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Frequency Analysis of Heart Rate Variability: A Useful Assessment Tool of Linearly Polarized Near-Infrared Irradiation to Stellate Ganglion Area for Burning Mouth Syndrome

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Abstract

Background. Burning mouth syndrome (BMS) is characterized by the following subjective complaints without distinct organic changes: burning sensation in mouth or chronic pain of tongue. BMS is also known as glossodynia; both terms are used equivalently in Japan. Although the real cause of BMS is still unknown, it has been pointed out that BMS is related to some autonomic abnormality, and that stellate ganglion near-infrared irradiation (SGR) corrects the autonomic abnormality. Frequency analysis of heart rate variability (HRV) is expected to be useful for assessing autonomic abnormality.

Objectives. This study investigated whether frequency analysis of HRV could reveal autonomic abnormality associated with BMS, and whether autonomic changes were corrected after SGR.

Subjects and Methods. Eight subjects received SGR; the response to SGR was assessed by frequency analysis of HRV.

Results. No significant difference of autonomic activity concerning low-frequency (LF) norm, high-frequency (HF) norm, and low-frequency/high-frequency (LF/HF) was found between SGR effective and ineffective groups. Therefore, we proposed new parameters: differential normalized low frequency (D LF norm), differential normalized high frequency (D HF norm), and differential low-frequency/high-frequency (D LF/HF), which were defined as differentials between original parameters just before and after SGR. These parameters as indexes of responsiveness of autonomic nervous system (ANS) revealed autonomic changes in BMS, and BMS seems to be related to autonomic instability rather than autonomic imbalance.

Conclusions. Frequency analysis of HRV revealed the autonomic instability associated with BMS and enabled tracing of autonomic changes corrected with SGR. It is suggested that frequency analysis of HRV is very useful in follow up of BMS and for determination of the therapeutic efficacy of SGR.

Key Words. Autonomic Instability; Burning Mouth Syndrome; Heart Rate Variability; Stellate Ganglion Near-Infrared Irradiation

Introduction

Burning mouth syndrome (BMS) is characterized by oral burning or painful sensations mainly involving tongue, lip, and palate, despite the absence of significant pathological changes in oral mucosa [1–3]. BMS is also known as glossodynia, and they are recognized as the same disease in Japan. BMS is six times more common in women over 50 years of age than in men, with a prevalence in the population of approximately 3.0–5.0% [2]; it is a considerable concern among the Japanese, as elsewhere. Although the real cause of BMS is still unknown, potential factors related to BMS are considered to be age, postmenopausal climacteric disorders, oral dryness, vitamin

Table 1 Clinical characteristics and results of SGR in the eight subjects of the series

Case No.	Age/ Gender	Glossalgia Duration	Glossalgia Type	Glossalgia Severity	Glossalgia Site	Complication	Results of SGR
1	40/M	0	Spont	Mild	Apex	NP	PR
2	79/F	24	Spont	Mild	Apex	HT	PR
3	82/F	2	Spont	Mild	Apex	Angina pectoris	PR
4	67/F	18	Spont	Mild	Apex	HC, Hypoacusis, RA	PR
5	63/F	51	Spont	Mild	Apex	NP	PR
6	72/F	13	Spont	Distressing	Dorsum	Dysgeusia	PD
7	68/F	29	Spont	Mild	Apex	HT, Insomnia	NC
8	68/F	41	Spont	Mild	Apex	CI, Nasal allergy	NC

CI = cerebral infarction; HC = hypercholesteremia; HT = hypertension; NC = no change; PD = progressive disease; PR = partial response; RA = rheumatoid arthritis; SGR = stellate ganglion near-infrared irradiation; Spont = spontaneous.
Glossalgia duration was expressed in months. Glossalgia severity was excerpted from the standard long-form McGill Pain Questionnaire.

deficiency, anemia, drugs, and psychosocial disorders; however, reports on the relative importance of these factors are conflicting [4]. Lack of diagnostic criteria, differences in sampling procedures, incomplete workups, and lack of controlled studies make a reliable interpretation of the importance of proposed causal factors and the efficacy of specific treatment modalities difficult [4]. For patients in whom no causative factor can be identified, empiric antifungal, nutritional, and estrogen replacement therapy can be initiated; even long-term therapy with antidepressants, benzodiazepines, and clonazepam can be considered [3]. Under such circumstances, the relationship between BMS and the function of the autonomic nervous system (ANS) has been pointed out; stellate ganglion near-infrared irradiation (SGR) has been reported to be beneficial in patients with BMS [5]. A single clinical trial of SGR in 37 patients with BMS revealed that 75.7% of the patients achieved symptom relief [5]. The mechanism by which SGR improves symptoms associated with BMS is thought to be as follows: SGR inhibits abnormally increased sympathetic activity associated with BMS, which is followed by normalization of decreased tongue blood flow that alleviates oral burning or painful sensations [5]. That is, the mechanism was validated by measuring not sympathetic activity but tongue blood flow. If the pathogenesis of BMS is some abnormality in the function of ANS, it is more necessary to measure autonomic activity for validation rather than tongue blood flow. Frequency analysis of heart rate variability (HRV) is useful to assess autonomic activity [6]. Frequency analysis of HRV involves measurement of beat-to-beat variations in the heart rate. It is usually calculated by analyzing the time series of beat-to-beat intervals from an electrocardiograph or of beat-to-beat intervals derived from arterial pressure tracing. HRV analyzer used in this study looks just like a pulse oxymeter and analyzes pulse-to-pulse variations in pulse rate by a built-in HRV analyzing system; it enables rapid and accurate measurement of autonomic activity without stressing subjects. In this study, we investigated whether frequency analysis of HRV could reveal some autonomic abnormality associated with BMS, and whether autonomic changes were corrected after SGR.

Methods

Subject Selection

Subjects were eight Japanese individuals: one male and seven females, attending the Department of Oral Medicine, Tokushima University Hospital, from January 2007 to December 2009. Their age ranged of from 40 to 82 years old, with an average of 68.6 years old. They were selected from among the 104 candidates according to the following criteria: 1) presence of pain or a burning sensation on the surface of the tongue; 2) absence of local or systemic disease related to the above tongue symptoms: candidiasis, xerostomia, glossitis, anemia, neuralgia, diabetes mellitus, and referred pain from dentalgia; and 3) absence of somatization of a psychiatric disorder. They were given the diagnosis of BMS as shown in Table 1. They all complained about night pain but didn't suffer from allodynia or hyperalgesia.

Stellate Ganglion Near-Infrared Irradiation and Frequency Analysis of Heart Rate Variability

All subjects received SGR under the following conditions: power of 1.32 W, cycle of 1 second on and 4 seconds off, duration of 10 minutes, once a week, and 10 times in all. The response to SGR was assessed by frequency analysis of HRV just before and after every irradiation, and evaluated with visual analogue scale (VAS: 0–100 mm) representing tongue pain intensity. HRV analyzer (SA-3000P, Tokyo Iken Co., Ltd, Tokyo, Japan) and the irradiation device (HA-2200, Tokyo Iken Co., Ltd, Tokyo, Japan) were kindly provided without charge by Tokyo Iken Co., Ltd. The curative effects of SGR were judged from the temporal development of the VAS value. That is, the first and second represent the

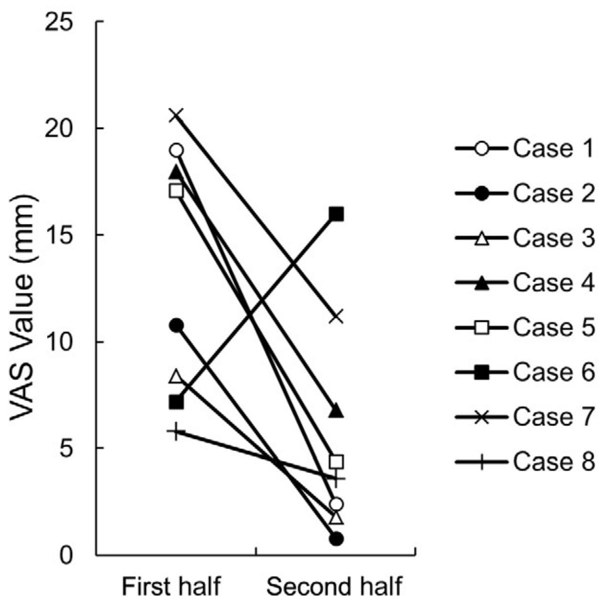

Figure 1 Time course of VAS value. VAS, visual analogue scale; first half, the first half of the treatment period; second half, the second half of the treatment period.

first half of the treatment period, five times, and the second one, five times, respectively; each VAS value represents mean value of VAS in each period. When the second VAS value was decreased up to 100%, by ≧50%, <50%, or ≦0% compared to the first one, complete response (CR), partial response (PR), no change (NC), or progressive disease (PD) was defined, respectively. In addition, cases of CR and PR, and those of NC and PR, were defined effective and ineffective, respectively.

The following frequency-domain HRV variables were obtained from the frequency content of the fluctuating heart rate [7]: low-frequency (LF) component (0.04–0.15 Hz), high-frequency (HF) component (0.15–0.4 Hz), and low-frequency/high-frequency ratio (LF/HF). LF norm represents normalized LF: the ratio of LF to total power (TP), and was used as an index of sympathetic and parasympathetic activity. Differential LF norm (D LF norm) was defined as the differential between LF norm values of just before and after irradiation. HF norm represents normalized HF as well as LF norm, and was used as an index of parasympathetic activity. Differential HF norm (D HF norm) was defined as well as D LF norm. LF/HF was used as an index of sympathetic to parasympathetic balance. Differential LF/HF (D LF/HF) was defined as the differential between LF/HF of just before and after irradiation.

Statistical Analysis

Statistical analyses were carried out with Excel-Toukei 2010 (Social Survey Research Information Co., Ltd, Tokyo, Japan), and based on paired Student's *t*-test for intergroup comparison or unpaired Student's *t*-test for within-group one. A value of $P < 0.05$ was considered significant.

The procedure was approved by an Institutional Review Board and explained to all subjects. Then, their informed consent was obtained.

Results

Figure 1 shows the time course of VAS value. In five subjects (62.5%), SGR was effective judging from the differential between the first and second VAS values, as shown in Figure 2.

Table 2 shows scores of frequency-domain HRV variables during stellate ganglion near-infrared irradiation. Scores are the mean values of frequency-domain HRV variables: LF norm, HF norm, and LF/HF. No significant difference in each variable was found within the groups and between the groups. Figure 3A and 3B show the time courses of D LF norm in the effective group and the ineffective group, respectively. The mean value of D LF norm of the first half of the treatment period, the first D LF norm, was –8.03 ± 12.34%, whereas that of the second one, the second D LF norm, was –21.47 ± 11.82% in the effective group. The first D LF norm was significantly higher ($P < 0.05$) than the second D LF norm. On the other hand, the first D LF norm was –10.17 ± 0.75%, whereas the second D LF norm was 0.72 ± 3.88% in the ineffective group. The first D LF norm was significantly lower ($P < 0.05$) than the second D LF norm. Furthermore, although no significant difference in the first D LF norm

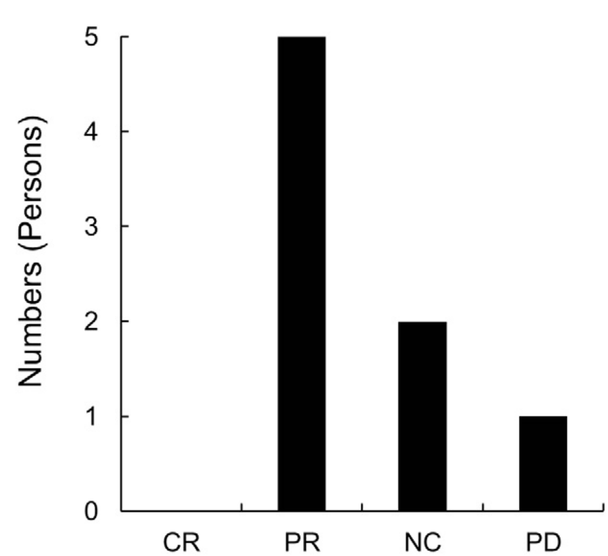

Figure 2 Results of SGR. SGR, stellate ganglion near-infrared irradiation; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table 2 Scores of frequency-domain HRV variables during stellate ganglion near-infrared irradiation

	Effective Group (N = 5)		Ineffective Group (N = 3)	
	First Half	Second Half	First Half	Second Half
LF norm (%)	65.27 ± 28.40	64.27 ± 26.98	69.55 ± 6.78	66.04 ± 14.21
HF norm (%)	34.45 ± 11.83	36.04 ± 10.48	30.45 ± 6.78	33.96 ± 14.21
LF/HF	2.85 ± 1.39	2.59 ± 1.76	2.95 ± 0.85	2.73 ± 1.93

Scores are the mean values of frequency-domain HRV variables: LF norm, HF norm, and LF/HF. No significant difference in each variable was found within the groups and between the groups.
First half = first half of the treatment period; Second half = second half of the treatment period; LF norm = normalized low-frequency component; HF norm = normalized high-frequency component; LF/HF = low-frequency/high-frequency ratio.

was found between the groups, the second D LF norm of the effective group was significantly lower ($P < 0.05$) than that in the ineffective group.

Figure 4A and 4B show the time courses of D HF norm in the effective group and the ineffective group, respectively. When the first and second D HF norms were defined as well as the first and second D LF norms, the first D HF norm was 8.03 ± 12.34%, whereas the second D HF norm was 21.47 ± 11.82% in the effective group. The first D HF norm was significantly lower ($P < 0.05$) than the second D HF norm. The first D HF norm was 10.17 ± 0.75%, whereas the second D HF norm was 0.72 ± 3.88% in the ineffective group. The first D HF norm was significantly higher ($P < 0.05$) than the second D HF norm. Furthermore, although no significant difference in the first D HF norm was found between the groups, the second D HF norm of the effective group was significantly higher ($P < 0.05$) than that in the ineffective group.

Figure 5A and 5B show the time courses of D LF/HF in the effective group and the ineffective group, respectively. The mean value of D LF/HF of the first half of the treatment period, the first D LF/HF, was –0.94 ± 1.36, whereas that of the second one, the second D LF/HF,

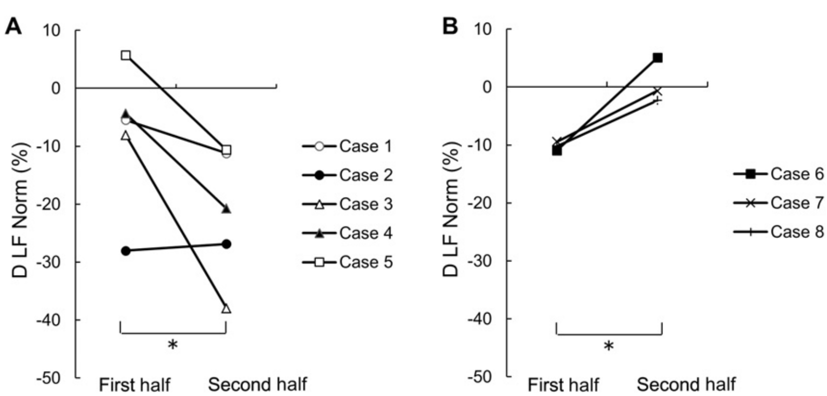

Figure 3 Time course of D LF norm. A: effective group, B: ineffective group. D LF norm, differential normalized low frequency; first half, the first half of the treatment period; second half, the second half of the treatment period. * Marks in the figure indicate significant difference ($P < 0.05$).

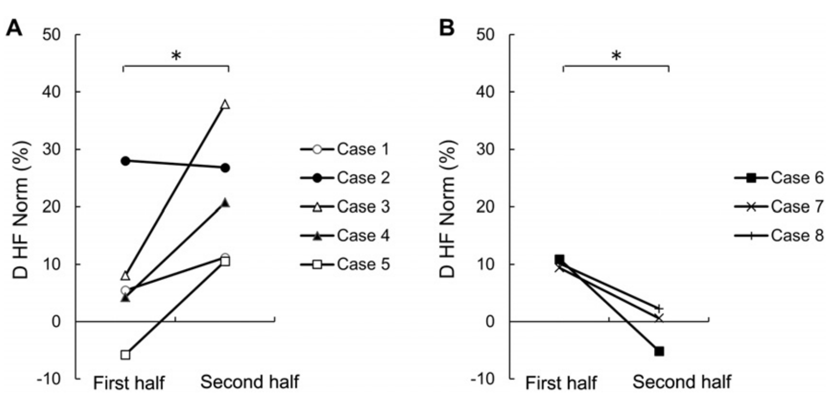

Figure 4 Time course of D HF norm. A: effective group, B: ineffective group. D HF norm, differential normalized high frequency; first half, the first half of the treatment period; second half, the second half of the treatment period. * Marks in the figure indicate significant difference ($P < 0.05$).

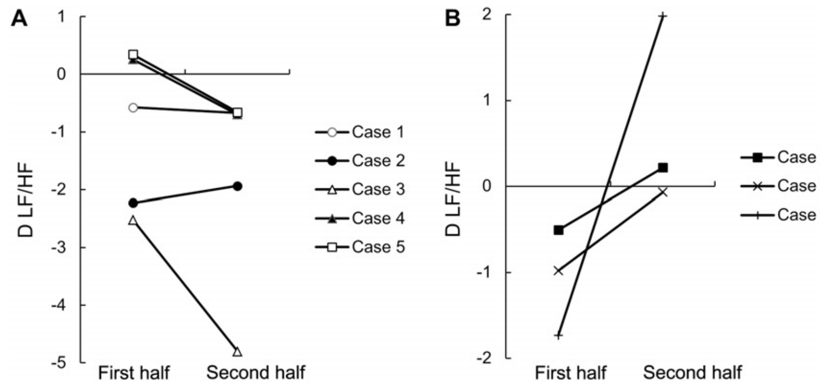

Figure 5 Time course of D LF/HF. A: effective group, B: ineffective group. D LF/HF, differential low-frequency/high-frequency ratio; first half, the first half of the treatment period; second half, the second half of the treatment period. * Marks in the figure indicate significant difference ($P < 0.05$).

was –1.75 ± 1.79 in the effective group without significant difference. On the other hand, the first D LF/HF was –1.07 ± 0.62, whereas the second D LF/HF was 0.71 ± 1.11 in the ineffective group without significant difference. Furthermore, although no significant difference ($P > 0.05$) in the first D LF/HF was found between the groups, the second D LF/HF of the effective group was significantly lower ($P < 0.05$) than that in the ineffective group.

Discussion

We found that newly proposed parameters: D LF norm, D HF norm, and D LF/HF, as indexes of responsiveness of ANS revealed autonomic changes in BMS, and BMS may be related to autonomic instability rather than autonomic imbalance.

The relationship between BMS and the function of ANS: increased sympathetic activity associated with BMS has been pointed out [5]. The function of ANS, sympathetic and parasympathetic components, is reflected in HRV as noninvasive and highly reproducible electrocardiographic markers [8]. Frequency analysis of HRV is used for testing the function of ANS and diagnosing autonomic neuropathy, and has emerged as a new useful tool in recent decades [9,10]. Moreover, an assessment of the function of ANS by frequency analysis of HRV is reported to be useful for comprehending clinical conditions of BMS [11]. Parameters calculated from frequency analysis of HRV are related to autonomic activity [10], which ranges from 0 to 0.5 Hz, and can be classified into the following: very low-frequency band (VLF), LF, and HF. LF and HF are usually expressed in absolute values (ms^2) or in normalized values (nu); the normalization of LF and HF is performed by subtracting VLF from TP, that is, LF or HF norm = 100 × LF or HF/(TP – VLF). TP means the total variance and corresponds to the sum of the following bands: VLF, LF, and HF [12–14]. LF is modulated by ANS: sympathetic and parasympathetic nervous systems, and HF is generally defined as a marker of parasympathetic modulation [13–15]. LF/HF reflects autonomic balance and can be used as its measure.

It has been pointed out that BMS is associated with increased sympathetic activity [5], while unexplained somatic complaints, which are often considered as psychogenic symptoms because not accompanied by any organic change, is considered to result from not an excessive increase of sympathetic activity but a pronounced reduction of parasympathetic activity [11]. In this study, LF/HF values in seven out of eight subjects were found to be elevated above the reference ranges, as shown in Table 2, even though they are usually maintained between 1 and 2. Hence, there must be some relationship between BMS and autonomic imbalance. However, no significant difference of autonomic activity concerning LF, HF, and LF/HF was found between the effective and ineffective groups, as shown in Table 2, even though no statistical examination was conducted between patients with BMS and healthy persons in this study. Furthermore, Table 2 shows that no significant difference of autonomic activity in all parameters was found between the first and second periods of the treatment in each group. These findings indicate that, even though there is some sort of relationship between BMS and autonomic activity on the basis of effects of SGR on BMS, these parameters might not necessarily be effective, especially when used to assess autonomic activity in giving SGR to patients with BMS. Therefore, we proposed new parameters: D LF norm, D HF norm, and D LF/HF, instead. These new parameters are considered to reflect responsiveness of ANS because they are defined as the differentials between original parameters just before and after stimuli such as SGR. These parameters as indexes of responsiveness of ANS revealed autonomic changes in BMS, and that BMS seems to be related to autonomic instability rather than autonomic imbalance. Autonomic instability is reported to characterize patients with migraine headache that was elucidated by spectral analysis of heart rate fluctuations [16]. The nature of BMS, that is, autonomic instability, is considered to play an important role in its pathogenic and healing processes. Naturally, in some cases, we experienced that SGR did not exert an effect on BMS or change the parameters. These findings suggest that there might be refractory or non-autonomic BMS. The former can be considered to have low-reactive autonomic nerves to SGR as a neurological feature. Meanwhile, the latter can be regarded to be far from having autonomic abnormality. It is still unclear how SGR works on ANS of patients with BMS, although SGR is considered to inhibit abnormally increased sympathetic activity associated with BMS as well as stellate ganglion block (SGB), and to normalize decreased tongue blood flow [5]. The effect of SGR on ANS is thought to be poorer than SGB because SGR incompletely blocks stellate ganglions. In fact, no patient who received SGR had distinct signs or symptoms suggestive of Horner's syndrome during irradiation. When SGR was performed in healthy subjects, there was no appreciable change associated with autonomic activity such as Horner's syndrome (data not shown). A further report indicated that the reason why pain was relieved by low-power infrared irradiation was that it probably induced Na^+, K^+-ATPase signal-transducing and pumping functions [17]. On the contrary, low-power infrared irradiation to the nociceptive neuron was suggested to diminish the voltage sensitivity of activation gating machinery of slow sodium channels [18]. Further investigation is required to clarify the functional mechanism of SGR for working on ANS and the relationship between the healing process of BMS and autonomic instability. The real cause of BMS has still not been found; currently there is no reliable method to diagnose it definitely. In the follow-up of BMS, frequency analysis of HRV using new parameters: D LF norm, D HF norm, and D LF/HF, may be one of possible ways to monitor therapeutic efficacy of SGR.

Conclusions

Frequency analysis of HRV reveals autonomic instability associated with BMS, and autonomic changes corrected after SGR. Frequency analysis of HRV may be very useful in the follow-up of BMS and for determination of therapeutic efficacy of SGR.

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