Effect of the Combination of Ginseng, Oriental Bezoar and Glycyrrhiza on Autonomic Nervous Activity as Evaluated by Power Spectral Analysis of HRV and Cardiac Depolarization-Repolarization Process

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Summary Background: Ginseng, oriental bezoar and glycyrrhiza are the most widespread herbs often used in Kampo. These three herbs have been used for a Kampo for a thousand years and a number of pharmacological and clinical studies have reported about their effects. However, it has not been previously described how the combination of these most commonly used herbs affects the autonomic nervous system (ANS). Objective: This is a randomized, double-blind, placebo-controlled experiment to examine the acute effects of Kampo on autonomic nervous activity by using power spectral analysis of heart rate variability (HRV) and cardiac depolarization-repolarization time intervals in humans. Design: Ten healthy men volunteered to participate in this study. The Kampo at a dose of two capsules contained the following ingredients: powdered ginseng 250 mg, powdered oriental bezoar 50 mg, and powdered glycyrrhiza 50 mg. The placebo capsules contained corn starch. A CM5 lead ECG was recorded before, and 30 min and 60 min after the oral administration of Kampo or a placebo on different days. Results: HF power (high frequency component in the HRV) was significantly increased and HR (heart rate) was significantly decreased after taking Kampo at 60 min (p<0.05) compared with the placebo. TP (total power) and LF power (low frequency component in the HRV) did not change significantly between the Kampo and placebo, and there were also no statistically significant differences in heart-rate-corrected ECG QT interval (QTc) or recovery time (RTc) between the Kampo and placebo. However, we observed that there was a tendency of decreased QTc interval and RTc after taking Kampo at 60 min compared with response of the placebo (p<0.1). Conclusions: These results indicated that the Kampo mainly potentiated parasympathetic nervous activity and may be useful for cardiovascular health.

Key Words Kampo, power spectral analysis of HRV, autonomic nervous system, depolarization-repolarization

Kampo, which pays attention to and can maintain the basic health by improving the natural resilience, strengthening the habitus, preventing diseases and adjusting the internal balance, attracts worldwide attention. Ginseng, oriental bezoar and glycyrrhiza have been widely used from ancient times as important components of Kampo. The descriptions of ginseng, oriental bezoar and glycyrrhiza appeared in Shen Nong Ben Cao Jing (the Divine Farmer’s Herbal Classic, 22–250 AD, the earliest monograph on medicinal materials in China). Among the 365 herbs listed in this book, these three herbs were recorded as top grade. It is stated that ginseng has various effects (e.g., replenishment of vital energy, tranquilization, elevation of mood and prevention of aging) and oriental bezoar has other effects (e.g., defervescence, anti-amnesia, spasmolysis, sedative, prevention of aging) and that glycyrrhiza has yet other effects (detoxification, harmonization of ingredients for Kampo). These pharmacological effects led us to consider that the ginseng, oriental bezoar and glycyrrhiza may affect the autonomic nervous system. In fact, there are several reports showing that the ginseng has effects on the autonomic nervous system (1). However, it has not been previously described how the combination of these most commonly used herbs affects the autonomic nervous system.

Autonomic nervous activity (ANS) was assessed by power spectral analysis of heart rate variability (HRV), a noninvasive and sensitive method of evaluating ANS activity by measuring instantaneous beat to beat variations in R-R interval length (2–5). In general, the high frequencies of HRV (>0.15 Hz) are associated solely with parasympathetic nervous system (PNS) activity, and the low-frequencies of HRV (<0.15 Hz) are associated with both SNS (sympathetic nervous system) and PNS activities (2, 5).

In addition, the ECG QT interval and recovery time...
(RT) represent cardiac depolarization-repolarization time and can be influenced by the autonomic nervous system. A prolonged QT interval has been shown to be related to an increased risk of sudden cardiac death in apparently healthy subjects (6) in addition to patients with coronary artery disease (CAD) (7) or diabetes mellitus (DM) (6–8). The QT interval measured on a surface electrocardiogram (ECG) was considered a marker to screen unwanted cardiac disturbances, as well as to study the factors and clinical conditions that predispose to their occurrence.

Accordingly, the purpose of this study was to shed some light on the effect of combined ginseng, oriental bezoar, and glycyrrhiza on human autonomic nervous activity by using power spectral analysis of HRV and cardiac depolarization-repolarization time intervals.

**MATERIALS AND METHODS**

**Subjects and informed consent.** Ten nonsmoking healthy male students (age: 29±1 y; height: 170.5±1.37 cm; weight: 63.7±1.23 kg) in Kyoto University volunteered to participate in this randomized, double-blind, placebo-controlled experiment. This study examined the acute effects of Kampo and a placebo on autonomic nervous activity. None of the subjects was taking any medication, and each subject was instructed to avoid beverages containing alcohol or caffeine and strenuous physical activity on the day before the measurements. The experiment administrator explained the purpose of the experiment, test protocol and bioactivity of Kampo prior to the experiment to all subjects. Then, informed consent to participate in this study was obtained from each subject.

**Kampo and placebo.** The Kampo capsule at a dose of 2 capsules contained the following ingredients: powdered ginseng 250 mg, powdered oriental bezoar 50 mg, and powdered glycyrrhiza 50 mg. The placebo capsules contained corn starch. Kampo and placebo capsules were kindly supplied by Nitto Pharmaceutical Industries, Ltd.

**Experimental Design.** The subjects came to the laboratory at 10:00 a.m., and the study was carried out from 10:00 until 12:00. In the study, none of the subjects was taking any medication, and each subject was instructed to avoid beverages containing alcohol or caffeine and strenuous physical activity on the day before the measurements. An electrocardiogram was recorded before, and 30 min and 60 min after the oral administration of two capsules of Kampo or placebo on different days.

**Recording and analysis of physiological variables**

**Electrocardiogram.** The laboratory room was temperature controlled at 25°C and quiet with minimization of arousal stimuli. An electrocardiogram was recorded by bipolar surface electrodes attached to the chest of subjects. The electrocardiogram signal (time constant 0.03 s) was A/D converted at a sampling rate of 1 kHz to obtain R-R interval data, and stored on a computer. These data were analyzed by frequency-domain analysis (trans Era HTB 410, Utah, USA). Power spectral analysis assesses sympathetic and parasympathetic activities (2). Higher frequencies of HR variability (HF power, set at 0.15–0.4 Hz) tend to reflect parasympathetic nervous system activity (9, 10). While lower frequencies (LF power, set at 0.03–0.15 Hz) reflect both parasympathetic and sympathetic nervous system activities (2, 4, 5), the ratio of low/high frequencies (L/H ratio, SNS index) represents the activity of the sympathetic nervous system.

We employed an ECG R-wave trigger averaging technique.
nique before calculating cardiac depolarization-repolarization related parameters. The R-R interval, recovery time (RT) and QT interval were measured by our automated computer programs (11). The points of QRS onset, the minimum dV/dt of the QRS and the maximum dV/dt in the T wave on ECG were determined automatically by our computer system from CM5 lead ECG. These points were checked visually on a high-resolution color monitor. The activation time (AT) was defined as the interval between the QRS onset and the maximum dV/dt of the QRS. Likewise, the activation recovery interval (ARI) was defined as the end point of AT and the maximum dV/dt in the ST-T segment (Fig. 1).

Moreover, the recovery time (RT) was defined as a sum of AT and ARI. The ARI and RT time and QT interval were corrected (ARIc, RTc, QTc) for heart rate by Bazett’s method. A representative computer-aided analysis of ECG is shown in Fig. 2.

Statistical analysis. All data are presented as the mean±SE. All of the statistical analyses were performed with the Statistical Package for Social Science (SPSS for Windows, version 11.5, SPSS Inc., Chicago, IL). A two-way ANOVA and Dunnett’s post hoc test were carried out for comparisons between Kampo and placebo trials. p values <0.05 were considered to be statistically significant.

RESULTS

Heart rate (HR)

Figure 3 shows heart rate (HR) changes before and after taking Kampo or the placebo. The heart rate significantly decreased after taking Kampo at 60 min (63±0.83 vs 61±0.62 bpm, mean±SE, p<0.05) compared with the response of the placebo.

R-R Interval Power Spectral Parameters

Figure 4 shows representative data sets of raw R-R intervals and the corresponding power spectral data obtained from the same subject before and after taking Kampo. We observed that the heart rate fluctuations were clearly increased and HF power was markedly enhanced by Kampo at 60 min.

Figure 5 shows the group data showing the changes in HF power, LF power and total power before and after taking Kampo or the placebo. In contrast with the placebo, the HF significantly increased after taking Kampo at 60 min (530.6±128.37 vs 723.9±178.42 ms², mean±SE, p<0.05). However, there were no statistically significant differences in the TP (total power) or LF power between the Kampo and placebo. This fact suggests that the Kampo mainly potentiated the parasympathetic nervous activity.

Cardiac depolarization-repolarization interval

Figure 6 shows the changes in QTc and RTc before and after the administration of the Kampo or placebo. There were no significant differences in QTc interval or RTc between the Kampo and placebo. However, we observed that there was a tendency of decreased QTc interval and RTc after taking Kampo at 60 min (QTc: 412.5±5.45 vs 407.3±4.25 ms, mean±SE, p<0.1; RTc: 259.9±6.63 vs 254.6±6.23 ms, mean±SE, p<0.1) compared with the response of the placebo.
DISCUSSION

Effect of Kampo on autonomic nervous activity

In attempts to understand the neurohumoral mechanism that modulates HR, HRV spectral analysis has been used to define the frequency content of HR in animals (2, 3), normal adults (4, 5, 12) and neonates (13) and in adults after resuscitation from myocardial infarction (14). Although HRV, defined by power spectral analysis, is widely used in cardiac and noncardiac diseases and clinical investigations, to the best of our knowledge, examining the effects of Kampo on the cardiac autonomic nervous activity using power spectral analysis of HRV in healthy subjects has not been previously described. A significant increase in HF power was observed after taking Kampo at 60 min compared with the response of the placebo.

It enhanced cardiac parasympathetic tone, which may be used to explain an important mechanism underlying the effects of Kampo on the cardiovascular system. Hayano et al. (10) suggested that a decrease in the power of the HF component was a significant risk factor for coronary atherosclerosis. Their observations suggest that an increase in the cardiac vagal tone may help to prevent heart disease. A number of studies have also demonstrated that coronary artery occlusion elicits reflex increases in cardiac sympathetic activity, often accompanied by reductions in parasympathetic tone (15, 16). These studies suggest that activation of the sympathetic nervous system tends to reduce the electrical stability of the heart, whereas parasympathetic nerve stimulation can protect against malignant arrhythmias (16). Furthermore, clinical (17) as well as experimental (18, 19) studies have shown that individ-
uals with the greatest reduction in parasympathetic tone and/or increase in sympathetic tone following a myocardial infarction also have the greatest propensity for sudden cardiac death.

In the present study, we found a significant reduction in heart rate after taking Kampo at 60 min. In general, reduced heart rate usually results from the decreased sympathetic activity and/or increased parasympathetic activity.

To summarize, our study reveals that the Kampo increases the HF power and decreases heart rate. We expected to observe an augmentation of both sympathetic and parasympathetic nerve (vagal) activities. However, only the HF-frequency component, which reflects the vagal activity, was significantly greater after taking Kampo and an enhancement of the LF-frequency component was not detected in this experiment. Therefore, the present data suggest that the Kampo mainly influences the vagal activity. In this study, we observed higher parasympathetic heart modulation and presumably higher autonomic nervous function after taking Kampo. This result suggests that the Kampo augments HRV, a noninvasive measure of the parasympathetic cardiac nerve outflow. Parasympathetic predominance may be the neuroautonomic feature that helps to protect against cardiovascular disease. Thus the augmented HRV after taking Kampo may have pharmacological cardio-protective impact and the pharmacological activities of the Kampo should be investigated clinically in the future.

**Effect of Kampo on the cardiac depolarization-repolarization process**

To elucidate whether the Kampo has adverse effects on ventricular repolarization, the QT interval and recovery time (RT) were measured and the following results were obtained. Kampo administration showed a tendency to decrease in the QT interval and RT compared with the response of the placebo.

The interval of QT reflects the activation time of myocardial cells and action potential duration (APD), and the extension of APD is based on the extension and delay of the repolarization phase. It is generally estimated that the longer the APD is, the more unstable the repolarization process will become, so it is considered that the instability during the repolarization process is the cause of arrhythmia such as torsade de pointes caused by after depolarization (20).

In this study, we found that the Kampo showed a tendency to decrease in the QT interval. This may have important clinical implications. An increase in the QT interval is associated with severe ventricular abnormalities and sudden death (21). Furthermore, the relationship between QT extension and cardiac death has been confirmed in many diseases such as hypertrophic heart disease, myocardial infarction, and hypertension, which belong to ischemic heart disease and long QT syndrome (22, 23). Besides, there are also reports that the relationship between the QT extension and cardiac death has been confirmed in healthy persons and alcoholic liver ailment, which does not belong to cardiac disease (6, 24).

However, because there are many problems in the measurement of the QT interval, RT was used. Taggart et al. (25) and Shimizu et al. (26) have estimated the myocardial depolarization-repolarization process in terms of RT and assessed quantitatively the degree of myocardial ischemia instead of evaluating changes in QT interval. RT is one of the new methods to measure cardiac depolarization-repolarization process, which has quite high degree of correlation with QT interval (11). We believe that RT is clinically useful for noninvasive estimates of depolarization and repolarization properties in human hearts.

In this study, we found that the Kampo showed a tendency to decrease in RT. This may also have useful effects on the heart. Ue et al. (11) confirmed by comparing the RT of healthy persons and the patients suffering ischemic heart disease that there is a significant delay in the patients suffering from ischemic heart disease compared with the healthy persons. It is considered that cardiac repolarization results from the operation of the Na-K pump by use of ATP and that the cardiac repolarization is delayed in the patients suffering from ischemic heart disease leading to insufficient blood supply because ATP supply is largely influenced by blood supply. In addition, Ue et al. (11), by comparing healthy persons and diabetic patients who are confirmed not suffering from peripheral nerve disorder, reported that there is significant delay in the RT of the diabetic patients who suffer from peripheral nerve disorder. It is considered that this is possibly caused by the cardiac microvascular disorder, and that heredity and abnormality of electrolytes may be the other causes.

Although the precise mechanisms are not thoroughly investigated in this study, it is shown that the reduction of QT interval and RT caused by the dosage of the Kampo will probably have an improvement effect on the cardiovascular diseases and contribute to the prevention of lethal arrhythmia.

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