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Lid wiper microvascular responses as an indicator of contact lens discomfort

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Abstract

Purpose—To analyze quantitatively the alterations in the microvascular network of the upper tarsal conjunctiva, lid wiper, and bulbar conjunctiva relative to ocular discomfort after contact lens wear.

Design—A prospective, cross-over clinical study.

Methods—Functional slit-lamp biomicroscopy (FSLB) was used to image the microvascular network of the upper tarsal conjunctiva, lid wiper, and bulbar conjunctiva. The microvascular network was automatically segmented, and fractal analyses were performed to yield the fractal dimension (D_{box}) that represented vessel density. Sixteen healthy subjects (nine female and seven male) with an average age of 35.5 ± 6.7 years old (mean $\pm$ standard deviation) were recruited. The right eye was imaged at 9 AM and 3 PM at the first visit (Day 1) when the subject was not wearing contact lenses. During the second visit (Day 2), the right eye was fit with a contact lens for 6 h. Microvascular imaging was performed before (at 9 AM) and after lens wear (at 3 PM). Ocular comfort was rated using a 50-point visual analogue scale before and after 6 h of lens wear, and its relationships with microvascular parameters were analyzed.

Results—There were no significant differences in D_{box} among the upper tarsal conjunctiva, lid wiper, and bulbar conjunctiva among the measurements at 9 AM (Day 1 and Day 2) and 3 PM

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(Day 1) when the subjects were not wearing the lenses ($P > 0.05$), whereas after 6 h of lens wear, the microvascular network densities were increased in all three of these locations. D_{box} of the lid wiper increased from 1.411 ± 0.116 to 1.548 ± 0.079 after 6 h of contact lens wear ($P < 0.01$). D_{box} of the tarsal conjunctiva was 1.731 ± 0.026 at baseline and increased to 1.740 ± 0.030 ($P < 0.05$). D_{box} of the bulbar conjunctiva increased from 1.587 ± 0.059 to 1.632 ± 0.060 ($P < 0.001$). The decrease in ocular discomfort was strongly related to the D_{box} change in the lid wiper ($r = 0.61$, $P < 0.05$). There were no correlations between the changes of ocular comfort and the microvascular network densities of either the tarsal or bulbar conjunctivas ($P > 0.05$).

Conclusion—This study is the first to show that the microvascular network of the lid wiper can be quantitatively analyzed in contact lens wearers. The microvascular responses of the lid wiper were significantly correlated with contact lens discomfort.

INTRODUCTION

According to the TFOS International Workshop on Contact Lens Discomfort, contact lens discomfort (CLD) is a frequently experienced problem that is estimated to affect as many as 50% of contact lens wearers worldwide.¹ As a condition characterized by episodic or persistent adverse ocular sensations related to contact lens wear, CLD occurs and results from reduced compatibility between the contact lens and the ocular environment. The resulting “discomfort” (which can vary in different individuals) stems from interactions among multiple psychophysical and neurobiological factors, which can lead to reduced lens wearing time or even termination of contact lens wear.² Previous studies have indicated that the interaction between the contact lens and ocular surface can result in ocular tissue alterations and therefore leads to CLD.³ Many clinically used approaches, such as the assessment of alterations in the pre-lens tear film,^{4–7} the Meibomian glands,⁸ bulbar and limbal conjunctival hyperemia,^{8,9} corneal and conjunctival staining, lid wiper epitheliopathy (LWE) and lid parallel conjunctival folds,^{8,10–13} have been used in attempts to determine the causes of CLD. However, so far, CLD is not well understood, and the relationships between CLD and ocular surface alterations have not yet been established.

While a contact lens wearer might exhibit a broad range of abnormal clinical signs, no single common sign has been identified as responsible for CLD. LWE was first described by Korb et al. in 2002¹⁴ and all subsequent works have been thoroughly reviewed by Efron et al. in 2016.¹⁵ LWE has been reported to be related to some CLD symptoms, such as lens awareness, irritation, sandiness and dryness. The lid wiper glides over the entire ocular surface during blinking. If a contact lens is worn, the lid wiper touches the contact lens surface, and the friction between the lens surface and lid wiper epithelium can cause prevalent and significant damage to the epithelium, resulting in LWE.^{10,16,17} It has been well documented that LWE often occurs in contact lens wearers, particularly symptomatic wearers.^{14,18–20} However, rough ranking (ranging from zero to three, total of four grades) of the LWE was not found to be correlated with CLD in clinical surveys (Schulze MM, et al. IOVS 2015;56:ARVO E-Abstract 6069).¹⁰ To analyze quantitatively the microvascular response of the ocular surface to contact lens wear, we developed a functional slit-lamp biomicroscope (FSLB) for quantifying the microvascular network of the human ocular surface, and we found that the microvascular network alters during contact lens wear.²¹ The

goal of the present study was to quantitatively analyze the microvascular network of the lid wiper in response to a short period of contact lens wear and its relationship with CLD.

METHODS

This is a prospective study and the protocol was approved by the institutional review board for human research at the University of Miami. Informed consent was obtained from each subject. All subjects were treated in accordance to the tenets of the Declaration of Helsinki.

The FSLB and imaging procedure have been previously described.²¹ In summary, a digital camera (Canon 60D, Canon Inc., Melville, NY, USA) was attached to a traditional slit-lamp (Nikon FS-2, Nikon Inc., Melville, NY, USA), creating the FSLB. The camera is a complementary metal-oxide semiconductor (CMOS)-based digital single lens reflex (DSLR) camera with an imaging sensor size of 22.3 mm × 14.9 mm, which acquires a maximum resolution of 5,184 × 3,456 pixels (~17.9 megapixels). The pixel dimension on the camera sensor is 4.3 μm × 4.3 μm.²¹ A diaphragm with an aperture of 5 mm was fixed in front of the lens of the FSLB to increase the focus depth (Fig. 1). The International Standards Organization (ISO) sensitivity was 2,500, and the time of exposure was 1/15s. With a built-in green filter and 15× magnifications, the field of view was approximately 15.74 × 10.50 mm².

The subject was looking down and fixing on a target at the 6 o'clock position while we imaged the upper lid wiper. To expose the upper lid wiper and tarsal conjunctiva, the upper lid was inverted. By observing the live view images on a high definition monitor, the operator focused the green light on the middle of the upper tarsal conjunctiva or the lid wiper before still images were captured. In addition, images of the temporal bulbar conjunctiva were also captured using the same photography procedure described in our previous study.²¹

Custom software was developed to process the images for fractal analysis. The raw images for each subject were resized from 5,184×3,456 pixels to 1,024×683 pixels. As described previously,^{21, 22} to enhance the contrast between blood vessels and the background, adaptive histogram equalization and morphological opening operations were performed to remove non-uniform illumination, background noise and non-vessel structures (Fig. 2). The field of interest (FOV) was outlined manually. For the upper tarsal conjunctiva, the FOV started from the inferior tarsal sulcus and ended at the upper edge of the tarsus. For the upper lid wiper, the FOV started with the posterior region and extended to the Meibomian gland ostia, ending with the sub-tarsal fold.²³ The FOV of the bulbar conjunctiva involved an area of 7.87 × 7.87 mm² around the limbus.

To maintain a similar area for repeated measures, the FOV of the first image of the same location (i.e., lid wiper, tarsal and bulbar conjunctiva) of the same subject was overlaid on the remaining images. Manual adjustment was undertaken by moving the FOV to maximize the similarity of the covered area for each of the subsequent images (Fig. 3). Then, the FOV was cropped. The cropped image was subsequently inverted with Image J software (NIH, Bethesda, MD, USA), converted to a binary format, skeletonized and analyzed for density

(D_{box}) using the fractal analysis toolbox from Benoit™ software (TruSoft Benoit Pro 2.0, TruSoft Inc., St. Petersburg, FL, USA).

Sixteen healthy subjects (seven males and nine females) with a mean age of 35.5 ± 6.7 years old were recruited. None of them had a history of contact lens wear. Subjects with anterior or posterior segment pathologies, laser treatment, trauma, eye surgery, systemic disease or tobacco or alcohol use were excluded. Additionally, those with the compounding factors of hypertension, diabetes, sickle cell anemia, cerebral small vessel disease, stroke and other cardiovascular/cerebrovascular diseases or vascular diseases were also excluded.

To validate the method, vascular images of the upper lid wiper, upper tarsal conjunctiva and temporal bulbar conjunctiva of the right eye were obtained at 9 AM and 3 PM (Day 1) without the subject wearing the contact lens. On Day 2 (lens study visit), the ocular vasculature of these three locations was imaged at baseline without contact lens wear (at approximately 9 AM) and at 6 h after wearing contact lenses (PureVision B.C 8.3 mm, power -0.50 D, Bausch & Lomb, Rochester, NY, USA). The subjects rated CLD using a 50-point visual analogue scale at baseline and at 6 h after lens wear on Day 2.

A statistical software package (SPSS for Windows 17.0, SPSS Inc., Chicago, IL, USA) was used for descriptive statistics and data analysis. Repeated analysis of variance (Re-ANOVA) was used, and post-hoc tests were used to determine pair-wise differences. $P < 0.05$ was considered a statistically significant difference. The coefficient of repeatability (CoR) was defined as two times the standard deviation of the difference between two measurements obtained by the same observer in different sessions for the same subject. The percentage of the coefficient of repeatability (CoR %) was calculated by dividing the CoR by the average of each of the two measurements between 9 AM and 3 PM.

RESULTS

There were no significant differences in microvascular network densities (D_{box}) in any of the three locations among the three measurements on the first day or on the second day before wearing contact lenses ($P = 0.95$) (Table 1, Fig. 4). The CoR of the D_{box} in the upper tarsal conjunctiva, lid wiper, and bulbar conjunctiva at 9 AM on Day 1 and 9 AM before contact lens wear on Day 2 (lens study visit day) was 1.6%, 3.3% and 1.2%, respectively.

After 6 h of contact lens wear, the microvascular network became apparently denser when observed using slit-lamp biomicroscopy. More profound changes were noted in the lid wiper (Fig. 4). The D_{box} of the upper tarsal conjunctiva, upper lid-wiper and bulbar conjunctiva were all increased from baseline ($P < 0.01$) (Table 1, Fig. 4). The increase in the lid wiper was significantly greater than in the two other locations ($P < 0.01$). After 6 h of contact lens wear, the comfort score decreased from 44.0 ± 8.2 to 29.9 ± 6.5 ($P < 0.01$) in the lens wearing eyes. The change in comfort score in the lens wearing eyes was correlated with the D_{box} changes in the lid wiper ($r = 0.61$, $P < 0.05$, Fig. 5). There were no correlations between the changes in the comfort score and the D_{box} changes in either the tarsal or bulbar conjunctiva ($P > 0.05$) (Fig. 5)

DISCUSSION

While contact lenses are commonly used to correct myopia, some contact lenses wearers discontinue wearing contact lenses, mainly due to CLD and dryness.^{24–27} The “dropout” rate has been consistently high, ranging from 34% to 51%, regardless of the introduction of new lens materials and designs.^{10, 24–27} While contact lens-related dryness is known to be driven by a compromised tear film,^{28–34} CLD might be more difficult to evaluate objectively. CLD is believed to be caused by interaction between the lens and ocular surface, including the surface of the upper lid wiper.^{10, 24, 26}

The ocular surface consists of a continuous mucosa that starts at the corneal limbus, extends to the bulbar and fornical conjunctiva and ends with the tarsal conjunctiva at the outermost region.³⁵ The tarsal conjunctiva is further subdivided into proximal and distal parts by a sub-tarsal fold, which is parallel to the lid margin and approximately 2 mm from the lid margin posterior border.^{35, 36} The distal part, which is called the marginal conjunctiva, is important for lid function during blinking, and it also extends from the fold to the mucocutaneous junction on the occlusal surface of the lid margin.

The conjunctiva at the “lid wiper” zone plays an important role in tear film distribution.³⁵ Histological studies have demonstrated that there are goblet cells in the lid wiper epithelium singularly or in cluster formats.³⁶ These goblet cells produce gel-forming mucins, which result in a thin mucin-water gel that lubricates the surfaces of the lid wiper and globe surface.³⁶ In normal eyes, the thin gel might facilitate the maintenance of low friction during blinking and protect the lid wiper from damage. Contact lenses separate the lid-wiper from the globe surface, creating a new environment for the interaction between the ocular surface and the lens.

It is well known that the interaction between the lens and ocular surface can result in the signs and symptoms of CLD, which can include conjunctival staining,³⁷ conjunctival flaps,³⁸ lid parallel conjunctival folds,³⁹ conjunctivochalasis⁴⁰ and bulbar conjunctiva hyperemia.⁴¹ Ocular vascular responses to contact lens wear are among the most important areas for understanding contact lens fitting and CLD. Developing an objective method for quantitatively analyzing the microvascular responses of the ocular surface is critical for studying the mechanism of CLD.

We previously validated the repeatability of our quantification method of microvascular changes in the bulbar conjunctiva.⁴² In the present study, we found that the repeatability of the vascular density, measured as the fractal dimension, was good in all three locations. In particular, the method might be helpful in determining the impact of the friction between the lens and lid wiper, which could lead to a better understanding of the pathophysiology of CLD, which constitutes a challenge for contact lens wearers, contact lens practitioners and the contact lens industry.

Bulbar hyperemia is a common sign that often presents shortly after lens insertion and in wearers with CLD.^{10, 43–45} In addition, other vascular abnormalities have been demonstrated in contact lens wearers.^{21, 46} Cheung et al. found a number of vasculopathies, including increased vessel diameter, and changes in vessel contour in contact lens wearers.⁴⁶ Jiang et

al. demonstrated alteration of the microcirculation of the bulbar conjunctiva after a short period of lens wear, and the hemodynamic changes were in agreement with the vessel morphological changes.²¹ In clinical trials, the bulbar conjunctival redness grading scale has been used to rank the microvascular responses, such as hyperemia grading, which is often used to determine contact lens fitting and tolerance. However, rough evaluations have not been sufficient to establishing a link between the bulbar vascular response, including microcirculation and vessel morphological changes, and CLD. This finding is in agreement with our results that showed no relationships between CLD and the changes in the microvascular network density of the bulbar conjunctiva.

In addition to the bulbar conjunctival hyperemia, studies have been performed to explore alterations in the lid wiper and tarsal conjunctiva. The human eye blinks 10–12 times per minute, resulting in the upper lid traveling approximately 100 meters per day, assuming a vertical interpalpebral aperture of 10 mm and 16 h of daily activity.³⁶ During blinking, the lid wiper is the only area on the lid margin that touches the globe surface, resulting in mechanical friction.⁴⁷ After blinking proceeds, the tarsal conjunctiva touches the globe. The neural sensitivity of the lid wiper zone is very high in the conjunctival and lid regions, almost similar to that of the central cornea.^{48, 49} This sensitivity helps in the sensing of possible damage to the lid wiper.

It has been suspected that the altered lid-wiper may be the culprit of CLD. Increased mechanical friction on the lid wiper is possible during blinking if the lid wiper epithelium sweeps over a rough or dry surface of a contact lens. If the surface is damaged or the mucin-water gel is not formed, the friction can further escalate. Indeed, hyperemia of the lid wiper was found to be elevated quantitatively in CL wearers, and the friction could clearly lead not only to lid wiper vascular response but also to LWE, which can be clinically determined by staining the lid wiper with commonly used ophthalmic dyes.^{16, 23, 50, 51} Long-term contact lens wear also induces tarsal conjunctiva changes, such as changes in the mucous membrane and papillary appearance as revealed by slit-lamp biomicroscopy.^{52–54}

Other than friction between the lid wiper and the ocular surface or lens surface, other possible etiological factors may also play a role in the microvascular response of the lid wiper due to contact lens wear. The notion of inflammatory response in uncomplicated contact lens wear was first proposed by Efron in 1985.⁵⁵ Korb et al. hypothesized that inflammation may be part of the etiology in developing LWE caused by friction-induced microtrauma, which results from the movement of the lid wiper against the ocular surface or lens surface.¹⁴

The vessel density increased 6 hours after contact lens wear in the present study, which supports the hypothesis that increased hyperemia is a cardinal sign of inflammation. Recent evidence also indicates the involvement of inflammatory process in LWE for contact lens induced dry eye. Alzhrani et al. used a laser scanning confocal microscope to image the Langerhans cells, presumably inflammatory cells in the stroma of the lid wiper, in response to contact lens wear.⁵⁶ They found Langerhans cell density was significantly increased in the lid wiper for contact lens wearers with dryness, indicating the involvement of inflammatory process.

While many studies have indicated that ocular surface clinical signs and symptoms presented with both short- and long-term contact lens wear, no studies have been able to identify any ocular surface signs directly related to CLD. One possible reason could be technological limitations. The redness scales and estimations of limbal vascularization might not be sufficiently sensitive for quantitative evaluation. In addition, LWE, ranked as a score from 0 to 3, might well document the severe lid wiper damage but not subtle pre-clinical signs. A recent multi-center study conducted by Schulze et al. failed to demonstrate a relationship between LWE and CLD in a larger sample of habitual lens wearers (Schulze MM, et al. IOVS 2015;56:ARVO E-Abstract 6069).⁵⁷

Fractal analysis of microvascular network of the lid wiper may be more sensitive in detecting the vascular response in the lid wiper. We were able to use a small sample of subjects to establish the relationship between fractal dimension of lid wiper vessel density and CLD. Our highly repeatable sample size calculation also presents a high detection power for observing subtle changes. The present study showed that microvascular network alterations of the lid wiper were correlated with comfort scales after 6 h of contact lens wear. Alterations in the microvascular network of the lid wiper might be a clinic indicator of CLD.

In a previous study, it was reported that contact lens wearers with dry eye symptoms exhibited significantly more LWE but not increased bulbar hyperemia or decreased tear break-up time.⁵⁸ In studies of the impact of contact lens on conjunctival hyperemia, increased bulbar hyperemia was reported in asymptomatic contact lens wears, but there was no correlation of conjunctiva hyperemia with CLD. Hyperemic changes in the tarsal conjunctiva occurred after long-term contact lens wear. However, the general, non-pathological changes in the palpebral conjunctiva were not directly linked to CLD.³ In the present study, the relationships between the microvascular responses of the lid wiper and ocular discomfort after a period of lens wear were established for the first time. These relationships could be further used to study different lens materials and designs as objective measurements.

The visual analogue scale for quantifying CLD are commonly used to subjectively determine CLD.^{57, 59–62} The 50-point visual analogue scale was used in one of the previous studies⁵⁹ and the subjective scale successfully documented the end-of-day discomfort in contact lens wearers. As this study focused on the new imaging approach, the simple 50-point visual analogue scale was used due to its simplicity. Further studies using more specific approach such as questionnaires for quantifying CLD may be applied.

There are limitations to the present study. Although a significant correlation was found between the microvascular network in the lid wiper and CLD, the sample size may be too small to test whether the associations between the microvascular network in the tarsal and bulbar conjunctivas and CLD exist. Using the software program GPower (Ver. 3.1.9),⁶³ we calculated the sample size based on the differences in the measured microvessel network results and the calculation indicated that we only need to have 8 cases to determine the true difference of the vessel density with a detection power of 95%. Therefore, our sample size may be sufficient for determining the vessel density differences between groups and establish the relation between lid wiper microvascular network and CLD.

Furthermore, the field of interest (FOV) was outlined manually and the same FOV mask was used to extract the FOV for different visits of each eye. Further development on automated outline of the FOV and image registration of the same FOV for all visits may improve the ability for measuring microvascular network changes in all three locations. Additionally, only one type of the contact lens (i.e., one lens design) was tested in this study and further studies with different lens types are necessary to establish the impact of lens types and designs on microvascular responses in these ocular surfaces.

We only studied a group of subjects who had no history of wearing contact lenses and results were collected after 6 hours of contact lens wear. The ocular surface and CLD changes related to this short period of lens wear may not be the same as that of real life situations, such as mid- and long-term CL wear. Further studies will be needed to test microvascular responses to contact lens wear in habitual lens wearers. Lastly, we did not evaluate the changes of the conjunctiva and Meibomian glands which are related to CLD. These additional evaluations need to be included in future studies.

In summary, this study was the first to establish the relationship between the lid wiper microvascular responses and CLD. The alteration in the microvascular response of the lid wiper might be an indicator of CLD. Future studies with larger sample sizes and different lens materials, designs and friction properties could further define the role of the lid wiper microvascular response in CLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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No focal depth enhancement

With focal depth enhancement

Figure 1.

Focal depth enhancement. A printed grid was imaged using the FSLB without (Left) and with (Right) a diaphragm (aperture 5 mm) to improve focal depth. The grid pad was placed with the tilt of a 15 degree angle to simulate the image depth. With enhancement, a wider field of view up to $10 \times 10 \text{ mm}^2$ was in focus, compared to the image without enhancement.

Figure 2.

Image processing to extract the microvascular network. Raw images of the upper tarsal conjunctiva (Top left), lid wiper (Top middle) and bulbar conjunctiva (Top right) were obtained using the FSLB. Custom software was used to segment the vessels to create the microvascular network (Middle row) by a series of image processing procedures, including adaptive histogram equalization and morphological opening operations. The images were then cropped and skeletonized for fractal analysis (Bottom row).

Figure 3.

Microvasculature changes after 6 h of contact lens wear. The microvascular network of the upper tarsal conjunctival, lid wiper, and bulbar conjunctiva of a study participant were imaged. The microvascular network was clearly visualized on the raw images (Top row), with the segmented vessel network in the outlined field before (Middle row) and after 6 h of contact lens wear (Bottom row). After 6 h of lens wear, the density of the vessels appeared to have increased from the baseline. The vessel density change was seemingly more prominent in the lid wiper than in the upper tarsal and bulbar conjunctiva.

Figure 4.

Microvascular network density (D_{box}) of the upper tarsal conjunctiva, lid wiper and bulbar conjunctiva. Images were obtained at the first visit at 9 AM and 3 PM and at the second visit at 9 AM when the lens had not yet been worn. No significant changes were found ($P > 0.05$) among these time points when the lenses were not worn (Left), whereas significant increases in D_{box} were found in all three locations ($P < 0.01$) after 6 h of contact lenses wear at the second visit, with the greatest changes in the lid wiper (Right).

Figure 5.

The relationships between the ocular comfort ratings and microvascular network density (D_{box}). The microvascular network was imaged in the upper tarsal conjunctiva (Left), upper lid wiper (Middle) and temporal bulbar conjunctiva (Right). Ocular comfort was rated before and after 6 h of contact lens wear. The change in ocular comfort score was significantly and negatively correlated with the change in the microvascular network density of the lid wiper ($r = 0.61$, $P < 0.05$). However, there were no significant relationships between the changes in the comfort scores and the changes in the microvascular network density of the upper tarsal and bulbar conjunctivas ($P > 0.05$).

Table 1Microvascular network densities (D_{box}) of tarsal conjunctiva, lid wiper and bulbar conjunctiva (n=16)

Day 1 (No lens wear)			
	9AM	3PM	P Value
Tarsal conjunctiva	1.734 ± 0.024	1.732 ± 0.034	0.83
Lid wiper	1.409 ± 0.129	1.414 ± 0.127	0.60
Bulbar conjunctiva	1.586 ± 0.066	1.586 ± 0.062	0.96
Day 2 (Contact lens study)			
	9AM(before contact lens wear)	3PM(6H after contact lens wear)	
Tarsal conjunctiva	1.731 ± 0.026	1.740 ± 0.030	0.02
Lid wiper	1.411 ± 0.116	1.548 ± 0.079	<0.01
Bulbar conjunctiva	1.587 ± 0.059	1.632 ± 0.060	<0.01