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Heart Rate Variability as a Predictor of the Outcome of Treatment with Kampo Medicines that Include Bupleuri Radix (Saiko)

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Research Article

ABSTRACT

Background: Kampo preparations that include Bupleuri Radix (saiko) are prescribed for neurosis, insomnia, and symptoms that have a strong association with autonomic nervous system disorders, especially for female patients. The aim of this study is to determine if any aspect of heart rate variability (HRV), as a surrogate marker of autonomic nervous system activity, is related to the outcome of treatment with Kampo medicines that include saiko, which would allow the determination of which patients these medicines would be most effective for.

Methods: We retrospectively analyzed the data of 54 new female patients (≥20 years) who visited the Kampo Medicine Clinic of Kyushu University Hospital from January 2008 to June 2013 to determine which HRV values can be used to predict the outcome of treatment for patients receiving medicines that include saiko. The patients were divided into an effective group (27 patients) and an ineffective group (27 patients) based on the physician's decision of effectiveness at two weeks after initiation of the drug.

Results: VLF (0.003 Hz to 0.04 Hz)/TF of the effective group was significantly higher than that of the ineffective group (effective group: 0.35 ± 0.05, ineffective group: 0.30 ± 0.08, P=0.009). Conversely, ULF-1(0.0001 Hz to 0.0003 Hz)/TF of the effective group was significantly lower than that of the ineffective group (effective group, 0.21 ± 0.07; ineffective group, 0.27 ± 0.08, P=0.006). The cut-off values from ROC analysis were 0.35 for VLF/TF (sensitivity, 63%; Specificity, 78%; AUC, 0.71) and 0.24 for ULF-1/TF (Sensitivity, 78%; specificity, 56%: AUC. 0.71).

Conclusion: Our data suggest that ULF-1/TF and VLF/TF have potential as predictors of the outcome of treatment for patients receiving medicines that include saiko.

Keywords: Heart rate variability, Holter electrocardiogram, Kampo, Saiko, Bupleuri Radix, Very low frequency band, Ultra low frequency band

INTRODUCTION

Kampo medicines are widely used in clinical practice in Japan, with 90% of Japanese physicians routinely prescribing them in daily practice to at least to some of their patients [1]. Kampo medicines are effective for indefinite complaints that are difficult to estimate and diagnose by contemporary medical practices. It has been reported that autonomic nervous dysfunction caused by stress might be a main factor in the indefinite complaints [2,3], and most patients who complain of it are female. Many Japanese physicians tend to use distinctive examinations and traditional concepts to diagnose these

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symptoms from the perspective of Japanese Kampo medicine. The examinations consist of visual observation, listening, smelling, inquiry, and palpation. The basic concepts include “Yin and Yo (hyper-function and hypo-function)”, “Kyojitsu (deficiency and excess)”, “Kiketsusui (qi, blood, and fluid)”, “Rokubyoui (six disease phase)” and “Gozo (five organs)” [4]. Medical diagnosis using these standardized Kampo techniques is described as “Sho”, a term for diagnosis based on Kampo principals and making an indication of the proper prescription. Because physicians prescribe Kampo medicines according to this “Sho”, it is critical that Sho be determined correctly.

Bupleuri Radix (saiko) is contained in the root of the Bupleurum plant. It has an anti-stress action, anti-allergic properties, steroid-like action, and an anti-inflammatory effect [5,6]. In Japan, Kampo medicine preparations that include saiko are used for neurosis, insomnia, and symptoms that have a strong association with stress [7]. Specific findings from abdominal diagnosis indicate the use of prescriptions that include saiko for hypochondriac discomfort and distension [8,9]. However, Kampo diagnosis is often criticized for a lack of objectivity because it is based on subjective judgments based on the physician’s sensory ability, experience, and knowledge. Thus, it is difficult to know in advance whether the Kampo medicine will be effective for an individual patient.

Heart rate variability (HRV) analysis is a non-invasive tool for the semi-quantitative assessment of the autonomic nervous control of the heart [10,11]. The power spectrum of HRV is categorized into high frequency (HF, 0.15 Hz to 0.4 Hz), low frequency (LF, 0.04 Hz to 0.15 Hz), ultra-low frequency (ULF, 0.0001 Hz to 0.003 Hz), and very low frequency (VLF, 0.003 Hz to 0.04 Hz) components. HF has been associated with the parasympathetic nervous system, while LF is associated with both the parasympathetic and sympathetic nervous systems. It was reported that HRV analysis can be used as predictor of the prognosis of patients with myocardial infarction or coronary artery disease [12,13]. In Kampo medicine, HRV analysis has been used for assessing the effect of Kampo medicines, including ephedra, glycyrrhiza, and oriental bezoar [14-16]. Similarly, we previously reported the effectiveness of HRV analysis on the assessment of an association between autonomic nervous activity and Yin- and Yo-sho [17]. However, only a few studies based on HRV have been done to elucidate the effectiveness of prescriptions that include saiko [18-21]. Thus, the aim of this study was to determine the ability of HRV analysis using Holter electrocardiogram (ECG) to predict the outcome of treatment for patients receiving Kampo medicines that include saiko.

MATERIALS AND METHODS

Patients and Kampo Prescription

To determine the difference in autonomic nervous activity, assessed by HRV analysis, of patients for whom the prescription of Kampo medicines containing saiko had been judged effective or ineffective, retrospective analysis was done on the data of 163 new female patients (≥20 years) who visited the Kampo Medicine Clinic of Kyushu University Hospital from January 2008 to June 2013. The patients had undergone 24 hr Holter Electrocardiogram (ECG) monitoring (Nihon Koden, Tokyo, Japan) before Kampo treatment. All the Holter ECG data were analyzed before the judgment of the effectiveness of the prescribed Kampo medicine. The patients’ age, BMI, sleeping time, Kampo medicine use, comorbidities, and HRV components were extracted from electronic medical records. The exclusion criteria included patients who had been taking Kampo medicine before the analysis. Of the remaining patients, those who had been prescribed Kampo medicine that included saiko were enrolled for study. We defined the prescription as effective when the chief complaints of each patient were substantially relieved by two weeks of treatment by a Kampo medicine that included saiko and divided them into an effective and an ineffective group completely independent of the result of HRV analysis. The study was conducted in accordance with the principles of the declaration of Helsinki and was approved by the ethics committee of Kyushu University Hospital (permission number: 28-40).

Electrocardiogram Monitoring

The ECG monitoring signals were analyzed using the maximum entropy spectral analysis method (Mem Calk; Suwa Trust, Tokyo, Japan) for the calculation of HRV. Total frequency (TF, 0.0001-0.5 Hz) band was divided into high frequency (HF, 0.15 Hz to 0.40 Hz), low frequency (LF, 0.04 Hz to 0.15 Hz), very low frequency (VLF, 0.003 Hz to 0.04 Hz), and ultra-low frequency (ULF, 0.0001 Hz to 0.003 Hz) components. Moreover, ULF was divided into ULF-1 (0.0001 Hz to 0.0003 Hz) and ULF-2 (0.0003 Hz to 0.003 Hz) for more detailed analysis. The power spectral density of each band was normalized by dividing it by the total power of TF. The LF/HF ratio was used as an index of the sympathetic nervous activity. Each patient reported the time of going to bed and waking-up, and we divided their sleep patterns into three categories; early, middle, and late phases of the sleep; to assess chronological change of the HRV components. It was confirmed by checking the medical records that no patients were taking sleeping pills or sedatives at the time of ECG monitoring.

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Statistical analysis

Values of the HRV components are expressed as mean ± standard deviation. Age, BMI, and sleeping time were compared using Wilcoxon's rank sum test. The number of patients taking antihypertensive or antidiabetic medicines was compared using the chi-square test. The values of the HRV components were compared using Wilcoxon's rank sum test, and ROC analysis was done to calculate the cut-off value, sensitivity (Se), specificity (Sp), and area under curve (AUC) of the HRV components. Wilcoxon's rank sum test and two-way ANOVA were used to assess chronological change of the HRV components. All analyses were conducted using JMP ver.11 software (SAS Institute Japan Ltd., Japan), and $p<0.05$ was considered significant.

RESULTS

Clinical Characteristics

After excluding the data of 109 female patients who visited our clinic during the study period, the data 54 patients remained for analysis (Figure 1). The Kampo medicines prescribed that include saiko are shown in Table 1. The patients were classified into effective and ineffective groups of 27 each. Clinical characteristics of the patients are shown in Table 2. The sleeping time of the effective group was significantly longer than that of the ineffective group (463.5 ± 83.9 minutes' vs 407.4 ± 60.3 minutes: $p=0.019$). There was no significant difference in the duration of treatment or dose of saiko (g/day).

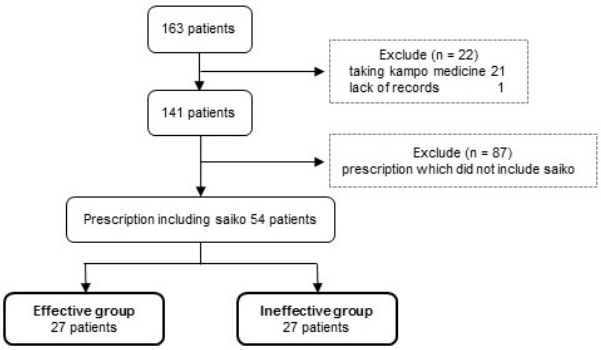

Figure 1: Participant selection: The exclusion criteria included patients who were taking Kampo medicine, those for whom electronic medical records were not available, and those taking prescriptions that did not include saiko. After taking a Kampo medicine for about two weeks, they were divided by their doctors into a group for whom saiko was effective and a group for whom it was ineffective.

Table 1: Prescriptions that include saiko

Prescription	Effective group n=27	Ineffective group n=27
Saikokeishikankyoto	15	12
Saikokaryukotsuboreito	7	8
Hochuekkito	2	1
Saibokuto	1	1
Kamikihito	2	0
Yokukansankachimpihange	0	2
Shigyakusan	0	1
Saikokeishito	0	1
Saishakurikkunshito	0	1

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Table 2: Clinical characteristics

	Effective group n=27	Ineffective group n=27	p
Age (years)	49.6 ± 10.7	50.6 ± 14.4	0.897
BMI (kg/m^2)	20.8 ± 3.1	21.3 ± 3.2	0.387
Duration of treatment (day)	14.4 ± 1.5	15.2 ± 4.2	0.387
Dosage of saiko (g/day)	6.4 ± 1.9	6.0 ± 2.0	0.409
Sleeping time (min)	463.5 ± 83.9	407.4±60.3	0.019
HT or DM	3	2	0.639
Data given as mean ± SD. Wilcoxon rank sum test, Chi-squared test. BMI, body mass index; DM, diabetes mellitus; HT, hypertension.			

Table 3: Comparison of Heart Rate Variability

	Effective group n=27	Ineffective group n=27	p
TF (ms2)	5406.0 ± 2829.2	5676.7 ± 3107.3	0.678
HF (ms2)	461.1 ± 507.4	317.6 ± 308.2	0.457
LF (ms2)	463.0 ± 330.0	382.6 ± 263.4	0.447
ULF (ms2)	2647.7 ± 1375.7	3198.0 ± 1730.5	0.246
ULF-1 (ms2)	1116.7 ± 662.7	1604.0 ± 1099.1	0.115
ULF-2 (ms2)	1531.1 ± 849.0	1600.1 ± 782.2	0.604
VLF (ms2)	1869.8 ± 1073.3	1766.2 ± 1227.3	0.795
LF/HF	1.49 ± 1.17	1.51 ± 0.66	0.261
ULF/TF	0.50 ± 0.11	0.57 ± 0.11	0.055
ULF-1/TF	0.21 ± 0.07	0.27 ± 0.09	0.006
ULF-2/TF	0.29 ± 0.10	0.30 ± 0.08	0.691
VLF/TF	0.35 ± 0.05	0.30 ± 0.08	0.009
LF/TF	0.09 ± 0.04	0.07 ± 0.03	0.233
HF/TF	0.07 ± 0.04	0.05 ± 0.04	0.074

Comparison of HRV Components

The data on the HRV components is shown in Table 3. The ULF-1/TF value of the effective group (0.21 ± 0.07) was significantly lower than that of the ineffective group (0.27 ± 0.08). In addition, the VLF/TF value of the effective group (0.35 ± 0.05) was significantly higher than that of the ineffective group (0.30 ± 0.08). In the ROC analysis, the cut-off value of ULF-1/TF was 0.24 (Se, 78%; Sp, 56%; AUC, 0.71) and that of VLF/TF was 0.35 (Se, 63%; Sp, 78%; AUC, 0.71) (Figure 2).

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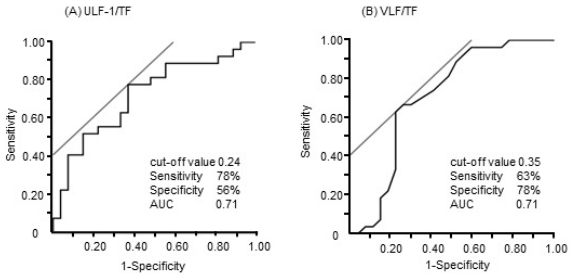

Figure 2: ROC analysis of the relation of ULF-1/TF (A) and VLF/TF (B) to the outcome of treatment with Kampo medicines that include saiko.

Change of the HRV components during sleep

The chronological change of the VLF/TF value during sleep is shown in Figure 3. Although the VLF/TF values were similar in the early sleeping phase for both groups, the VLF/TF value of the effective group became higher than that of the ineffective group in the middle and late phases (p=0.030). The VLF/TF value (0.35 ± 0.07) of the effective group in the late phase was significantly higher than that (0.30 ± 0.08) of the ineffective group (p=0.040).

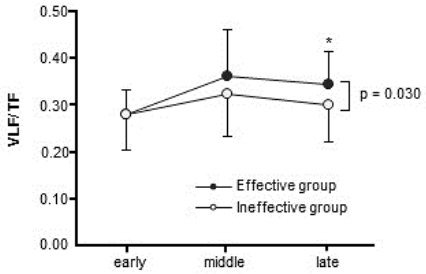

Figure 3: Change of VLF/TF during sleep. The mean VLF/TF was the same in the early phase, but there was a significant difference in the late phases. Data given as mean ± SD. p=0.030, two-way ANOVA; *p=0.040, Wilcoxon rank sum test.

DISCUSSION

This is the first report to demonstrate the ability of HRV analysis for the prediction of the outcome of treatment with Kampo medicines that include saiko for female patients who were diagnosed as having autonomic imbalance. As for the usefulness of HRV in the diagnostic process of Kampo medicine, we recently reported a relation between HRV and "Yin-Yo", which implies the basic status of patients and is one of the basic concepts of traditional Chinese and Kampo medicine [17]. In that paper, we demonstrated that the ULF-1 in a Yin-sho (rather weaker patients) group was significantly higher than that of a Yo-sho group. Saiko containing medications are principally prescribed to patients who show neural imbalance or continuous inflammation, but not for Yin-sho [5,22]. The fact that the patients for whom saiko containing medication showed effectiveness had a significantly lower ULF-1/TF value than did the ineffective group, especially in the late sleeping periods, supports our previous research because prescriptions that include saiko are basically for Yo-sho patients who showed a lower ULF-1 in our previous study.

We also demonstrated that the VLF/TF ratio of the effective group was significantly higher than that of the ineffective group. VLF is known to be related to sympathetic nervous activity and partly to the activity of the parasympathetic nervous system [19] and to be an equal or better marker of the prognosis of autonomic function disturbance than a simple analysis based on HF or LF [23]. An increase in resting VLF power has been reported to be produced intrinsically by heart and to reflect increased sympathetic activity, and the modulation of its rhythm due to physical activity and stress responses affects LF power [24]. This suggests that our patients in the effective group might have suffered from more stress, which resulted in a more unbalanced autonomic nervous system than was seen in the patients of the ineffective group. Moreover, Blood et al. reported that VLF/TP (total power) was related to depression symptom severity [25], which may imply the possibility that our patients in the effective group had such depression symptoms as a stress response. Similarly, there are many studies about the efficacy of prescriptions that include saiko for nervousness and irritation [26-33]. Thus, our results suggest that VLF/TF can be an index not only of the efficacy of saiko containing medication but also for hidden depression or stress severity.

Our results of chronological change of VLF/TF during sleep showed that the difference of this index in the effective and ineffective groups became obvious in the late sleep phase and that the VLF/TF of the effective group became significantly higher toward the end of sleep. In general, the deeper the sleep, the more parasympathetic nerve activity increases [34]. Additionally, there is a report that VLF power during rapid eye movement (REM) sleep is significantly higher than that during slow wave sleep (SWS), which is the deepest sleep [35]. Hence, our results indicate that the sleep of the effective group was comparably shallow in the late phase of sleep, which resulted in increasing sympathetic nerve activity due to a reason such as stress response. In addition, our result that the sleeping time of the effective group was significantly longer than that of the ineffective group could be interpreted as the effective group not having high quality sleep and thus needing a longer sleeping time, though there is no data about the quality of the patients' sleep. Thus, further studies that include electroencephalography and HRV will be necessary.

Diagnosis and treatment by Japanese Kampo Medicine is ambiguous compared with contemporary medicine. Therefore, research has been done to improve objectivity, including the development of a simulator of abdominal palpation as used in Kampo medicine diagnosis [36] as well as the standardization of Kampo medical diagnosis. However, there are still many problems confronting the standardization of Japanese Kampo medicine because doctors tend to interpret the words and diagnostic processes in their own way and to avoid standardization [37]. From this point of view, our results are of significant value in that they provide an objective predictor of the outcome of the prescription of Kampo medicines that contain saiko. As for the diagnostic value of our ROC analysis, the sensitivity and specificity are high, but sufficient.

Our study has some limitations. First, saiko is the main ingredient, but only one of several ingredients included in the Kampo medications that contain it. Thus, it is impossible to conclude that saiko itself is related to the treatment outcome or if it is acting synergistically with the other ingredients. Secondly, it was done with only female patients because of the overwhelmingly high number of female patients who complain of autonomic nervous instability in our clinic. Thirdly, we did not compare HRV before and after prescribing the Kampo medicines because of the retrospective nature of the analysis. Therefore, a prospective study that includes many male patients is necessary.

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