into symptomatic and asymptomatic groups based on comfortable wearing time (CWT) and CLDEQ-8 score (<8 hours CWT and 14 CLDEQ-8 stratified the symptom groups). Detection thresholds were estimated using an ascending method of limits and each threshold was the average of the three first-reported flow rates. The magnitude of intensity, coolness, irritation and pain at detection of the stimulus were estimated using a 1-100 scale (1 very mild, 100 very strong).

Results—In all measurement conditions, the symptomatic CL wearers were the most sensitive, the asymptomatic CL wearers were the least sensitive and the control group was between the two CL wearing groups (group factor $p < 0.001$, post hoc asymptomatic vs. symptomatic group, all p 's < 0.015). Similar patterns were found for the estimated magnitude of intensity and irritation (group effect $p=0.027$ and 0.006 for intensity and irritation, respectively) but not for cooling ($p>0.05$) at detection threshold.

Conclusions—Symptomatic CL wearers have higher cold detection sensitivity and report greater intensity and irritation sensation at stimulus detection than the asymptomatic wearers. Room temperature pneumatic esthesiometry may help to better understand the process of sensory adaptation to CL wear.

Keywords

hypersensitivity; pneumatic cool stimuli; contact lens discomfort

Contact lens discomfort (CLD), characterized by episodic or persistent adverse ocular sensations with or without visual disturbances,¹ is commonly reported among contact lens wearers,² according to the report of The TFOS International Workshop on Contact Lens Discomfort. Despite the advances in lens design, materials and solution, CLD remains a great challenge for short- or long-term success with contact lens wear,² perhaps partly because the underlying mechanisms involved are still poorly understood, as summarized in the report.³

The lacrimal functional unit comprises the ocular surface (cornea, conjunctiva, and meibomian glands), the lacrimal glands, and the sensory afferent and efferent sympathetic and parasympathetic nerves that connect them.⁴ The complex neural network of the functional unit plays an important role in linking the components into a homeostatic loop regulating tear secretion and maintaining the health of the ocular surface.⁴ Dysfunction of any part of the integrated unit may compromise the ability of the functional unit to respond to environmental and physiological changes.⁴

Contact lenses closely interact with several areas of the functional unit including the cornea, conjunctiva and the eyelids during lens wear. All of these tissues are densely innervated by sensory fibers⁵ and stimulation from a contact lens will give rise to sensory input to the integrated functional unit. Most of the sensory nerve fibers innervating the cornea are polymodal nociceptors that are activated by near-noxious or noxious mechanical, thermal and chemical stimuli while cold-sensitive receptors that represent about 10-15% of the total population are activated by temperature reduction of the ocular surface.⁶ These cold receptors also respond to the drying and increasing tear osmolarity of the ocular surface, and thus may control the level of tear secretion.^{7,8}

Altered functioning of sensory nerves during contact lens wear assessed by psychophysical sensitivity measurement has been widely reported⁹⁻¹³ although the mechanisms involved in this change are not known. This altered functioning has been demonstrated in short- and long-term lens wearers as well as in wearers of lenses with different materials.¹¹⁻¹³ Reduction in corneal sensitivity, particularly measured using a Cochet-Bonnet esthesiometer, has been noted with polymethyl methacrylate (PMMA),¹⁰ rigid gas permeable,¹¹ orthokeratology¹⁴ and conventional hydrogel lenses¹¹ while recent studies have shown increased corneal and conjunctival sensitivity to pneumatic stimuli with silicone hydrogel lens wear and in discontinued lens wearers.^{12,13,15} Because these changes in sensitivity appear reversible,⁹ sensory adaptation to the mechanical effect of the lenses^{16,17} and hypoxia resulting from lens materials with low permeability to oxygen¹⁸ have been proposed as potential factors that may account for the loss of sensitivity in contact lens wear. However, it is unclear how these changes in sensory processing with contact lens wear could contribute to CLD, although recently it has been suggested that differences in sensory adaptation in symptomatic and asymptomatic lens wearers may play a role.¹⁹ Little is known about the relationship between the presence of CLD symptoms and corneal sensitivity as well as subjective experiences of the cooling stimulation, although recent evidence has suggested that cold receptors may contribute to ocular dryness and discomfort.²⁰ In order to investigate these questions, the current study was designed to examine the differences in pneumatic cool thresholds and sensation magnitude at threshold in symptomatic and

asymptomatic contact lens wearers and non-lens wearing normal controls. Given that we do not currently understand the sensory etiology of either dry eye or CLD and there was no consensus in the dry eye research community in how best to differentiate mild dry eye from CLD, we took the approach of including symptomatic contact lens wearing subjects because this would be representative of patients one might desire to help in practice.

METHODS

This study was conducted in accord with the Declaration of Helsinki and approved by the Institutional Review Board of Indiana University. Informed consent was obtained from all participants after the nature of the study had been fully explained. Each subject signed the consent form prior to enrollment.

Subjects

Sixty-four participants comprising 24 symptomatic/intolerant, 25 asymptomatic lens wearers and 15 non-contact lens wear normal controls completed the study. The normal control group was served as to examine the effect of chronic contact lens wear on corneal sensitivity to cooling stimulation.

Subjects were included if they were between 18 to 45 years of age, were willing and able to follow instructions and maintain the visit schedule, and had an ocular examination in the last two years. Contact lens wearers were further classified into symptomatic and asymptomatic group based on self-reported comfortable lens wearing time and Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8)²¹ scores (see details in Table 1). We chose CLDEQ-8 score of 14 as a cut-off because the cutoff was the mean score of the subjects' overall opinion of "good" and it excluded the majority of subjects in the "very good" and "excellent" categories (according to the error bars shown on Figure 2 of the paper).²¹ Subjects were not enrolled in the study if they had any ocular disease, history of an ocular surgery, had a systemic condition that could affect a study outcome variable or were using any systemic or topical medications that may could affect ocular health. In addition, contact lens wearing subjects were excluded if their CWT fell between the symptomatic and asymptomatic groups.

Sensitivity Measurement

Corneal detection thresholds were estimated using a computer-controlled Belmonte pneumatic esthesiometer developed at Indiana University.²² The esthesiometer is a dual chamber mechanical, chemical (CO₂) and thermal pneumatic device with computer control of flow, %CO₂ and temperature and computerized collection of subject responses. A temperature sensing circuit provides feedback to maintain a steady stimulus temperature independent of air-flow and ambient temperature. A calibrated video camera continuously monitored the distance between and orthogonal alignment of the tip of the esthesiometer and the ocular surface.

Detection thresholds were measured on the left eye only. Measurements were undertaken between 9 AM and 7 PM mostly in the afternoon, at least three hours after subjects awoke to minimize diurnal variation.²³ A training session was conducted at the screening visit.

Subjects were instructed to view a fixation target. The tip of the esthesiometer was set 5 mm from the corneal surface. The stimuli, consisting of a series of air pulses at room temperature (20°C, an air stimulus with a cooling effect^{24,25}) with flow varying from 0 to 200 ml/min, were delivered to the central cornea. The subjects were informed that they could blink freely during testing, that they could close their eyes or look down between stimuli, and that they could interrupt or stop the trials at any time. The stimulus duration was two seconds. A computer-generated warning tone sounded before stimulation to allow subjects to blink before the onset of the stimulus. Subjects were asked to view the fixation target during stimulus presentation. The ascending method of limits with a randomly selected initial level of stimulus was used. The increment of flow rate was 10 ml/min. Detection thresholds were determined by the average flow rate of three first reports of the stimulus presence.

There were four visits in this study. Following successful screening and training, contact lens wearing subjects returned for baseline threshold estimation (BL-1) after wearing their habitual contact lenses for approximately three to six hours. Lenses were removed before threshold testing. Thresholds estimates were repeated under the same conditions within a week (BL-2) to examine repeatability of threshold measurement following habitual contact lens wear. Subjects were then asked to stop wearing their contact lenses for approximately two weeks, after which thresholds were again measured in the third study visit (NL). For this visit, subjects were instructed to come in for testing after they had been awake for at least three to six hours. Subjects were then instructed to begin wearing their habitual contact lenses as before. The final study visit (CL) occurred approximately two weeks later under the same conditions as the first two study visits. The normal control group followed the same schedule of four visits, but without wearing contact lenses. They were instructed to be awake for three to six hours before each measurement session.

Estimated Magnitude of the Stimuli

Magnitude estimation²⁶ is a psychophysical scaling method in which the subject is required to make direct numerical estimation of the sensory magnitude produced by a physical stimulus (e.g. pneumatic cooling stimulus in the study). Immediately following the report of the stimulus presence, subjects were asked to rate their subjective experience of the stimulus intensity, coolness, irritation and pain on a 1-100 scale with 1 being very mild and 100 very strong.

Clinical Sign Evaluation

Corneal fluorescein staining was graded using the NEI/Industry Workshop system²⁷ (from 0 to 3) for central, superior, inferior, nasal, and temporal cornea. Conjunctival staining was graded using the Oxford scale²⁸ (from 0 to 5) for superior, inferior, nasal, and temporal conjunctiva. The sum score of all areas was used for data analysis.

For tear film break-up time (TBUT) assessment, a regular fluorescein strip wetted with a drop of non-preserved buffered saline was used. The TBUT was recorded with a stopwatch and measured three consecutive times. The average of three measurements was calculated.

Data Analysis

Data were analyzed using mixed models and repeated measures ANOVA in SPSS 22 (IBM SPSS) and $p = 0.05$ was considered to be statistically significant. Detection thresholds and magnitude estimations were outcomes, with groups, visits and their interactions as predictors. To minimize the effects of violating assumptions about data sphericity for repeated-measures ANOVA, Huynh-Feldt corrected p values²⁹ were reported. Although the analyses of esthesiometry data were done on thresholds, the term sensitivity, which is the reciprocal of threshold, was also used in discussing the study outcomes due to its common usage.

RESULTS

Participant characteristics for each group are summarized in Table 2. The average duration of lens wear in the asymptomatic and symptomatic groups were 10 ± 2.5 years (range 6-15) and 7.6 ± 3.8 (range 2-15). Subjects were selected by symptoms, so it is not surprising that the symptomatic group showed significantly lower CWT and higher symptoms by CLDEQ-8. TFBUT was also significantly lower in the symptomatic group.

Corneal thresholds for detection of pneumatic stimuli at room temperature for each measurement session are summarized in Table 3 and shown in Figure 1. On average, symptomatic group was the most sensitive (i.e., had the lowest threshold), the asymptomatic were the least sensitive and the controls' sensitivity was between the two lens wearing groups, although there was some overlap of the thresholds. There were significant visit and group main effects (Repeated-measures ANOVA $p=0.025$ and <0.001 for visit and group respectively) and a significant interaction between visit and group ($p=0.031$). At all study visits, the symptomatic group had lower thresholds (higher sensitivity) than the asymptomatic group (Tukey HSD all $p<0.015$) while the difference between symptomatic and control groups was significant at the 2-week lens-wearing visit (Tukey HSD $p=0.027$), as seen in Figure 1.

The magnitudes of intensity, coolness and irritation of threshold stimulus for the three groups at each visit are shown in Figures 2-4, respectively. The differences in estimated intensity and irritation were significant between groups (repeated-measures ANOVA $p=0.027$ and 0.006 for intensity and irritation, respectively) but not significant between visits ($p=0.082$ and 0.166 for intensity and irritation, respectively). The symptomatic group showed significant greater intensity than the control group ($p=0.032$) and greater irritation than both the asymptomatic and control groups ($p=0.008$ and 0.042 respectively), regardless of study visits. There was a significant difference in coolness between visits ($p<0.001$), but not between groups ($p=0.086$). Post hoc tests showed that coolness greater at the BL-1 visit compared to the other visits regardless of group (all $p = 0.003$). There were no significant interactions between visit and group for the intensity, coolness and irritation outcomes.

Typically, pain is not anticipated at these very low stimulus levels i.e. at detection threshold. One subject in the symptomatic group reported mild pain at the CL visit but did not report mild pain at any other time during testing. Thus this one instance was not included in the data analysis.

DISCUSSION

In this study, symptomatic contact lens wearers exhibited both lower detection thresholds and enhanced responsiveness (stronger estimated intensity) to the stimuli used in this investigation than asymptomatic wearers and normal controls, suggesting a link between alterations in sensory function and CLD.^{15,19}

Sensitivity measurement is one way to assess the functioning of sensory nerves and is considered to be a useful clinical indicator of corneal health in diseases, contact lens wear, and during the healing process following corneal injuries and surgeries.^{11,30-33} In the present study we investigated the effects of CLD on corneal sensitivity to cooling pneumatic stimuli in contact lens wearers and we showed differences in sensory function between groups (Figure 1). Consistent with previous results,^{11,12} sensitivity in the asymptomatic group tended to be reduced compared to controls suggesting neural adaptation.¹⁹ In contrast, the symptomatic group was the most sensitive.

Neural control of the lacrimal functional unit is important in maintaining the health of tear film and ocular surface,⁴ which has direct and/or indirect impact on the success of contact lens wear. Sensory nerves signal the physiological condition of the body such as local metabolism (e.g. acidic pH, hypoxia), immune and hormonal activity, in addition to serving a protective mechanism signaling potential danger in or injury from the external environment.³⁴ There is experimental evidence that contact lens wear affects tear film structure and thickness as summarized in the report of The TFOS International Workshop on Contact Lens Discomfort,³⁵ which results in more rapid tear film thinning theoretically due to increased evaporation.³⁶ It is likely that this is the cause of increased tear and contact lens osmolality noted in some contact lens wearers.^{37,38} As seen in Table 2, in this experiment, tear film BUT was shorter in contact lens wearers compared to the non-wearing controls, and the symptomatic group had the shortest BUT, supporting the notion that tear film integrity was compromised with contact lens wear,³⁵ particularly in symptomatic wearers. Additionally, studies have shown that the level of several cytokines increases with contact lens wear.³⁵ The sustained alteration of the tear film and ocular surface may result in sustained stimulation to the underlying sensory receptors and affect the neural control of the integrated functional unit. This in turn, compromises its ability in responding to environmental and physiological changes induced by contact lens wear. In this study, the symptomatic group showed hypersensitivity (lower threshold) to cool stimuli, similar to previous findings reported in dry eye symptomatic subjects.³⁹ These suggest the development of sensitization and the alteration of neural control of the functional unit in symptomatic wearers,⁴⁰ although maybe additional adaptation mechanisms could also affect the sensory processing in symptomatic wearers.¹⁹

Stimuli to the ocular surface are detected and coded by different functional types of sensory receptors. This information is relayed via trigeminal ganglion neurons (TG) where the primary afferent neurons are located, to the higher levels in the central nervous system (CNS).⁶ Various ion channels associated with TG neurons such as the transient receptor potential (TRP) ion channels have been identified.^{41,42} They function as molecular detectors of environmental stimuli, providing the receptor potential that initiates signaling to the

CNS.^{41,42} The ion channels-transducing proteins, which play an important role in sensory processing, are synthesized in the cell body of trigeminal ganglion (TG) neurons and transferred to the peripheral and central terminals of the neuron by axonal transport. Under conditions of tissue injury induced by repeated noxious stimulation and resultant inflammation, the expression of these ion channels and the sensitivity of voltage-gated ion channels such as sodium, potassium and calcium voltage-sensitive channels and ligand-gated channels are enhanced, leading to sensitization of sensory neurons.³ Sensitization is characterized by lowered excitation thresholds of sensory neurons (and thus for the elicitation of a sensation) and an increase in responses to suprathreshold stimulation.⁶ We found evidence of sensitization, with both lower detection thresholds and enhanced responsiveness (stronger estimated intensity) to the stimuli in the symptomatic wearers in the study (Figures 1 and 2, respectively). Although the potential causes of sensitization in the symptomatic group remain unknown, there are several possible factors may be involved, such as hyperosmolarity^{36,37} and inflammation³⁵ induced by contact lens wear, and the close interaction between the lenses and ocular surface. These factors may result in alterations in the operation of the TRP and voltage-gated ion channels. This could lead to the development of CLD if the integrated lacrimal functional unit is compromised and its ability to compensate is reduced.

Besides lower thresholds and enhanced stimulus intensity, the symptomatic wearers in the study reported greater irritation/discomfort with a stimulus (Figure 4) that is typically yielding non-painful sensation akin to a “cool breeze”.^{24,25} It has been suggested that a subpopulation of high-threshold cold (HTC) receptors respond to strong cooling and may account for the unpleasant and painful cold sensations.²⁰ However, the contribution of this type of neurons to CLD remains unclear. In our experiment, only innocuous cooling occurs, so it is unlikely that these high threshold mechanisms were operating. A recent study has shown that hyperosmolar tears enhanced cooling sensitivity of high-threshold corneal nerves; perhaps this might allow activation of the ocular surface HTC by subtle temperature changes.⁸ This apparent cold allodynia (pain evoked by innocuous stimulation) may indicate altered functionality of these cold receptors in CLD.

There was an interesting effect that coolness estimates were greatest at the first study visit for all groups in this investigation (Figure 3). There are a number of possible causes of changes over time, including learning effects, temporal changes such as something seasonal and instrument errors, among others. Each of these appears to be straightforwardly discountable because the change we found only occurred with the ratings of coolness. If the extraneous variables mentioned earlier may account for the changes in coolness rating overtime, this effect of visit would appear to have consistently affected different stimulus attributes (Figures 2 and 4) and not only coolness. This leaves us with the possibility that this is a sampling issue, with unfortunate statistical effect that is just random. While we cannot dismiss the possibility of a type I error, the data in the Figure 3 do appear to be somewhat more systematic than might be expected from a simple chance occurrence. We therefore are left with a plausible possibility that on average, participants rated coolness systematically differently during this experiment. The exact explanation is unknown and needs to be elucidated and examined in future experiments.

We have also found little changes in corneal sensitivity to pneumatic cool stimuli following the 2-week period of no contact wear (Figure 1), often considered a washout period. Similarly, previous studies have shown no significant change¹² or even a slight decrease⁴³ in corneal sensitivity to pneumatic mechanical (ocular surface temperature) stimulation after stopping contact lens wear for a week. This may suggest that the effect of wearing contact lenses on corneal sensitivity is small, or alternatively, that the washout period is too short for adapted contact lens wearers. The trend toward a reduction of irritation magnitude (Figure 4) in the symptomatic group may favor the latter explanation.

In conclusion, although the underlying neural mechanisms involved in CLD remain not fully understood, the current study provides evidence that sensory function with contact lens wear (assessed by sensitivity to the pneumatic cool stimuli) is different in the symptomatic and asymptomatic groups despite the younger age of participants in this study. The results of this study support the hypothesis that alterations in the neural control of the functional unit and accompanying sensitization of the sensory neurons are likely to be key players in CLD. The details and possible causes of these alterations in sensory function, and their possible parallels in the dry eye condition in broader age range will be the subject of future experiments.

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Figure 1.

The symptomatic group had lower thresholds (higher sensitivity) than the asymptomatic group at all visits (all $p < 0.015$) and than the control group at the 2-week lens-wearing visit ($p = 0.027$) (* $p < 0.05$ symptomatic vs. asymptomatic; ** $p < 0.05$ symptomatic vs. asymptomatic and control). Error bar denoted 95% Confidence Interval.

Figure 2.

Regardless of study visits, the symptomatic group rated the stimulus intensity at detection significantly greater compared to the control ($p=0.0027$). Error bar denoted 95% Confidence Interval.

Figure 3.

Regardless of group, the stimulus coolness was rated higher at the BL-1 visit compared to the other visits (all $p < 0.003$). Error bar denoted 95% Confidence Interval.

Figure 4.

Regardless of study visits, the symptomatic group rated significantly greater irritation with the stimulus at detection threshold than both asymptomatic and control groups ($p=0.008$ and 0.042 respectively). Error bar denoted 95% Confidence Interval.

Table 1

Grouping criteria for contact lens wearer group.

	Asymptomatic	Symptomatic
Reported comfortable lens wear time (CWT)	>10 hours & minimal reduction in comfort over the course of the day (i.e. lens wearing time - CWT <1 hour)	<8 hours & a noticeable reduction in comfort over the course of the day
CLDEQ-8 score	<14	14

Table 2

Participant characteristics.

	Control	Asymptomatic	Symptomatic	p value
Number of subjects	15	25	24	-
Age ($\pm$ SD)	25 $\pm$ 3	23 $\pm$ 2	23 $\pm$ 4	0.157
Female: Male	8: 7	17: 8	18: 6	-
Refractive error and K readings in Diopter ($\pm$ SD)				
Sphere	-1.15 $\pm$ 2.33	-3.35 $\pm$ 1.71	-3.66 $\pm$ 1.57	<0.001
Cylinder	-0.57 $\pm$ 0.44	-0.50 $\pm$ 0.50	-0.66 $\pm$ 0.65	0.613
Flat K	43.52 $\pm$ 1.25	43.27 $\pm$ 1.43	43.31 $\pm$ 1.47	0.859
Steep K	44.38 $\pm$ 1.48	43.95 $\pm$ 1.46	44.43 $\pm$ 1.73	0.523
Corneal cylinder	-1.10 $\pm$ 0.65	-0.78 $\pm$ 0.32	-1.20 $\pm$ 0.77	0.049
Wearing time (WT) hours/day	N/A	14.1 $\pm$ 1.7	10.1 $\pm$ 3.9	<0.001
Comfortable WT hours/day	N/A	13.9 $\pm$ 1.8	5.1 $\pm$ 1.7	<0.001
Days/week	N/A	5.9 $\pm$ 1.4	5.4 $\pm$ 1.7	0.193
CLDEQ-8 score	N/A	7.2 $\pm$ 3.8	22.4 $\pm$ 3.8	<0.001
TFBUT (second) *	12.20 $\pm$ 6.19	10.42 $\pm$ 7.08	6.45 $\pm$ 3.25	0.001
Sum corneal staining * (mean $\pm$ SD)	0.27 $\pm$ 0.59	0.76 $\pm$ 0.88	0.38 $\pm$ 0.58	0.087
Sum conjunctival staining * (mean $\pm$ SD)	0.33 $\pm$ 0.49	2.56 $\pm$ 1.85	3.17 $\pm$ 2.55	<0.001

* Statistics was done using Kruskal-Wallis H test due to non-normal distribution of the data, the rest were done using one-way ANOVA.

Table 3Cool stimuli thresholds (mean ml/min $\pm$ SD, range).

Visit	Control	Asymptomatic	Symptomatic
BL-1	64.2 $\pm$ 21.4 (26.7 – 96.7)	66.3 $\pm$ 21.0 (36.7 – 126.7)	49.7 $\pm$ 17.4 (28.3 – 85.0)
BL-2	56.0 $\pm$ 18.3 (38.3 – 101.7)	70.3 $\pm$ 23.0 (26.7 – 135.0)	46.3 $\pm$ 20.0 (23.3 – 108.3)
NL	59.0 $\pm$ 16.9 (33.3 – 86.7)	69.5 $\pm$ 20.1 (36.7 – 113.3)	50.1 $\pm$ 16.5 (23.3 – 90.0)
2wkL	66.2 $\pm$ 17.0 (38.3 – 95.0)	77.0 $\pm$ 27.3 (26.7 – 138.3)	47.5 $\pm$ 16.3 (23.3 – 86.7)