Conjunctival Vascular Adaptation Related to Ocular Comfort in Habitual Contact Lens Wearers

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• PURPOSE: We sought to investigate the bulbar conjunctival vascular responses in habitual contact lens (HCL) and non–contact lens (NCL) wearers after short-term lens wear and their relationships with ocular comfort.

• DESIGN: A prospective, comparative before-and-after study.

• METHODS: Twenty-seven subjects (13 HCL and 14 NCL wearers) were enrolled. Microvasculature and microcirculation on the temporal bulbar conjunctiva were imaged at baseline and 0.5 and 6 hours after wearing contact lenses (1-Day Acuvue TruEye; base curve, 8.5 mm; power, −0.50 diopters) on both eyes. The measurements included vessel diameter (D), axial (VA), and cross-sectional (VS) blood flow velocities, blood flow volume (Q), and vessel density (Dbox) and complexity (D0). A Contact Lens User Experience (CLUE) questionnaire was used to assess ocular comfort.

• RESULTS: No significant change ($P > .05$) was observed in D, VA, VS, Q, Dbox, and D0 in the HCL wearers after contact lens wear. By contrast, VA, VS, Q, Dbox, and D0 increased significantly after lens wear (after 0.5 and 6 hours) in NCL wearers compared with baseline ($P < .05$). Moreover, the changes from the baseline to 0.5 hours (VA, VS, and Dbox) and 6 hours (VA, VS, Q, Dbox, and D0) after contact lens wear in NCL wearers were significantly greater than that in HCL wearers ($P < .05$). The CLUE score 6 hours after lens wear was higher in HCL wearers than in NCL wearers ($P < .05$). It was also significantly correlated with VA, VS, and D0 after 6-hour lens wear in HCL wearers ($P < .05$).

• CONCLUSIONS: This is the first study to reveal the relationship between ocular comfort and conjunctival vascular responses in habitual contact lens wearers. (Am J Ophthalmol 2020;216:99–109. © 2020 Elsevier Inc. All rights reserved.)

Accepted for publication Mar 20, 2020.

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Wearing contact lenses is the main choice of a method to correct refractive error for both medical and cosmetic purposes, in addition to wearing spectacles.[1,2] With improvements in lens materials and designs as well as the health consciousness of the wearers, the risks of contact lens–related complications have reduced.[3,4] However, contact lens–induced alterations, such as ocular surface indentation,[2] disturbance of the tear film,[5] and changes caused by some level of low oxygen supply,[6] even with the use of silicone hydrogel, occur and result in vascular responses.[7] The common manifestation of vascular responses to contact lens wear is ocular redness (hyperemia).[7–19] Ocular redness is considered as one of the main indicators for evaluating the success and tolerance of the contact lens fit.[6,20,21] In addition, ocular redness often reflects the underlying subclinical ocular inflammation associated with wearing contact lenses.[22] Therefore, quantitative evaluation of conjunctival hyperemia is essential for a better understanding of the interaction between the ocular surface and contact lenses, which could further facilitate improvements in lens materials and designs.

The traditional grading scales of conjunctival redness have been widely used in clinical trials of contact lenses.[6,21,23] However, redness grading scales do not provide direct information about circulation and may not be sensitive to subtle changes in redness. Recently, the traditional slit lamp microscope was modified to form a high-speed imaging system with high magnifying power to image conjunctival blood flow velocity and vessel network.[22,24–29] Cheung and associates[24] applied slit lamp imaging to study habitual contact lens (HCL) wearers and reported that bulbar conjunctival microvascular abnormalities occurred in long-term (>2 years) contact lens wearers. Our previous studies used an advanced vascular imaging modality, the functional slit lamp biomicroscope (FSLB), to image the conjunctival microvascular morphology and microcirculation.[22,25–29] These studies demonstrated that the bulbar conjunctival microvasculature and microcirculation altered in HCL wearers,[26,29] suggesting that the adapted contact lens wearers might have a chronic subclinical ocular inflammatory state, which may be beneficial.[30] By contrast, the conjunctival vascular response to short-term contact lens wear in non–contact lens (NCL) wearers may be quick and strong to the presence of the contact lens (for the first time) on the ocular surface.[26,28] These

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.03.031

rapid vascular responses may be attributed to factors such as mechanical pressure, friction, or some degree of hypoxia.[22,25,28] In addition, studies demonstrated that ocular comfort decreased during daily contact lens wear in NCL[22,31] and HCL wearers.[11,13] However, the relationship between vascular responses and ocular comfort in HCL wearers remains untested, which may be a barrier to better understanding the mechanism of ocular comfort, lens fitting comparability, and ocular vascular response. The goal of the present study was to determine the bulbar conjunctival vascular responses after short-term lens wear and their relationships with ocular comfort in both HCL and NCL wearers.

TABLE 1. Characteristics of HCL and NCL Wearers

	HCL Wearers	NCL Wearers
Subjects, n	13	14
Gender, male/female	3/10	5/9
Age, y, mean ± SD	25.9 ± 4.5	25.7 ± 4.1
Duration of CL wear in a day, hours, mean ± SD	11.5 ± 2.4	N/A
Duration of CL wear in a week, days, mean ± SD	5.9 ± 1.7	N/A
Duration of CL wear, years, mean ± SD	8.5 ± 3.4	N/A

CL = contact lens; HCL = habitual contact lens; NCL = non–contact lens; N/A = not applicable; SD = standard deviation.

METHODS

• **SUBJECTS AND THE IMAGING PROCEDURE:** This was a prospective study approved by the Human Subject Research Office at the University of Miami (study ID 20150359). Two groups of subjects were recruited (Table 1). HCL wearers were those who had worn soft contact lenses daily for ≥ 3 years, and the NCL wearers included self-reported healthy subjects who had never worn contact lenses. The exclusion criteria included a history of extended (overnight) contact lens wear, rigid gas permeable lens wear, ocular trauma or surgery, tobacco or alcohol use, and long-term use of medications, as well as systemic diseases like hypertension, diabetes, sickle cell anemia, cerebral small vessel disease, stroke, cardiovascular diseases, and other vascular diseases. A total of 27 subjects were recruited, including 13 HCL wearers (10 females and 3 males, 25.9 ± 4.5 years of age) and 14 NCL wearers (9 females and 5 males, 25.7 ± 4.1 years of age). Informed consent was obtained from each subject, and all subjects were treated by the tenets of the Declaration of Helsinki.

All subjects were required to report in the morning (between 8:30 AM and 11:00 AM), and the HCL wearers were asked not to wear their own contact lenses. FSLB imaging of each subject was performed at baseline. Subsequently, each subject wore a pair of new narafilcon A contact lenses (1-Day Acuvue TruEye, Johnson & Johnson Vision Care, Inc., Jacksonville, Florida, USA) with a base curve of 8.5 mm and power of −0.50 diopters. FSLB imaging was repeated 0.5 and 6 hours after wearing the lenses. Thirty minutes and 6 hours after the lenses were inserted, the participants were required to subjectively assess their ocular comfort using a Contact Lens User Experience (CLUE) questionnaire.[32]

• **BULBAR CONJUNCTIVAL MICROCIRCULATION AND MICROVASCULATURE MEASUREMENT USING FSLB:** The FSLB imaging system and the imaging protocol used in the present study have been previously described.[25–27,29] Briefly, a high-speed digital camera (Canon 60D; Canon Inc., Melville, New York, USA) was adapted into a standard slit lamp microscope, and a video movie cropping function in the camera added approximately 7× digital magnification, which was sufficient for imaging a cluster of red blood cells. In the present study, the FSLB was set to have a field of view of 0.9 × 0.7 mm^2. Six fields of the temporal bulbar conjunctiva located approximately 1 mm radially from the circumference of the limbus ring were imaged, and video clips were acquired at a speed of 60 frames per second. To process the video and measure the conjunctival microcirculation, vessel diameter (D), axial (VA), and cross-sectional (VS) blood flow velocities, and blood flow volume (Q) were obtained using the custom software described in our previous studies.[25–28,33,34] Briefly, the software exported multiple frames in sequence from the acquired video clips containing sharply focused vessels and subsequently registered these exported images for compensating eye movements. The vessels were then segmented, and the diameter of the vessel was defined as the full width at half maximum of the intensity profile crossing the vessel centerline perpendicularly. To measure VA and VS, a space-time image was created by computing a reflectivity profile of the vessel path with a length of 75 pixels. The reflectivity profile was used as the vertical line (Y axis) of a time point. The X axis represented the time in the video, and each time point represented 1 frame in the video sequence. The prominent bands in the space-time image represented the axial distance traveled by a red blood cell or a plasma gap over a fixed time interval. A straight line was marked manually in the band, and the software calculated VA as the slope of the marked line. Therefore, $VA = D_{ax}/\Delta t$, where D_{ax} is the displacement of a red blood cell near the axis of a vessel, and Δt is the time interval. VS and Q were calculated using the equations published previously.[35] VS was calculated from VA under 2 conditions. If the division of D by the diameter of the human erythrocyte (ie, 7.65 μm) was ≤ 0.6, VS was equal to VA; if it was > 0.6, VS was calculated as $VS = VA/[1.58 \times (1 - e^{-\text{sqrt}\,(2D/Dc)})]$, where Dc is the diameter of the erythrocyte. Q was

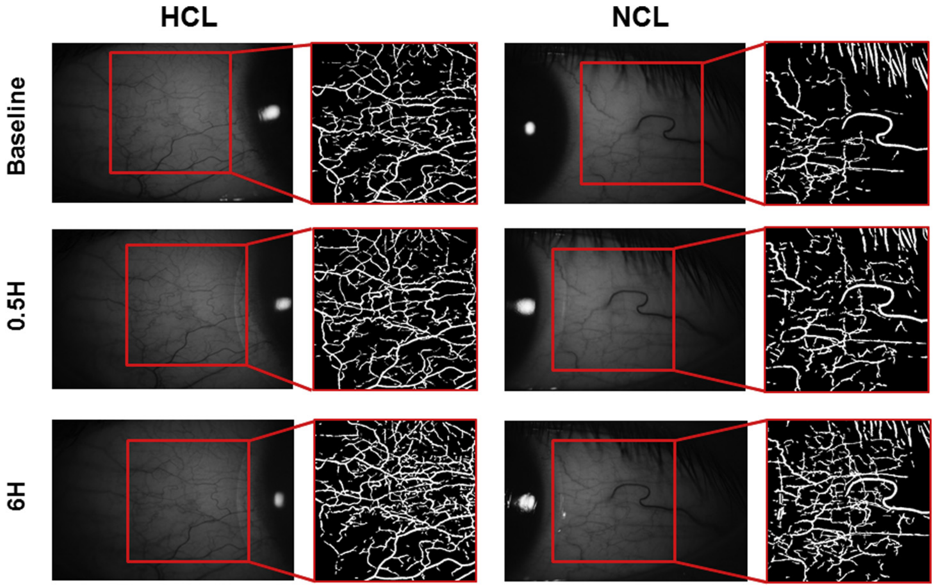

FIGURE 1. Bulbar conjunctival microvascular responses after contact lens wear in habitual contact lens (HCL) wearers and non-contact lens (NCL) wearers. In the HCL wearers, subtle changes appeared in the vessels 6 hours after lens wear. In contrast, NCL wearers showed a noticeable increase in the number of vessels after 6 hours of lens wear. Note: the segmented vessels were from the area in the red rectangle.

estimated using the following equation: $Q = VS \times \pi \times D^2/4$. It has been reported that the blood flow velocity is different in arterioles and venules, and only conjunctival venules were measured in the present study.[27]

To measure vessel density (Dbox) and complexity (D0), images with a field of 7.87×7.87 mm^2 were taken using a previously reported image processing software,[25] the microvascular network was automatically segmented with a series of image-processing procedures, and fractal analysis was performed using a commercially available software program (Benoit; TruSoft Inc., St. Petersburg, Florida, USA). Monofractal and multifractal analyses were performed to yield Dbox and D0 of the bulbar conjunctival microvasculature.[22,25,26,28,29] Larger values of Dbox and D0 indicated more dense vessels and more complex branching patterns, respectively.

• **STATISTICAL ANALYSES:** Descriptive statistics and data analyses were conducted using SPSS software (version 26.0; IBM Corp., Chicago, Illinois, USA), and the threshold for statistical significance was set at $P < .05$. Values were presented as means ± standard deviations. Analysis of variance was used to test significant differences in the measured parameters over time. Post hoc tests were used to determine pairwise differences. Independent-samples t tests were used to determine any differences in the values at each time point between groups. Pearson correlation was used to test relationships between CLUE scores and the vascular parameters after 6-hour contact lens wear.

RESULTS

IN HCL WEARERS, SUBTLE CHANGES WERE OBSERVED IN THE vessels after 6 hours of lens wear (Figure 1). By contrast, NCL wearers showed a noticeable increase in vessels after 6 hours of lens wear. None of the FSLB parameters (D, VA, VS, Q, Dbox, and D0) in the HCL group changed significantly after contact lens wear (Table 2, Figure 2). By contrast, in the NCL group, VA ($P = .030$), VS ($P = .030$), and Dbox ($P = .025$) increased significantly after 30 minutes of contact lens insertion compared with the values at baseline (Table 2, Figure 2). After 6-hour lens wear, VA ($P = .004$), VS ($P = .004$), Q ($P = .013$), Dbox ($P = .002$), and D0 ($P = .005$) significantly increased compared with the values at baseline. However, no significant differences were found between the HCL and NCL groups at each time point ($P > .05$).

Compared to that after 30 minutes of lens wear, the mean value of the CLUE score showed an increasing trend in HCL wearers and decreasing trend in NCL wearers after 6-hour lens wear. However, they did not reach statistical significance (Table 2, Figure 2). The difference of CLUE score between the 2 groups reached a significant difference 6 hours after lens wear ($P = .028$) as analyzed using a 1-tailed t test.

The changes in VA ($P = .011$), VS ($P = .010$), and Dbox ($P = .012$) from the baseline to 30 minutes after lens wear and the changes in VA ($P = .003$), VS ($P = .004$), Q ($P = .013$), Dbox ($P = .036$), and D0 ($P = .044$) from the baseline to 6 hours after lens wear were all significantly different

TABLE 2. Comparisons of the Conjunctival Microvasculature and Microcirculation Parameters at Baseline and 0.5 Hours and 6 Hours After Lens Wear in the HCL and NCL Groups

	Baseline	0.5 Hours	6 Hours	*P* Value (0.5 Hours vs Baseline)	*P* Value (6 Hours vs Baseline)
HCL, mean ± SD					
D	17.4 ± 3.9	17.0 ± 3.2	17.2 ± 2.6	.714	.878
VA	0.52 ± 0.17	0.55 ± 0.19	0.57 ± 0.17	.552	.294
VS	0.37 ± 0.12	0.39 ± 0.14	0.41 ± 0.12	.550	.288
Q	136.0 ± 115.1	130.7 ± 70.9	137.7 ± 61.6	.824	.945
Dbox	1.64 ± 0.04	1.64 ± 0.04	1.66 ± 0.05	.784	.246
D0	1.71 ± 0.05	1.71 ± 0.05	1.72 ± 0.05	.863	.253
CLUE score	—	60.5 ± 23.6	66.9 ± 26.1[a]	N/A	N/A
NCL, mean ± SD					
D	16.9 ± 2.8	17.1 ± 2.8	17.4 ± 2.9	.724	.522
VA	0.47 ± 0.15	0.60 ± 0.23	0.65 ± 0.25	.030	.004
VS	0.34 ± 0.11	0.43 ± 0.16	0.46 ± 0.18	.030	.004
Q	109.3 ± 51.7	147.9 ± 83.4	163.1 ± 95.2	.070	.013
Dbox	1.61 ± 0.07	1.65 ± 0.06	1.66 ± 0.05	.025	.002
D0	1.69 ± 0.06	1.71 ± 0.05	1.73 ± 0.04	.107	.005
CLUE score	—	49.2 ± 19.7	47.1 ± 25.1[a]	N/A	N/A

CLUE = Contact Lens User Experience questionnaire; D = diameter; D0 = fractal dimension using multifractal analysis; Dbox = fractal dimension using monofractal analysis; HCL = habitual contact lens; N/A = not applicable; NCL = non–contact lens; SD = standard deviation; VA = axial velocity; VS = cross-sectional velocity.

[a]No significant differences between 0.5 hours and 6 hours in the HCL (P = .515) and NCL (P = .807) groups, respectively.

between the HCL and NCL groups (Figure 3). The changes in the NCL group were significantly greater than those in the HCL group ($P < .05$, Figure 3).

In the HCL group, the CLUE score after 6-hour lens wear was positively correlated with VA (r = 0.40, P = .041) and VS (r = 0.43, P = .029) and negatively correlated with D0 (r = −0.48, P = .013, Figure 4). The CLUE score was not related with D, Q, and Dbox in the HCL group ($P > .05$). No significant correlations were found in the NCL group between the CLUE score and the conjunctival vascular parameters ($P > .05$).

DISCUSSION

THIS IS THE FIRST STUDY TO CHARACTERIZE THE MICROvasculature (D, Dbox, and D0) and microcirculation (VA, VS, and Q) of the bulbar conjunctiva during the short-term lens wear in both the HCL and NCL groups. This study revealed the relationship between conjunctival vascular responses (ie, microvasculature and microcirculation) and ocular comfort in the HCL group, but not in the NCL group. The key finding was that the vascular response of HCL wearers during the short-term lens wear was minimal, which was different from the vascular responses experienced by NCL wearers. This phenomenon indicates that HCL wearers are possibly better adapted to wearing contact lenses than NCL wearers are, and the responses of microvasculature and microcirculation remained similar before and after the short period of lens wear.

Another key finding of the current study was the relationship between ocular comfort and some vascular response parameters (VA, VS, and D0) in the HCL group. Eyes experiencing lesser hyperemia (ie, lower D0) may have more comfort during shorter periods of lens wear in the HCL group, although the HCL group did not show significant alterations of these vascular responses as a group. These findings may help better understand the interaction between ocular surface and contact lenses and the ocular responses. Knowing the relations and the vascular responses may help better understand the underlying mechanism of ocular discomfort and its contributing factors, including lens materials and designs and ocular characteristics. The results of the present study may also help design future clinical trials for new lenses and the selection of the study population. While the NCL group may provide insight into the initial experience of contact lens wear, HCL wearers, the experienced lens wearers, may provide information about delineated responses that directly impact ocular comfort.

HCL wearers are adapted and experienced lens wearers, who may already have some adjustments (ie, alterations) in response to contact lens wear. The bulbar conjunctival vascular responses to the short-term contact lens wear in the HCL group showed minimal changes in microvasculature and microcirculation, which has never been reported

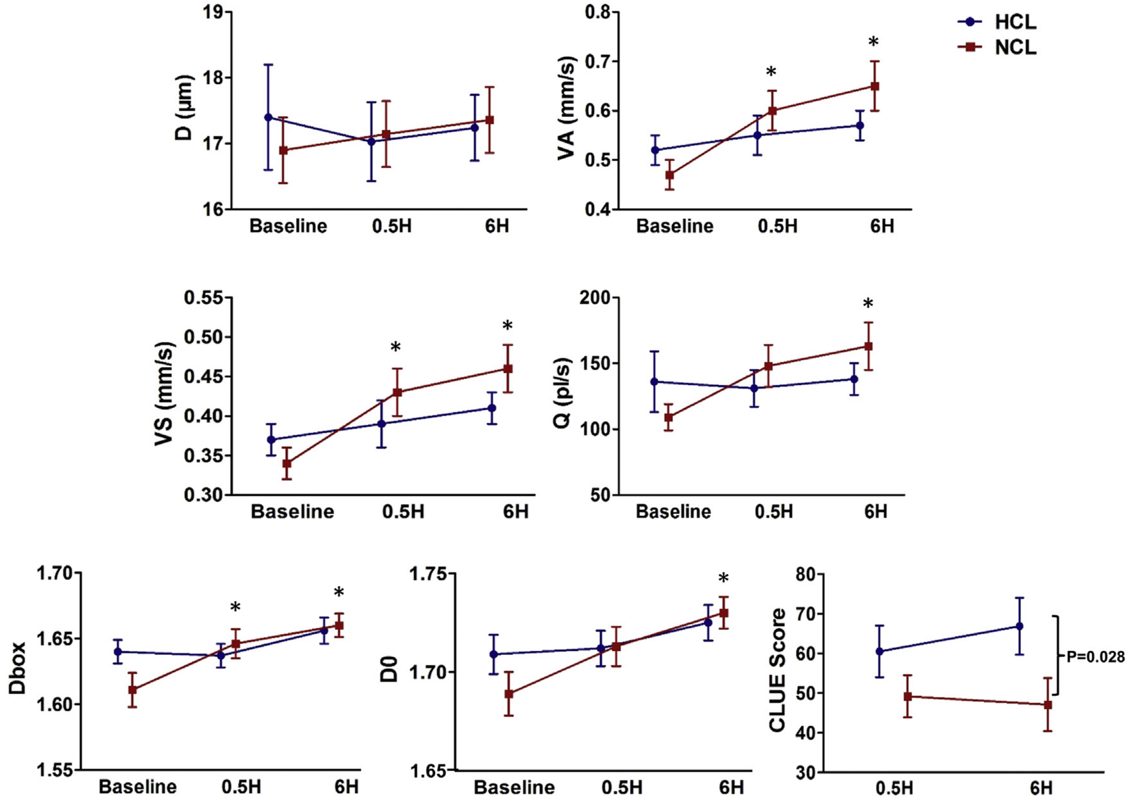

FIGURE 2. Bulbar conjunctival microvascular responses and ocular comfort before and after contact lens wear in habitual contact lens (HCL) wearers and non-contact lens (NCL) wearers. In the HCL wearers, there were no significant differences in the vessel diameter (D), axial and cross-sectional blood flow velocities (VA and VS, respectively), blood flow volume (Q), vessel density (Dbox), and vessel complexity (D0) at the baseline and 0.5 and 6 hours after lens wear (Top, Middle, and Bottom, respectively). In the NCL wearer group, VA (Upper Right), VS (Middle Left), and Dbox (Bottom Left) after 0.5-hour lens wear and VA (Upper Right), VS (Middle Left), Q (Middle Right), Dbox (Bottom Left), and D0 (Bottom Center) after 6-hour lens wear significantly increased compared to the values at baseline (asterisk, $P < .05$). As for the CLUE scores, the P-value of the differences between the two groups after 6-hour lens wear was .028 (Bottom Right). The vertical bars represent the standard errors.

before. It was noted that the blood flow, calculated from the vessel diameter and blood flow velocity, remained almost the same throughout the 6 hours of lens wear. This implies that the blood perfusion around the ocular surface was steady during the short-term lens wear in these wearers who have been "adapted" to the contact lens. This steady state may be reached by the coordination of the decreased vessel diameter and the increased blood flow velocity, as shown in the present study.

The adapted lens wearers have existing changes in vascular responses, which may be beneficial. The conjunctival vascular responses in the long-term experienced contact lens wearers exist even when they do not wear the contact lens.[24,26,29] As the immune system in the bulbar conjunctiva is upregulated, such vascular responses in HCL wearers keep the eye prepared against any extrinsic noxious challenge.[30] Efron[30] suggested that wearing contact lenses might lead to a chronic and low-grade subclinical inflammation, which might have a positive and protective effect on successful contact lens wearers. Due to this "heightened alert state," the conjunctival vasculature may not need to respond any further to the lens worn for a short period in the present study. This may explain the minimal changes in microvasculature and microcirculation in HCL wearers in this study. This may also be referred to as "vascular adaptation," in contrast to the vascular responses in the NCL group.

The significantly increased vascular responses after wearing contact lens for the first time in neophyte lens wearers has been well documented.[22,25,28] This may also indicate that in neophyte lens wearers, the conjunctival vasculature responded from a relatively low level of vasculature by triggering and mobilizing the immune system (resulting in vascular responses) to protect the ocular surface from possible damage. Interestingly, the differences between the 2 groups at each checkpoint were not different, although the changes from the baseline to short-term lens wear were significantly different, which may indicate that the contact lens itself may not trigger extreme responses in comparison to physical injury to the eye.

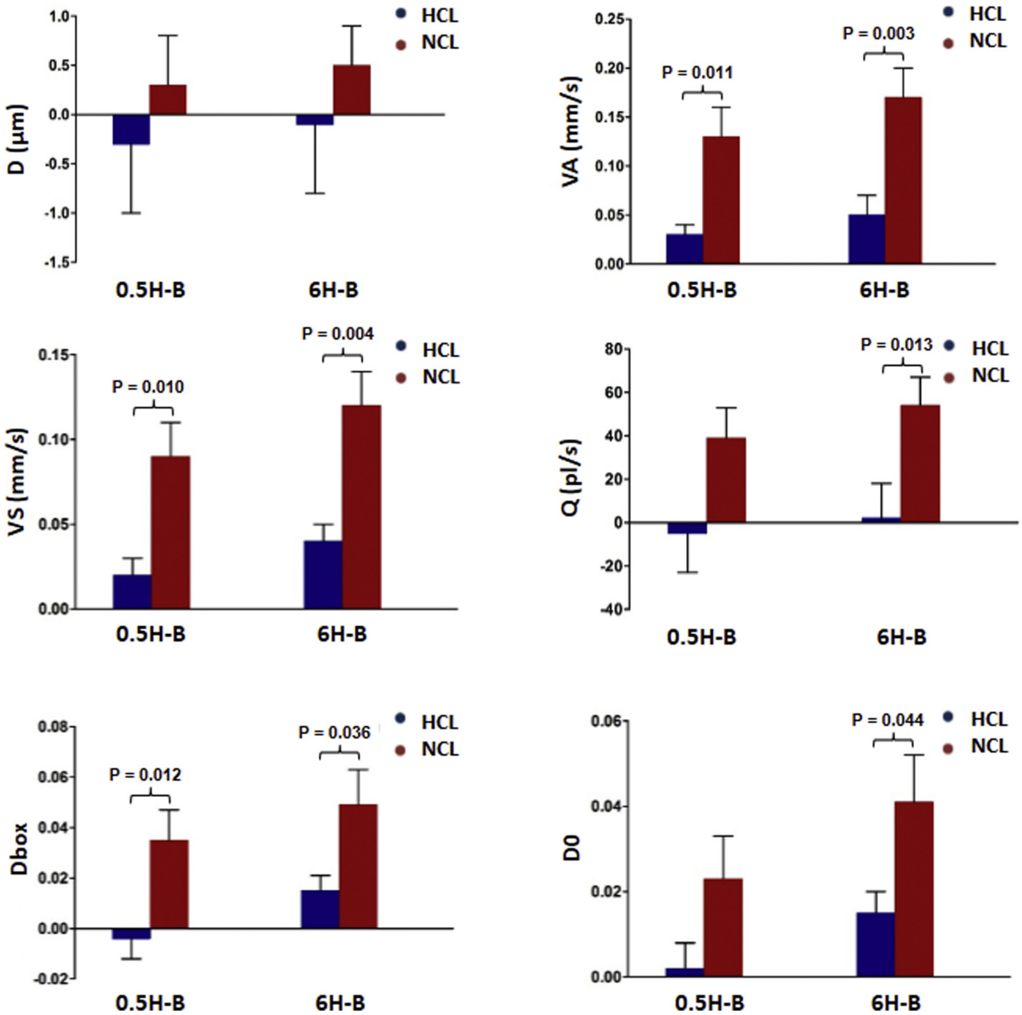

FIGURE 3. Changes in the bulbar conjunctival microvascular responses after contact lens wear in habitual contact lens (HCL) and non-contact lens (NCL) wearers. For the vessel diameter (D), there were no significant differences in the changes from baseline to both 0.5 and 6 hours after lens wear between the HCL and NCL wearers (Top Left). The changes in VA (Top Right), VS (Middle Left), and Dbox (Bottom Left) from the baseline to 30 minutes after lens wear and in VA (Top Right), VS (Middle Left), Q (Middle Right), Dbox (Bottom Left), and D0 (Bottom Right) from the baseline to 6 hours after lens wear were all significantly different between the two groups. The vertical bars represent the standard errors.

Alternatively, this may also indicate that there is a "ceiling effect," which limits the vascular response to contact lenses. This might help new contact lens wearers to stay at a relatively safe ocular surface environment by avoiding excessive immune response, which may cause ocular surface damage.

Contact lens discomfort occurs in up to 50% of contact lens wearers.[36] Many studies have demonstrated that the signs and symptoms of the ocular surface are present in both short- and long-term contact lens wearers.[37,38] Many approaches, such as the assessment of alterations in the tear film,[39,40] the Meibomian glands,[41] corneal and conjunctival staining,[42,43] lid wiper epitheliopathy, and lid-parallel conjunctival folds,[22] were used to find out the causes of discomfort related to wearing contact lenses. The relationship between contact lens–related discomfort and ocular surface alterations has not yet been established. A possible reason might be that ocular discomfort stems from interactions among multiple psychophysical and neurobiologic factors.[44] Also, several studies have focused on both ocular comfort and conjunctival hyperemia, which was generally assessed by the clinical grading scales of ocular redness (Table 3). These studies reported that improved ocular comfort coexisted with decreased (or lesser) hyperemia in contact lens wearers with different lenses, designs, and fits.[8,9,15–18,45] Conversely, studies have demonstrated that aggravated hyperemia was accompanied with decreased ocular comfort during lens wear,[11,13,22] though there were some deviations in some studies.[10,12,14,19,46,47] However, only 1 study has reported

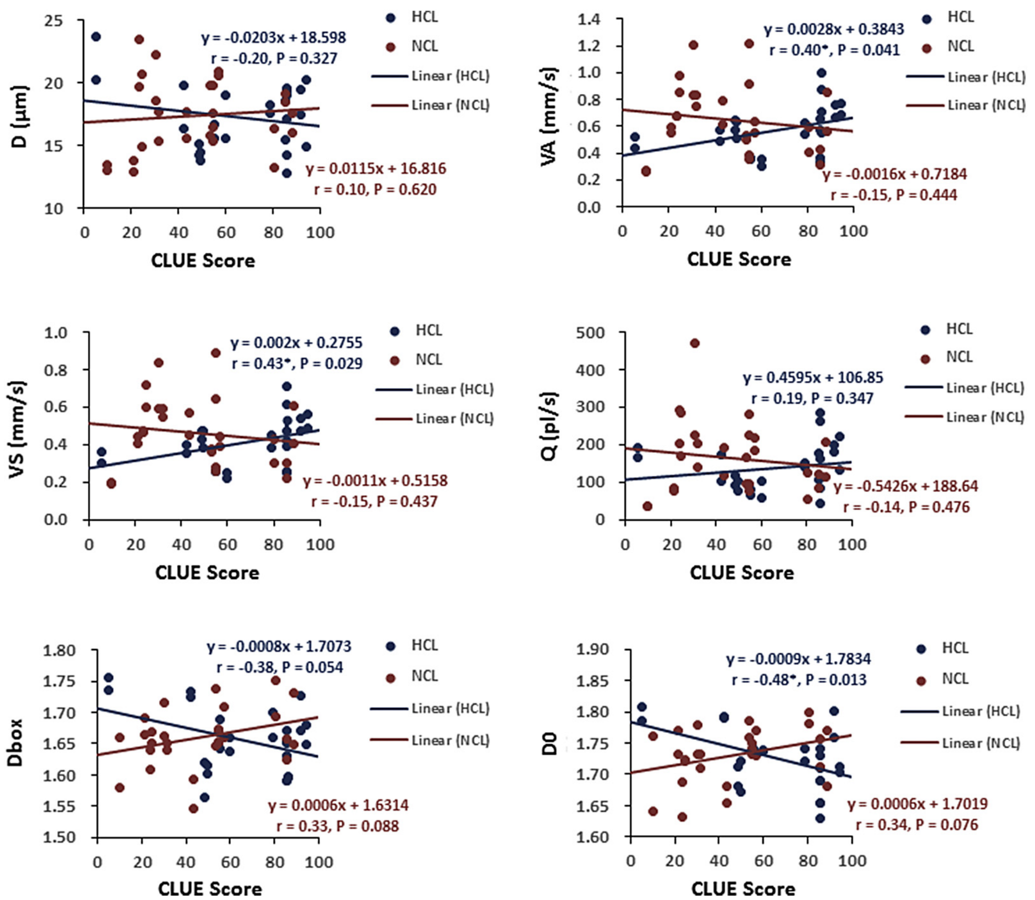

FIGURE 4. Correlations between ocular comfort and the bulbar conjunctival microvascular responses to contact lens wear in habitual contact lens (HCL) wearers and non-contact lens (NCL) wearers. In the HCL group, the CLUE score after 6-hour lens wear was correlated with VA, VS, and D0. However, no significant correlations were found in the NCL group.

the relationship between contact lens comfort and vascular responses on the ocular surface.[22] Deng and associates[22] reported that the increased vessel density (ie, Dbox) in the lid wiper conjunctiva was significantly correlated with decreased comfort rating in the NCL subjects. In the present study, the CLUE score showed an increasing trend (more comfort) in HCL wearers and a decreasing trend in NCL wearers after 6-hour lens wear. At 6 hours of lens wear, the difference in CLUE scores between the 2 groups reached a significant level. Furthermore, the HCL group developed some relations between individual responses of microvasculature and microcirculation and the comfort at the end of 6-hour lens wear. Clinically, it is understandable that eyes with less hyperemia at the end of the day of wearing contact lens may have less ocular discomfort. The present study provides evidence of this clinical manifestation that the comfort level remains high with well-adapted eyes. Interestingly, the comfort was positively correlated with conjunctival blood flow velocity (ie, VA and VS), but not with the blood flow volume (ie, Q). The relatively higher blood flow velocity in comfortable eyes could be related to the relative constriction of vessels (narrower vessel diameters). The relationship between CLUE and microcirculation may warrant further investigation.

There were some limitations in this study. First, although significant differences in conjunctival responses to the short-term contact lens wear were found between the HCL and the NCL wearers, the sample size might be too small to test whether there was a significant relationship between the bulbar conjunctival values and ocular comfort. We used GPower[48] to calculate the sample size based on the differences in conjunctival vascular changes between the 2 groups and found that only 12 cases were needed in each group to determine the differences with a detection power of 0.8. In the present study, 13 HCL and 14 NCL subjects were recruited, ensuring enough power. Second, the measurement of blood flow velocity was not fully automatic.[25,27] Therefore, further development of fully automated image processing for measuring the velocity might eliminate the intergrader variation. Finally, we only investigated the bulbar conjunctival vascular responses and their relationship with ocular comfort during the contact lens wear. However, ocular comfort is influenced by multiple

TABLE 3. Comfort and Vascular Response in Contact Lens Wearers in Studies Conducted Within the Last 15 Years

			Comfort		Vascular Response		Relationships (comfort versus vasculature)
Study (Year)	Subjects (Eyes)	Contact Lens	Methods	Findings	Methods	Findings	
Current study (2019)	13 HCL (26); 14 NCL (28)	Narafilcon A	CLUE	HCL with comfort ↑ vs NCL at 6 hours	FSLB (D, VA, VS, Q, Dbox, D0)	HCL with changes ↓ in VA, VS, Q, Dbox, and D0 vs NCL in Bulbar conjunctiva	In HCL: vs VA ($r = 0.40$) vs VS ($r = 0.43$) vs D0 ($r = -0.48$)
Deng and associates (2016)[22]	16 NCL (16)	Balafilcon A	VAS	Comfort ↓ after 6-hour lens wear	FSLB (Dbox)	Dbox in the lid wiper and conjunctiva ↑ after 6-hour lens wear	vs Dbox (r = 0.61) in the lid wiper
Wolffsohn and associates (2018)[9]	25 NCL and HCL (50)	Methafilcon A (different diameters)	Comfort analog scale	Comfort tended to ↑ with large diameter lenses vs optimum lenses during 1 week	Hyperemia (CCLRU grading scales)	Hyperaemia tended to ↓ with large diameter lenses vs optimum lenses during 1 week	Not reported
Vidal-Rohr and associates (2018)[10]	19 HCL (38)	Formofilcon B (coated or uncoated)	VAS	Comfort ↑ with coated lenses vs uncoated lenses after 1 week and 1 month of wear	Ocular redness (Jenvis grading scale)	Bulbar and limbal redness were similar for both contact lenses after 1 week and 1 month of wear	Not reported
López-de la Rosa and associates (2017)[11]	54 HCL (54)	Omafilcon A, Comfilcon A	VAS	Comfort ↓ with Comfilcon A is larger than Omafilcon A after 90 minutes of lens wear	Hyperemia (Efron grading scale)	Limbal and bulbar hyperemia ↑ in the adverse environment after 90 minutes of lens wear	Not reported
Wolffsohn and associates (2015)[12]	39 HCL (39)	Narafilcon A, Filcon II 3, Delefilcon A	Comfort analog scale	No relations between lens fits and comfort after 1-week lens wear	Hyperemia (Efron grading scale)	No relations between lens fits and hyperemia after 1-week lens wear	Not reported
Wolffsohn and associates (2015)[13]	39 HCL (39)	Narafilcon A, Filcon II 3, Delefilcon A	Comfort analog scale	Comfort ↓ with time during 16-hour lens wear	Hyperemia (Efron grading scale)	Limbal hyperemia ↑ with time during 16-hour lens wear, however, bulbar hyperemia did not.	Not reported
Morgan and associates (2013)[14]	74 NCL (74)	Narafilcon A	VAS	No difference between the lens and nonlens groups for 12 months	Hyperemia (Efron grading scale)	No difference between the lens and nonlens groups for 12 months	Not reported
Best and associates (2013)[46]	60 NCL (60)	Lotrafilcon B	OSDI	No changes after 6-month lens wear	Hyperemia (CCLRU grading scales)	Bulbar hyperemia ↑ after 6-month lens wear	Not reported
Brennan and associates (2007)[15]	45 HCL (90)	Comfilcon A, Lotrafilcon A, Balafilcon A	Comfort analog scale	Comfort ↑ with comfilcon A vs other 2 lenses after 12 months	Hyperemia (0–4 grading)	Limbal hyperemia ↓ with comfilcon A vs other 2 lenses after 12 months	Not reported
Riley and associates (2006)[16]	257 HCL (257)	Senofilcon A	4-point descriptive scale	Comfort ↑ after refitted with senofilcon A for 2 weeks	Hyperemia (0–4 grading)	Limbal and bulbar hyperemia ↓ after refitted with senofilcon A for 2 weeks	Not reported

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TABLE 3. Comfort and Vascular Response in Contact Lens Wearers in Studies Conducted Within the Last 15 Years (*Continued*)

			Comfort		Vascular Response		Relationships (comfort versus vasculature)
Study (Year)	Subjects (Eyes)	Contact Lens	Methods	Findings	Methods	Findings	
Dumbleton and associates (2006)[8]	87 HCL (87)	Lotrafilcon A	VAS	Comfort ↑ after refitted with lotrafilcon A for 2 months	Hyperemia (0–100 scale)	Limbal and bulbar hyperemia ↓ after refitted with lotrafilcon A for 2 months	Not reported
Brennan and associates (2006)[17]	56 HCL (56)	Galyfilcon A, Lotrafilcon A	Questionnaires	Significantly more comfort ↑ with galyfilcon A vs lotrafilcon A lens	Hyperemia (0–4 grading)	Limbal and bulbar hyperemia ↓ with both lenses, however, Limbal hyperemia was lower with Lotrafilcon A than Galyfilcon A	Not reported
Peterson and associates (2006)[47]	34 HCL (68)	Nelfilcon A with polyvinyl alcohol (PVA), Ocufilcon B	Comfort analog scale	Comfort ↑ with Nelfilcon A with PVA vs Ocufilcon B for 1 week	Hyperemia (CCLRU grading scales)	No differences of limbal, palpebral and bulbar hyperemia between 2 lenses for one week	Not reported
Barabino and associates (2005)[18]	29 HCL (29)	Habitual lens and a 0.9% sodium chloride ophthalmic solution	VAS	Comfort ↑ using the ophthalmic solution for 21 days	Hyperemia (0–3 grading)	Hyperemia ↓ using the ophthalmic solution for 21 days	Not reported
Coles and associates (2004)[45]	59 HCL (59)	Etafilcon A (conditioned and unconditioned lenses)	Comfort analog scale	Comfort ↑ with conditioned lens vs unconditioned lens during a single day of wear	Standard grading scales	Limbal, palpebral and bulbar hyperemia ↓ with conditioned lens vs unconditioned lens during a single day of wear	Not reported
Aakre and associates (2004)[19]	32 HCL (32)	Lotrafilcon A, Balafilcon A	VAS	No difference in comfort between the 2 lenses for 3 and 6 months	Hyperemia (Efron grading scale)	Hyperemia ↓ with Lotrafilcon A and Balafilcon A vs habitual hydrogel lens for 3 and 6 months	Not reported

CCLRU = Cornea and Contact Lens Research Unit; CLUE = Contact Lens User Experience questionnaire; D = diameter; D0 = fractal dimension using multifractal analysis; Dbox = fractal dimension using monofractal analysis; HCL = habitual contact lens wearers; NCL = non–contact lens wearers; OSDI = Ocular Surface Disease Index; VA = axial velocity; VAS = visual analog scale; VS = cross-sectional velocity.

factors. Other factors like lid wiper friction will need to be included in future studies.

In summary, this is the first study to reveal the relationship between ocular comfort and conjunctival vascular responses in HCL wearers. This may help better understand the underlying mechanism of ocular discomfort and its contributing factors, including lens materials and designs and ocular characteristics.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

QI CHEN: FORMAL ANALYSIS, INVESTIGATION, WRITING - original draft, Writing - review & editing. **Hong Jiang:** Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Jianhua Wang:** Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST.
Funding/Support: Supported by a research grant from Johnson & Johnson Vision Care, Inc., Jacksonville, Florida, USA.
Financial Disclosures: The authors indicate no financial conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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