Background: The Yo/Yin concept is fundamental to making a Kampo (sho) diagnosis and may be deeply related to the autonomic nervous system. There is, however, little objective data to confirm the validity of these concepts.

Methods and Results: After diagnosis using standardized Kampo techniques, 20 men and 67 women (mean age, 52.4 years) for whom the prescribed Kampo medication was effective were judged to be correctly classified as Yo- (n=49) or Yin-sho (n=38) and enrolled. Autonomic nervous function was assessed at first visit using HRV obtained from 24-h Holter ECG. Nocturnal ultra low frequency-1 (ULF-1, 0.0001–0.0003 Hz) and ULF-2 (0.0003–0.003 Hz) were significantly higher in the Yin-sho than in the Yo-sho group (P=0.030, P=0.016), suggesting a higher variation of autonomic nervous activity according to sleep stage. On multivariate analysis BMI (≥23.0 kg/m²) and ULF-1 (≥1,150 ms²) were identified as independent factors associated with a differential diagnosis of Yo- or Yin-sho (odds ratio [OR], 11.63, P=0.002; OR, 0.30, P=0.038, respectively). When the sleep period was divided into 3 phases, the ULF-1 of the Yin-sho group was significantly higher than that of the Yo-sho group in the late phase of sleep (P=0.023).

Conclusions: On heart rate variability analysis there was a sleep stage-related difference in the autonomic nervous activity of patients treated with standard Yo- and Yin-sho Kampo medicines. (Circ J 2014; 78: 1924–1927)

Key Words: Heart rate variability; Kampo; Ultra low frequency band; Yin-sho; Yo-sho
Kampo Classification Using HRV

Statistical Analysis

Data are expressed as number (%), mean ± SD, or median with quartiles (25–75%). Patient characteristics and the HRV measurements using Holter ECG were compared between the Yo-sho and Yin-sho groups using Fisher’s exact test for categorical variables and unpaired t-test, Mann-Whitney test for continuous variables (univariate analysis) and repeated-measures analysis of variance. Variables with a P<0.1 difference between Yo-sho and Yin-sho on univariate analysis were used in multivariate analysis to determine independent, significant predictors for the sho. Odds ratio (OR) and 95% confidence interval were calculated from the multiple logistic regression model after adjustment with each variable. All statistical analysis was done on a personal computer using SPSS for Windows (PASW 18, Tokyo).

Results

Baseline Characteristics

Table 1 lists the baseline clinical characteristics of the enrolled patients, 49 of whom were assigned to group A (Yo-sho) and the remaining 38 to group B (Yin-sho) according to the effectiveness of the prescribed Kampo medicine, as described in the previous section. Body mass index (BMI) was slightly but significantly higher in group A than group B (P=0.015), but the other baseline characteristics were the same.

Comparison of HRV

No significant difference in the HRV of groups A and B was found in the awake period. Mean ULF, however, was significantly higher in group B than in group A in the sleep period (P=0.009). Furthermore, even when ULF was divided into ULF-1 (0.0001–0.0003 Hz) and ULF-2 (0.0003–0.003 Hz), the mean frequency of both were significantly higher in group B than in group A (P=0.030, 0.016 respectively; Table 2).
Positive Predictors of Yo or Yin Kampo Prescription

To determine the relative influence of the background factors for predicting a patient being in group A or group B, univariate followed by multivariate analysis was done. Univariate analysis extracted BMI, ULF-1, and ULF-2 as significantly associated with a differential diagnosis of group A or group B. Only BMI and ULF-1 (OR, 11.625, 2.890–79.255, P=0.002; OR, 0.299, 0.090–0.906, 0.038, respectively; Table 3) were extracted in multivariate analysis.

Temporal Change of ULF-1 During Sleep

When the total sleep period was divided into early, middle, and late phases of equal length, the ULF-1 was the same in the early period, but became significantly higher in group B (Yin-sho) than in group A (Yo-sho) in the middle and late phases (P=0.038, between all group A and B, 2-way ANOVA; *P=0.023 at late phase).

Table 3. Multivariate Predictors of Differential Diagnosis of Yo/Yin-Sho

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ≥60</td>
<td>0.504</td>
<td>0.169–1.432</td>
<td>0.205</td>
</tr>
<tr>
<td>Male</td>
<td>1.001</td>
<td>0.294–3.420</td>
<td>0.998</td>
</tr>
<tr>
<td>BMI (kg/m²) ≥23</td>
<td>11.625</td>
<td>2.890–79.255</td>
<td>0.002*</td>
</tr>
<tr>
<td>ULF-1 (ms²) ≥1,150</td>
<td>0.299</td>
<td>0.090–0.906</td>
<td>0.038*</td>
</tr>
<tr>
<td>ULF-2 (ms²) ≥2,200</td>
<td>1.226</td>
<td>0.356–4.400</td>
<td>0.748</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; ULF, ultra-low frequency.

Discussion

This is the first report to demonstrate that objective autonomic nervous balance expressed by HRV is clearly different during the sleep of patients diagnosed as Yo-sho or Yin-sho after strictly applying traditional Kampo diagnostic techniques.

Another research group also used HRV to investigate the effect of Kampo medicines on the autonomic nervous system, and reported an effect of ephedra on autonomic nervous modulation. The ingestion of ephedra dry tract tilted the sympathovagal balance toward increased sympathetic activity.12,13 No data, however, on the usefulness of HRV in making a Kampo diagnosis of Yo- or Yin-sho has been published to date. Also, several trials involving objective Kampo diagnosis of Oketsu syndrome have reported that α-sympathetic nervous activity is increased in the Oketsu state.14,17 Again, however, there were no objective data on the differences between Yo-sho and Yin-sho diagnosis, one of the most fundamental aspects of the diagnosis and the prescription of Kampo medicines. Although an increasing number of physicians, even in Western countries, have been using complementary and alternative medicine (CAM) including Kampo medicine in recent years18 and might have found in their experience that CAM includes the detection of factors affecting autonomic nervous activity to restore the disturbed balance, there was very little objective evidence to show that the diagnostic techniques of Kampo can truly be used to classify different types of patients in terms of autonomic nervous activity, using Western methodology. The present data have shown that HRV analysis would be a helpful tool that clinicians can use in daily medical practice to differentiate patients who need Yo-sho and Yin-sho medicine. A significant, objective difference was seen in autonomic nervous activity, especially during sleep and probably involving the sympathetic nervous system judging from the ULF band.

ULF has been shown to be a marker of physical activity, and the sleep cycle is well known to be closely related to changes in autonomic nervous activity. Any changes in this length of time represent a change in the sleep cycle, because the sleep cycle appears to be around 90 min,19 which is included in the ULF band. We have shown that the ULF-1 power during sleep is higher in the Yin-sho patients. ULF has been shown to be a marker of physical activity,20 and the sleep cycle is well known to be closely related to changes in autonomic nervous activity that directly affect HR and, hence, HRV. The increase in the power of ULF-1 of the Yin-sho patients could indicate that the swing in the autonomic nervous system of Yin-sho patients is larger than that of Yo-sho patients, indicating a relatively unstable state of the autonomic nervous system in this patient group. We consider this to be related to the basic physiological status of the patients and not related to an effect of the Kampo medicine that was prescribed.

From the point of view of Kampo, the Yin-sho patients are relatively inactive and the parasympathetic nerve is predominant. The present results, however, show that there is no direct increase in the parasympathetic nervous system expressed as...
an increase in the amplitude of the power of the HF band or a decrease in LF/HF. This indicates that the characteristics of Yin-sho patients lie not in high parasympathetic tones but in the fluctuating nature of parasympathetic control of HR during sleep. In general, non-rapid eye movement (non-REM) sleep usually appears relatively more in the early phase of sleep and REM sleep increases in the late phase. Given that the difference of the power in ULF-1 in the present study became prominent during the late phase of sleep, the difference in Yo-sho and Yin-sho may be related to REM sleep.

It is difficult in medical clinics to treat patients with medically unexplained or non-specific physical symptoms using Western-style medicine. Thus, these patients might be good candidates for Kampo medicine, given that most such patients have autonomic nervous system imbalance and, empirically, Kampo has been shown to successfully restore the balance of the autonomic nervous system. The present HRV analysis will enable better understanding of the patient condition and make more objective Kampo diagnosis and treatment possible. We believe that accumulation of such knowledge is very important for the further understanding of Kampo medicine.

There were some limitations to this study. First, the number of participants was small, especially that of male patients. The fact, however, that differences in ULF power between Yo- and Yin-sho patients could be clearly observed suggests that this number may have been sufficient for this particular purpose. Larger prospective studies with more male patients are necessary to further clarify the differences and to obtain robust cutoffs. Second, we did not analyze the association of autonomic nervous parameters and other concepts of Kampo, such as Ki, Ketsu, and Sui. Another study specifically targeting these concepts would be useful for clarifying the impact of these concepts on the autonomic nervous system and on sleep.

Finally, we did not compare HRV before and after Kampo. To examine the changes in HRV after treatment is of fundamental importance to understanding the underlying mechanisms of the difference of HRV in Yo-sho and Yin-sho patients. Therefore, further experiments including a post-treatment analysis must be done to provide more detailed information on the relationship between Kampo therapy and autonomic nervous balance.

**Conclusions**

On HRV a difference was seen in the autonomic nervous balance of patients diagnosed as Yo- or Yin-sho, based on traditional Kampo methodology. This difference occurred during sleep, especially in the late phase. This simple HRV method would be useful for classifying patients into Yo or Yin groups to more efficiently and effectively prescribe Kampo medicine.

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No conflict to disclose.

**Disclosures**

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**References**


