Disruption in Autonomic Nervous Activity Is Associated With Central and Peripheral-Level in Dry Eye With Unstable Tear Film

Minako Kaido,[1,2] Reiko Arita,[2,3] Yasue Mitsukura,[4] Brian Sumali,[4] and Kazuo Tsubota[2]

[1]Wada Eye Clinic, Chiba, Japan
[2]Tsubota Laboratory, Inc., Tokyo, Japan
[3]Itoh Clinic, Saitama, Japan
[4]Faculty of Science and Technology, Keio University, Kanagawa, Japan

Correspondence: Minako Kaido, Wada Eye Clinic, Houjyo 2578-27, Tateyama-shi, Chiba 294-0045, Japan; tomoulton777@ff.em-net.ne.jp.

Received: June 29, 2024
Accepted: February 5, 2025
Published: February 27, 2025

Citation: Kaido M, Arita R, Mitsukura Y, Sumali B, Tsubota K. Disruption in autonomic nervous activity is associated with central and peripheral-level in dry eye with unstable tear film. *Invest Ophthalmol Vis Sci.* 2025;66(2):69. https://doi.org/10.1167/iovs.66.2.69

Purpose. To measure autonomic nerve activity (ANA) in several eye conditions and verify whether ANA modulation is regulated by peripheral or central control in short tear film break-up time dry eye (sBUTDE).

Methods. This study included 23 eyes of 23 patients with sBUTDE (mean age 55.2 ± 16.1 years; range 21–88 years) and 24 eyes of 24 age-matched non-dry eye (DE) controls. An ANA measurement, personality questionnaire, and Ocular Surface Disease Index were administered. ANA was continuously measured for 10 minutes under three conditions: eyes closed, eyes open, and eyes open under ocular surface anesthesia.

Results. The low-frequency (LF)/high-frequency (HF) ratio (LF/HF) with eyes closed was significantly higher in the sBUTDE group than in the control group ($P < 0.05$). In the sBUTDE group, HF increased and LF/HF decreased with eye opening compared with those in the control group; HF with eyes open decreased with ocular surface anesthesia and reached the same level as that in the control group. Among patients where HF decreased or LF/HF increased with eye opening, 57.1% or 64.3% showed a tendency to return to the ANA state with eyes closed by ocular surface anesthesia, respectively. Factors associated with DE symptoms included break-up time, HF with eyes open, and "openness" ($P < 0.05$).

Conclusions. ANA modulation can be caused by peripheral, central, or mixed abnormalities in sBUTDE. Furthermore, personality traits may play a role in symptom induction. Understanding the pathogenesis of sBUTDE may aid in the treatment of cases that are refractory to conventional treatments.

Keywords: autonomic nerve activity, dry eye, parasympathetic nerve, personality, symptom, tear film

Dry eye (DE) is defined by TFOS DEWS II as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1] This definition suggests the involvement of neurological abnormality in DE pathogenesis.[1,2] Neuropathies include peripheral and central abnormalities. Galor et al.[3] demonstrated a method to differentiate between peripheral or central sensitization using topical anesthesia to observe whether symptoms disappear.

Regarding peripheral neuropathy, three different receptors present on the corneal surface have been discussed: mechanoreceptors that respond to mechanical stimuli; polymodal nociceptors that respond to mechanical, chemical, and thermal stimuli; and cold receptors that respond to cold stimuli.[4] Concerning corneal sensitivity to mechanical stimulation in DE disease, studies have reported hypersensitivity[5–8] and hypoesthesia[9,10]; however, no conclusion has been reached. Transient receptor potential V1, present in polymodal nociceptors, is involved in "pain perception" and has been suggested to contribute to discomfort and pain in DE disease.[11] Regarding sensitivity to cold stimuli, in DE disease, TRPM8 is activated even by small temperature changes that do not normally cause dryness or pain, leading to dryness and pain.[12]

Functional magnetic resonance imaging suggests central abnormalities in DE.[13–17] Most studies have reported low activity in brain areas such as the frontal gyrus and cerebellothalamocortical network.[14–17]

We have studied the pathogenesis of short break-up time of tear film DE (sBUTDE), which exhibits a discrepancy between finding signs and symptoms, focusing on neurological abnormality. Our previous report suggested that in sBUTDE, emotional sensations, rather than somatosensory abnormalities, may be involved in the neural pathways of perception.[18] Furthermore, we discovered that fluctuations

in the autonomic nervous balance are significantly related to the intensity of DE symptoms in sBUTDE, suggesting that modulation of autonomic nervous activity (ANA) may be involved in symptom manifestation.[19–24] In this study, we verified whether this modulation of ANA is due to peripheral or central control.

Methods

The study protocol was reviewed and approved by the Ethics Committee of the Institutional Review Board of Ito Clinic, Saitama, Japan. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all participants. This study was registered with the University Hospital Medical Information Network (Registry ID: UMIN 000053808).

Participants

This prospective, cross-sectional, comparative clinical study included 23 eyes of 23 patients with sBUTDE (mean age 55.2 ± 16.1 years; range 21–88 years), refractory to conventional treatments, such as eye drops, anti-inflammatory therapy, lacrimal punctal occlusion and/or intense pulsed light therapy, and 24 eyes of 24 non-DE controls (mean age 54.4 ± 15.8 years; range 29–80 years) (Supplementary Table S1). The sample size was determined based on a previous study.[25] SBUTDE was diagnosed based on the presence of DE symptoms, break-up time (BUT) ≤5 seconds, and negative keratoconjunctival damage (keratoconjunctival vital staining <3 out of 9 points). Non-DE was determined based on the absence of DE symptoms and keratoconjunctival vital staining <3 points. The Schirmer test value was not considered when distinguishing between sBUTDE and non-DE. The exclusion criteria were as follows: ocular surgery and trauma within the last 12 months, permanent structural damage because of ocular trauma, receiving pressure-lowering agents for glaucoma treatment, current contact lens use, and systemic diseases, including metabolic, cardiovascular, and pulmonary diseases that may affect heart rate, other than hypertension. In addition, smokers and those taking medications for colds and allergies to pollen were also excluded. The eye with the more prominent symptoms in each patient was selected for evaluation. The right eye was selected if the symptoms were equal in both eyes.

DE Questionnaire

We administered the Japanese version of the Ocular Surface Disease Index (J-OSDI).[21] A J-OSDI score of 13 or higher was defined as a positive presence of symptoms.

Personality Questionnaire

We administered the Japanese version of the 10-Item Personality Inventory personality questionnaire. This short questionnaire measures five key personality dimensions: extraversion, agreeableness, conscientiousness, neuroticism, and openness.[22,23] The manual was used as a reference to calculate the scores for these dimensions.[24]

Slit-Lamp Examinations

The patients underwent slit-lamp examinations for lid margin abnormalities, including vascular engorgement, plugging of the meibomian gland orifices, and properties of the meibum. Vascular engorgement and plugging of the meibomian gland orifices were assessed at the upper and lower eyelid, and properties of the meibum were assessed at the upper alone. On the basis of the Bron scale, the clinical severity grading scores were determined as 0–3 points for vascular engorgement and properties of the meibum and as 0–2 points for the plugging of the meibomian gland orifices.[25]

We performed DE examinations, including BUT measurement, keratoconjunctival vital staining, and the Schirmer test. BUT was measured after instilling 2 µL of preservative-free 1% sodium fluorescein into the conjunctival sac using a micropipette. Keratoconjunctival epithelial staining and the property of the meibum were evaluated after BUT measurement. The overall epithelial damage was scored on a scale of 0–9 points, as described previously.[26] The Schirmer test was performed last during eye surface evaluations.

ANA Measurement

The Fitbit device and Fitbit Charge 5 app (Fitbit, Inc., San Francisco, CA, USA) were used for the ANA measurement.[27] Fitbit Charge 5 uses photoplethysmography and a method to derive heart rate from photoplethysmography to calculate heart rate variability.[28] ANA was continuously measured in the sitting position for 10 min. under each of three conditions: eyes closed, eyes open with natural blinking, and eyes open under ocular surface anesthesia with natural blinking, at least 10 min after the Schirmer test to minimize the effect of the Schirmer test on ANA. Benoxil ophthalmic solution 0.4% (Santen Pharmaceutical Co., Ltd.) was used for ocular surface anesthesia and was applied bilaterally. Breathing was measured naturally without any instruction to breathe deeply or shallowly. The room temperature was maintained at 23 °C–26 °C with 50%–60% humidity during the examinations.

Autonomic nerve function was assessed by frequency analysis of the cardiac beat movements (fluctuations in heart rate intervals) and quantification of sympathetic and parasympathetic activity.[29,30] This technique partitions the total variance ("power") of a continuous series of beats into its frequency components, typically identifying two main peaks: component of low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz).[31,32] The HF peak reflects the cardiac parasympathetic nerve activity, whereas LF reflects cardiac sympathetic and parasympathetic nerve activity.[29–33] The LF/HF ratio is proposed to quantify the degree of sympathovagal balance and used as an index of sympathetic nerve function.[29,30,34–37] Coefficient of component variance of LF (ccvLF) and HF (ccvHF) reflect the variation of LF and HF, respectively.[38] The values of ccvLF and ccvHF were calculated using the following formulas: ccvLF = $\sqrt{}$LF average (RR) × 100; ccvHF = $\sqrt{}$HF/average (RR) × 100. The heart rate variability metrics assessed in this study were LF, HF, LF/HF ratio, ccvLF, and ccvHF.

Statistical Analyses

Data are presented as the mean ± standard deviation, wherever applicable. The scores of J-OSDI and the personal-

Investigative Ophthalmology & Visual Science

ity questionnaire and the DE and ANA parameters were compared between the sBUTDE and control groups using the Student *t*-test. ANA in the eyes open, eyes closed, and eyes open under ocular surface anesthesia conditions were compared within each group by using one-way ANOVA. Further analysis was performed using Dunnett's test. The differences in ANA levels between eyes open and eyes closed conditions, as well as between eyes open and eyes open under ocular surface anesthesia conditions, were compared between the groups. In the sBUTDE and control groups, the proportion of cases in which ANA increased or decreased because of eye opening and ocular surface anesthesia was examined using the χ^2 test.

To determine the factors associated with the presence and absence of DE symptoms overall, multiple regression analysis was performed. An ANCOVA test was performed to adjust for age and sex as covariates on ANA under closed eyes (the baseline) and to adjust for ANA under closed eyes as covariates on ANA under other eye conditions (the baselines). The proportion of patients showing fluctuating patterns of HF and LF/HF according to eye conditions was analyzed using the χ^2 test.

All statistical analyses were performed using SPSS statistical software (version 17.0 J for Windows; IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

Results

Demographics of the Study Population

Table 1 presents the demographic characteristics of the patients in the sBUTDE and control groups. No significant differences were observed in the grading scores relating to DE parameters and lid abnormalities ($P > 0.05$) except for BUT value, J-OSDI scores and vascular engorgement of lid margin at the lower lid ($P < 0.05$).

Personality Questionnaire

The personality test showed a tendency to be higher in "neuroticism" ($P = 0.07$) and significantly lower in "openness" ($P < 0.05$) in the sBUTDE group (Table 2).

ANA

The heart rate was 72.2 ± 9.4 beats/min with eyes closed, 72.0 ± 9.5 beats/min with eyes open, and 72.2 ± 9.4 beats/min with eyes open under topical anesthesia in the sBUTDE group whereas it was 76.3 ± 10.0 beats/min, 76.6 ± 10.1 beats/min, and 76.4 ± 9.6 beats/min in the non-DE group.

Figure 1 shows the ANA associated with the three ocular conditions in the sBUTDE and control groups. LF/HF and ccvHF with eyes closed were significantly higher and lower, respectively, in the sBUTDE group than in the controls ($P < 0.05$). Regarding the difference between open and closed eyes, ΔHF, ΔccvHF, and ΔLF/HF were greater in sBUTDE than in non-DE (0.002 ± 0.005 vs. −0.0014 ± 0.005, $P < 0.05$; 0.009 ± 0.020 vs. −0.008 ± 0.020, $P = 0.10$; −1.916 ± 4.480 vs. 0.548 ± 2.113, $P < 0.05$). No significant differences were observed in all parameters between the sBUTDE and control groups for eyes open with and without topical anesthesia (−0.009 ± 0.04 vs.0.002 ± 0.030, $P = 0.33$; -0.005 ± 0.026 vs. −0.0004 ± 0.017, $P = 0.56$; 0.427 ± 2.441 vs. −0.383 ± 2.3319, $P = 0.31$). In sBUTDE, HF increased and LF/HF decreased with eye opening ($P = 0.21$ and $P = 0.05$, respectively), and showed trends opposite to those in the control; HF with eyes open decreased with ocular surface anesthesia ($P = 0.38$) and reached the same level as the controls. Figure 2 shows the individual trends in LF, HF, and LF/HF, and Table 3 shows the proportions of patients in the sBUTDE and control groups with changes in ANA in response to eye conditions. Regarding the changes in HF and LF/HF with eye opening, HF increased in 14 of 23 eyes (60.9%), and LF/HF decreased in nine of these

Table 1. Demographics of the Study Population

	sBUTDE Group $N = 23$	Control Group $N = 24$
Age (years)	55.2 ± 16.1	54.2 ± 15.8
Age range	21-88	29-80
Gender		
Male	7	8
Female	16	16
J-OSDI (pts)	52.6 ± 18.3*	2.5 ± 3.0
Punctal occlusion		
One	2	0
Both	0	0
DE findings		
BUT (s)	3.7 ± 1.9*	6.9 ± 2.5
VS score (pts)	0.3 ± 0.6	0.2 ± 0.5
Schirmer value (mm)	9.9 ± 10.9	12.5 ± 11.1
MGD findings		
Vascular engorgement of lid margin (pts)		
Upper	0.7 ± 0.9	0.5 ± 0.7
Lower	0.7 ± 0.9*	0.3 ± 0.4
Plugging of the meibomian gland orifices (pts)		
Upper	1.6 ± 1.2	1.3 ± 1.1
Lower	1.3 ± 1.0	1.1 ± 0.9
Meibum (pts), Upper	0.8 ± 1.1	0.5 ± 0.8

MGD, Meibomian gland dysfunction.
*$P < 0.05$, Student *t*-test.

Investigative Ophthalmology & Visual Science

Table 2. Personality Assessments of Patients in the sBUTDE and Control Groups

Ten-Item Personality Inventory	sBUTDE Group $N = 23$	Control Group $N = 24$
Extraversion	9.1 ± 2.4	8.3 ± 3.3
Agreeableness	10.8 ± 1.5	10.0 ± 1.9
Conscientiousness	9.0 ± 2.8	8.1 ± 2.4
Neuroticism	9.3 ± 2.1	8.1 ± 2.0
Openness	7.1 ± 2.5*	8.7 ± 2.2

*Student's *t*-test.

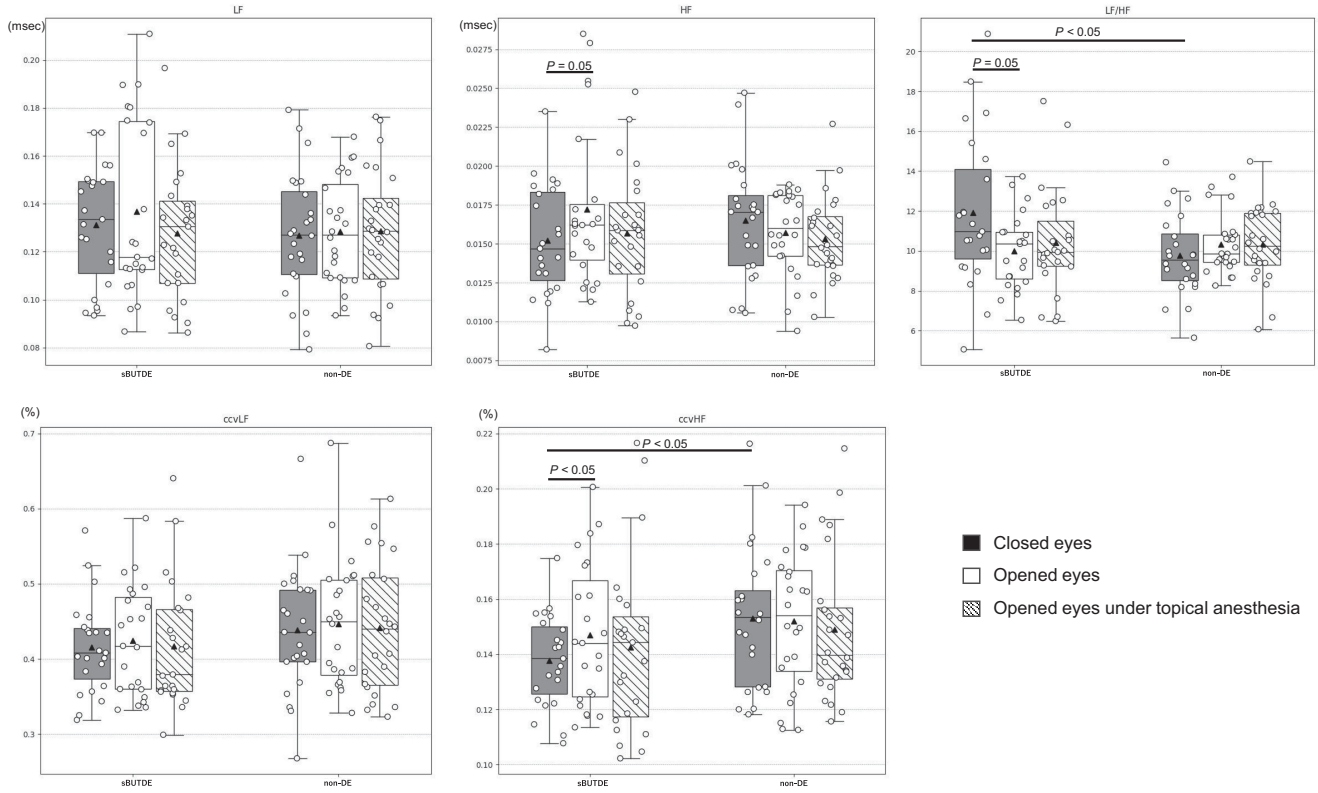

Figure 1. Autonomic nerve activity in the sBUTDE and control groups. The *black triangle* indicates the average value. In the sBUTDE group, HF and ccvHF were higher ($P = 0.05$ and $P < 0.05$, respectively), and LF/HF was lower ($P = 0.05$) when the eyes were open than when the eyes were closed, whereas there were no significant differences between eyes open and closed in each parameter in the control group. Compared with controls, LF/HF of sBUTDEs when eyes were closed was significantly higher than that of controls. ($P < 0.05$), and ccvHF of sBUTDEs when the eyes were closed was significantly lower than that of controls ($P < 0.05$).

14 eyes (64.3%) with eye opening ($P = 0.51$) in the sBUTDE group. In the control group, there was a tendency for LF/HF to increase (11 of 14 eyes [78.6%]; $P = 0.07$) when HF decreased (14 of 24 eyes [58.3%]; $P = 0.07$) (i.e., the two moved in opposite directions), whereas no consistent trend was observed in the sBUTDE group. Next, regarding the changes in HF and LF/HF with eye opening and with subsequent ocular surface anesthesia, in the sBUTDE group, HF increased from closing to opening the eyes in 14 cases (60.9%); in these, HF decreased with ocular surface anesthesia in eight cases (57.1%; $P > 0.05$). Similarly, LF/HF decreased from closing to opening the eyes in 14 cases (60.9%), and, of these, LF/HF increased with ocular surface anesthesia in nine cases (64.3%; $P > 0.05$). In the control group, HF decreased from closing to opening the eyes in 14 cases (58.3%), and, of these, HF increased with ocular surface anesthesia in 11 cases (78.6%; $P < 0.05$). Similarly, LF/HF decreased from closing to opening the eyes in 15 cases (62.5%), and, of these, LF/HF increased with ocular surface anesthesia in 10 cases (66.5%; $P > 0.05$). In the ANCOVA test, the covariates age and sex had $P = 0.89$ and $P = 0.45$ for HF values with closed eyes, respectively, and $P = 0.24$ and $P = 0.33$ for LF/HF values with closed eyes, respectively. Furthermore, the covariates HF under closed eyes had $P = 0.25$ on HF value under opened eyes and $P = 0.86$ on HF value under opened eyes with topical anesthesia; the covariates LF/HF under closed eyes had $P = 0.58$ on HF value under opened eyes and $P = 0.76$ on HF value under opened eyes with topical anesthesia. Figure 3 illustrates the typical sBUTDE and non-DE cases of ANA.

Factors Associated With HF Increase or LF/HF Decrease With Eye Opening in the sBUTDE Group

Multivariate regression analyses, with the dependent variables of age, sex, personality trait "openness," OSDI, and

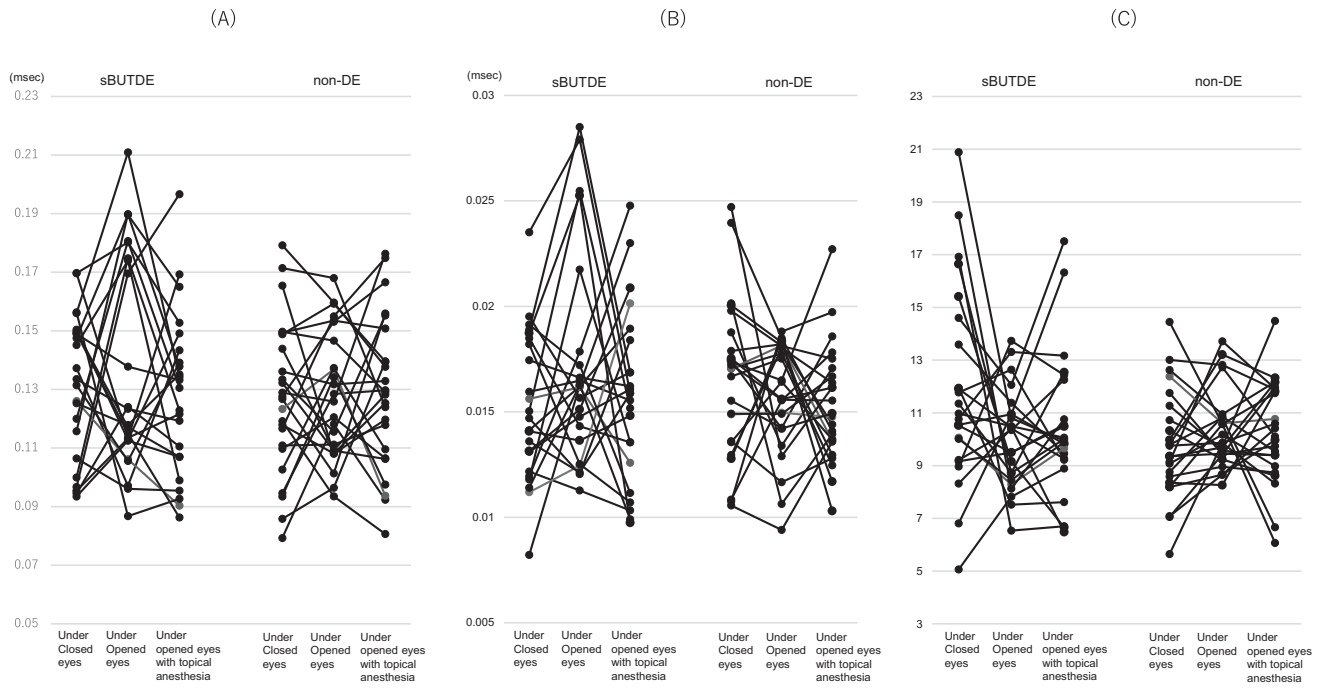

Figure 2. Individual trends in LF, HF and LF/HF. **(A)** LF; **(B)** HF; **(C)** LF/HF. The changes following eye opening and subsequent ocular surface anesthesia were large in some cases in the sBUTDE group compared with those in the control group.

Table 3. Proportion of Patients in sBUTDE and Control Groups Regarding Changes of Autonomic Nervous Activity in Response to Eye Condition

	sBUTDE Group			Control Group		
	Decreased	**Increased**	**Total**	**Decreased**	**Increased**	**Total**
Changes in HF and LF/HF with eye opening						
Decreased	5	4	9	3	11	14
Increased	9	5	14	6	4	10
Total	14	9	23	9	15	24
P value	0.51			0.07		
Changes in HF with eye opening and ocular surface anesthesia						
Decreased	5	4	9	4	10	14
Increased	8	6	14	8	2	10
Total	13	10	23	12	12	24
P value	0.64			0.02		
Changes in LF/HF with eye opening and ocular surface anesthesia						
Decreased	5	9	14	3	6	9
Increased	5	4	9	10	5	15
Total	10	13	23	13	11	24
P value	0.31			0.12		

Pearson's χ^2 test.

BUT, were performed to examine whether there were specific characteristics in patients in whom HF increased and in whom LF/HF decreased with eye opening.

No factors were significantly associated with HF increases with eye opening (Age, $P = 0.55$; Sex, $P = 0.50$; Openness, $P = 0.17$; OSDI, $P = 0.78$; BUT, $P = 0.19$). However, low "openness" in the personality trait was associated with LF/HF decreases with eye opening (Age, $P = 0.21$; Sex, $P = 0.55$; Openness, $P = 0.04$, OSDI, $P = 0.25$; BUT, $P = 0.31$).

Factors Associated With the Presence or Absence of DE Symptoms

In the multivariate analysis, "openness" among personality traits, BUT, vascular engorgement of lid margin (lower lid), and HF and LF/HF with closed and opened eyes were selected as dependent variables. The independent variables were independent factors without associations with each other; LF reflecting the activity of both sympathetic and parasympathetic nerves, and ccvLF and ccvHF, calculated

Investigative Ophthalmology & Visual Science

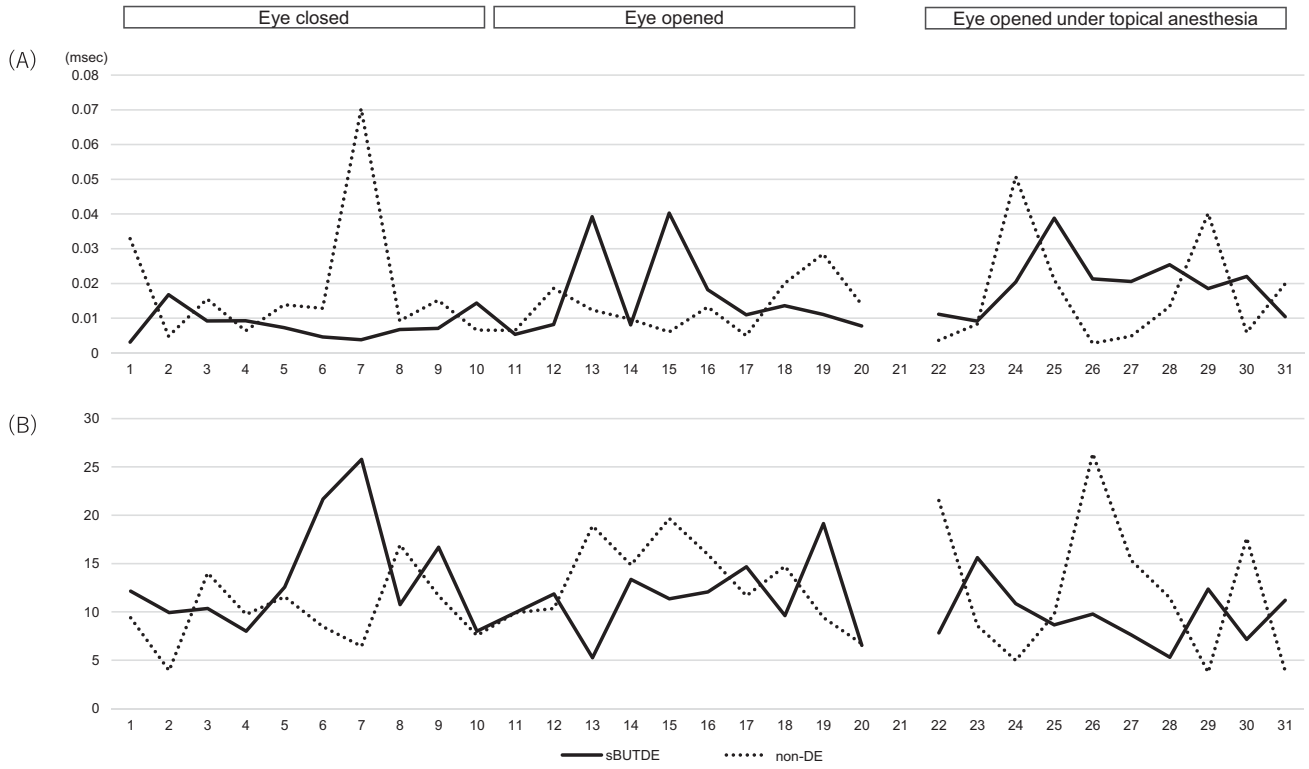

Figure 3. Typical cases in the sBUTDE and control groups. **(A)** HF; **(B)** LF/HF. The sBUTDE case is a 52-year-old male patient with a J-OSDI score of 45.8 points, BUT of 0 sec, VS score of 1 point, and Schirmer value of 1 mm. The non-DE case is a 57-year-old man with a J-OSDI score of 0, BUT of 5.3 sec, VS score of 0 points, and Schirmer value of 9 mm. VAS, visual analog scale.

Table 4. Association Between ANA Parameters and Dry Eye Symptoms

Factor	Standardization Coefficient β	t-Value	*P*
(Constant)		−0.018	0.986
Openness	−0.291	−2.212	0.033
BUT	−0.374	−2.932	0.006
Vascular engorgement of lid margin (Lower)	0.239	1.928	0.061
HF under closed eyes	0.239	1.782	0.083
LF/HF under closed eyes	−0.119	−0.791	0.434
HF under opened eyes	0.370	2.790	0.008
LF/HF under opened eyes	0.116	0.893	0.377

Dependent variable: presence and absence of DE symptoms; Adjusted $R = 0.68$

using LF and HF parameters, were excluded from the independent variables.

Table 4 presents the results of multiple regression analysis to determine the factors associated with the overall presence or absence of DE symptoms. BUT, HF under opened eyes, and "openness" were significantly associated with the presence or absence of DE symptoms ($P < 0.05$).

Discussion

This study clarified several interesting findings regarding ANA modulation in sBUTDE: (1) When the eyes were closed, sympathetic nerve activity was high, and parasympathetic nerve activity was relatively low. Opening the eyes decreased sympathetic nerve activity, whereas the trend was the opposite in the control group. Patients whose sympathetic nervous activity decreased with eye opening were more likely to have low "openness" as a personality trait. In addition, the ANA balance, in which parasympathetic nervous activity decreased when sympathetic nervous activity increased and vice versa, was disrupted, and the amount of change in ANA from eyes closed to eyes open was large. These results suggest that ANA may be disrupted in sBUTDE. (2) The presence and absence of DE symptoms was significantly associated with the BUT value, the HF value with eyes open, and the personality trait of "openness." The ANA results are consistent with our previous studies, which revealed that ANA modulation, particularly parasympathetic nerve activity, may be involved in the manifestation of sBUTDE symptoms. (3) Furthermore, regarding the peripheral receptor or central level control of ANA modulation, which is the primary objective of this study, ocular surface anesthesia had no statistically significant effect on ANA in patients with sBUTDE overall. However, ocular

Investigative Ophthalmology & Visual Science

surface anesthesia altered sympathetic and parasympathetic nerve activity levels to the same level as that of non-DE. Looking at the details, in approximately 60% of patients in which sympathetic activity decreased or parasympathetic activity increased with eye opening, ocular surface anesthesia tended to return to the activity state when the eyes were closed. This suggests that in sBUTDE, ANA modulation can be caused by peripheral, central, or mixed abnormalities.

Parasympathetic activity becomes dominant when the eyes are closed (relaxed state),[38] whereas sympathetic activity is dominant when the eyes are open. Opening the eyes stimulates receptors in the Müller muscle of the upper eyelid, which is controlled by the sympathetic nervous system and awakens the brain.[39] However, contrary to the general concept, in patients with sBUTDE, low HF and high LF/HF were observed when the eyes were closed, and high HF and low LF/HF were observed when the eyes were opened, implying a predominance of sympathetic activity in closed eyes and a predominance of parasympathetic nerve activity in opened eyes.

The specific ANA modulation observed in sBUTDE may be related to the peculiarities of the eyes. It is generally accepted that the sympathetic nervous system is activated under stress, and the parasympathetic nervous system is activated during relaxation. In the context of the eyes, stress is associated with the eyes being open, and relaxation is associated with the eyes being closed. Opening the eyes (a state of stress) induces pupillary and accommodative responses to visual stimulation.[40] We previously reported that accommodative microfluctuation is larger in DE than in non-DE,[41,42] consistent with this study's findings that parasympathetic nerve activity is greater in DE when the eyes are opened. Furthermore, exposure of the ocular surface by opening the eyes induces tear secretion,[43] a response predominantly controlled by the parasympathetic nervous system. In modern society, where near-vision tasks are common, the parasympathetic nervous system is likely to become more dominant, causing stress. Therefore stress on the eyes may be the opposite of general stress, representing increased parasympathetic nerve activity.

The number of individuals with DE (particularly sBUTDE) is increasing rapidly because of stressful lifestyle changes associated with the recent increase in the use of visual display terminals and the aging of the population.[44,45] On the other hand, personality traits have been shown to be related to stress.[46] Given that stress affects ANA,[20,47,48] we thought that investigating the relationship between personality traits and ANA may lead to the elucidation of the etiology of sBUTDE. Regarding the personality test, the sBUTDE group exhibited lower levels of "openness" and higher levels of "neuroticism." In particular, low openness was associated with decreased sympathetic nerve activity with eye opening and the presence of DE symptoms. Low openness is characterized by a dislike for adventure, not expressing emotions, a lack of interest in new ideas, reluctance to change the current situation, and a high value on authority and tradition.[49] Additionally, "high neuroticism" is characterized by being easily emotionally reactive, pessimistic, anxious, easily hurt, and sensitive to other people's opinions.[49] Regarding the relationship between stress and personality traits, there is a negative relationship with "openness" and a positive relationship with "neuroticism."[46] These suggest that patients with sBUTDE have defensive physical reactions in terms of emotions and feelings and a tendency to seek fulfillment through perseverance, resulting in stress accumulation. Stress is known to cause various diseases. Stress-related diseases include gastric and duodenal ulcers,[50] bronchial asthma,[51] back pain,[52] cardiovascular disease,[53] atopic dermatitis[54]; sBUTDE may also be one of them. Soriano et al.[55] demonstrated a relationship between personality traits and neuropathic pain: Patients with chronic neuropathic pain exhibit high neuroticism, low extraversion, low openness to experience and responsibility, and moderate agreeableness. This finding suggests that personality traits may be involved in sBUTDE pathogenesis.

Our study has a few limitations. First, the sample size of the study is small. A study with a larger population should be conducted in the future. Second, we did not examine confounding factors that could affect autonomic function, such as body position, menopause, lifestyle, or presence of other systemic diseases. Third, although a subject survey evaluating five personality traits was used in this study, more sophisticated personality evaluation should be recommended because patient reporting may not be very reliable. Moreover, we did not investigate the degree of subjective symptoms under ocular surface anesthesia. Fourth, the Fitbit system may underestimate heart rates.[56] However, this study focused on heart rate variability and not heart rate values. It might be recommended to combine the data obtained by the Fitbit system with medical-grade devices.

In conclusion, ANA modulation in sBUTDE can be caused by peripheral, central, or mixed abnormalities and exhibits the following characteristics: high sympathetic nerve activity at rest with eyes closed, high and unstable parasympathetic nerve activity with eyes open, and large changes in ANA when the eyes are opened and closed. In addition to ANA modulation, the unique personality trait of sBUTDE patients, namely, low "openness," may be involved in the manifestation of DE symptoms. Understanding the pathogenesis of sBUTDE may aid in treatment strategies for cases that are refractory to conventional treatments.

Acknowledgments

Disclosure: **M. Kaido**, None; **R. Arita**, None; **Y. Mitsukura**, None; **B. Sumali**, None; **K. Tsubota**, Tsubota Laboratory, Inc. (E)

References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;15:276–283.
2. Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD. Neuropathic ocular pain: an important yet underevaluated feature of dry eye. *Eye (Lond).* 2015;29:301–312.
3. Galor A, Zlotcavitch L, Walter SD, et al. Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. *Br J Ophthalmol.* 2015;99:665–668.
4. Belmonte C, Aracil A, Acosta MC, Luna C, Gallar J. Nerves and sensations from the eye surface. *Ocul Surf.* 2004;2:248–253.
5. De Paiva CS, Pflugfelder SC. Corneal epitheliopathy of dry eye induces hyperesthesia to mechanical air jet stimulation. *Am J Ophthalmol.* 2004;137:109–115.
6. Situ P, Simpson TL, Jones LW, Fonn D. Conjunctival and corneal hyperesthesia in subjects with dryness symptoms. *Optom Vis Sci.* 2008;85:867–872.
7. Spierer O, Felix ER, McClellan AL, et al. Corneal mechanical thresholds negatively associate with dry eye and ocular pain symptoms. *Invest Ophthalmol Vis Sci.* 2016;57:617–625.

8. Kaido M, Kawashima M, Ishida R, Tsubota K. Relationship of corneal pain sensitivity with dry eye symptoms in dry eye with short tear break-up time. *Invest Ophthalmol Vis Sci.* 2016;57:914–919.
9. Bourcier T, Acosta MC, Borderie V, et al. Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2005;46:2341–2345.
10. Benítez-Del-Castillo JM, Acosta MC, Wassfi MA, et al. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2007;48:173–181.
11. Stucky CL, Dubin AE, Jeske NA, Malin SA, McKemy DD, Story GM. Roles of transient receptor potential channels in pain. *Brain Res Rev.* 2009;60:2–23.
12. Masuoka T, Gallar J, Belmonte C. Inhibitory effect of amitriptyline on the impulse activity of cold thermoreceptor terminals of intact and tear-deficient guinea pig corneas. *J Ocul Pharmacol Ther.* 2018;34(1-2):195–203.
13. Pan P, Wei S, Ou Y, et al. Reduced global-brain functional connectivity of the cerebello-thalamo-cortical network in patients with dry eye disease. *Front Hum Neurosci.* 2020;14:572693.
14. Yan H, Shan X, Wei S, et al. Abnormal spontaneous brain activities of limbic-cortical circuits in patients with dry eye disease. *Front Hum Neurosci.* 2020;14:574758.
15. Yu K, Guo Y, Ge QM, et al. Altered spontaneous activity in the frontal gyrus in dry eye: a resting-state functional MRI study. *Sci Rep.* 2021;11(1):12943.
16. Feng C, Jiang W, Xiao Y, et al. Comparing brain functional activities in patients with blepharospasm and dry eye disease measured with resting-state fMRI. *Front Neurol.* 2021;12:607476.
17. Sun T, Shu HY, Wu JL, et al. Investigation of changes in the activity and function of dry eye-associated brain regions using the amplitude of low-frequency fluctuations method. *Biosci Rep.* 2022;42(1):BSR20210941.
18. Kaido M, Inoue S, Kawashima M, Ishida R, Nakamura S, Tsubota K. Role of transient receptor potential melastatin 8 activity in menthol-induced cold sensitivity and its qualitative perception in dry eye. *Ocul Surf.* 2021;19:307–312.
19. Kaido M, Arita R, Mitsukura Y, Ishida R, Tsubota K. Variability of autonomic nerve activity in dry eye with decreased tear stability. *PLoS One.* 2022;17(11):e0276945.
20. Kaido M, Arita R, Mitsukura Y, Tsubota K. Autonomic nerve activity features according to dry eye type. *Invest Ophthalmol Vis Sci.* 2023;64(7):19.
21. Midorikawa-Inomata A, Inomata T, Nojiri S, et al. Reliability and validity of the Japanese version of the Ocular Surface Disease Index for dry eye disease. *BMJ Open.* 2019;9(11):e033940.
22. Goldberg LR. An alternative "description of personality": the big-five factor structure. *J Pers Soc Psychol.* 1990;59:1216–1229.
23. Gosling SD, Rentfrow PJ, Swann WB, Jr. A very brief measure of the Big-Five personality domains. *J Res Pers.* 2003;37;504–528.
24. Manual TIPI-J. Available at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://jspp.gr.jp/doc/manual_TIPI-J.pdf. Accessed January 11, 2024.
25. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. *Eye (Lond).* 1991;5(Pt. 4):395–411.
26. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. *Arch Ophthalmol.* 1969;82(1):10–14.
27. Fitbit charge 5. Available at: https://help.fitbit.com/manuals/manual_charge_5_ja.pdf. Accessed March 1, 2024.
28. Giardino ND, Lehrer PM, Edelberg R. Comparison of finger plethysmograph to ECG in the measurement of heart rate variability. *Psychophysiology.* 2002;39:246–253.
29. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science.* 1981;213(4504):220–222.
30. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol.* 1985;248(1 Pt. 2): H151–H153.
31. Dabas PK, Shaw D. Reliability of frequency domain HRV analysis. *IFMBE Proc.* 2010;31:1615–1618.
32. Burma JS, Graver S, Miutz LN, Macaulay A, Copeland PV, Smirl JD. The validity and reliability of ultra-short-term heart rate variability parameters and the influence of physiological covariates. *J Appl Physiol (1985).* 2021;130(6):1848–1867.
33. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J.* 1996;17:354–381.
34. Sayers BM. Analysis of heart rate variability. *Ergonomics.* 1973;16:17–32.
35. Hayano J, Sakakibara Y, Yamada A, et al. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol.* 1991;67:199–204.
36. Hayano J, Taylor JA, Yamada A, et al. Continuous assessment of hemodynamic control by complex demodulation of cardiovascular variability. *Am J Physiol.* 1993;264(4 Pt. 2):H1229- H1238.
37. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res.* 1986;59:178–193.
38. Ookuma T. *Clinical EEG.* 5th ed. Tokyo: Igaku Shoin; 1999.
39. Abdelhady A, Anatomy Patel BC., Head and Neck: Eye Superior Tarsal Muscle (Muller Muscle). 2022. In: *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing; 2024.
40. Owens DA, Wolf-Kelly K. Near work, visual fatigue, and variations of oculomotor tonus. *Invest Ophthalmol Vis Sci.* 1987;28:743–749.
41. Kaido M, Kawashima M, Ishida R, Tsubota K. Severe symptoms of short tear break-up time dry eye are associated with accommodative microfluctuations. *Clin Ophthalmol.* 2017;11:861–869.
42. Kaido M, Kawashima M, Shigeno Y, Yamada Y, Tsubota K. Relation of accommodative microfluctuation with dry eye symptoms in short tear break-up time dry eye. *PLoS One.* 2017;12(9):e0184296.
43. Belmonte C, Nichols JJ, Cox SM, et al. TFOS DEWS II pain and sensation report. *Ocul Surf.* 2017;15:404–437.
44. Uchino M, Uchino Y, Dogru M, et al. Dry eye disease and work productivity loss in visual display users: the Osaka study. *Am J Ophthalmol.* 2014;157:294–300.
45. Yokoi N, Uchino M, Uchino Y, et al. Importance of tear film instability in dry eye disease in office workers using visual display terminals: the Osaka study. *Am J Ophthalmol.* 2015;159:748–754.
46. Luo J, Zhang B, Cao M, Roberts BW. The stressful personality: a meta-analytical review of the relation between personality and stress. *Pers Soc Psychol Rev.* 2023;27:128–194.
47. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244–1252.
48. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet.* 1995;345(8942):99–103.

Investigative Ophthalmology & Visual Science

49. Big five personality facets: descriptions of high and low values. Available at: https://web.archive.org/web/20181126015751/https://watson-developer-cloud.github.io/doc-tutorial-downloads/personality-insights/Personality-Insights-Facet-Characteristics.pdf. Accessed March 1, 2024.
50. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol.* 2011;62:591–599.
51. Priftis KN, Anthracopoulos MB. The causal relationship between stress and asthma. *Allergol Immunopathol (Madr).* 2008;36:343–346.
52. Choi S, Nah S, Jang HD, Moon JE, Han S. Association between chronic low back pain and degree of stress: a nationwide cross-sectional study. *Sci Rep.* 2021;11(1):14549.
53. Santosa A, Rosengren A, Ramasundarahettige C, et al. Psychosocial risk factors and cardiovascular disease and death in a population-based cohort from 21 low-, middle-, and high-income countries. *JAMA Netw Open.* 2021;4(12):e2138920.
54. Morren MA, Przybilla B, Bamelis M, Heykants B, Reynaers A, Degreef H. Atopic dermatitis: triggering factors. *J Am Acad Dermatol.* 1994;31(3 Pt. 1):467–473.
55. Soriano PJF, Monsalve DV, Ibáñez GE, et al. [Personality and coping in neuropathic chronic pain: a predictable divorce]. *Psicothema.* 2010;22:537–542.
56. Chevance G, Golaszewski NM, Tipton E, et al. Accuracy and precision of energy expenditure, heart rate, and steps measured by combined-sensing Fitbits against reference measures: systematic review and meta-analysis. *JMIR Mhealth Uhealth.* 2022;10:e35626.