Differentiation between Hangekobokuto and Kososan based on pupillary dynamics
—Evaluation of autonomic nerve function—

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Hangekobokuto and Kososan are representative Kampo medicines for the treatment of autonomic abnormalities and are used for Ki stagnation with neurosis or depressive states. Since the targets of the treatment with these two Kampo medicines largely overlap, the differentiation between the precise indications for which each is used is difficult. In order to clarify the relationship between the treatment effects of Kampo medicines and the autonomic nervous system, we performed studies by binocular infrared video pupillography (Irisorder® C-7364, Hamamatsu Photonics, Hamamatsu, Japan). This study was performed to determine whether an objective differentiation between Hangekobokuto and Kososan is possible based on the pupillary dynamics in terms of autonomic nerve function. A comparison between the observed states before and after the administration of Hangekobokuto has revealed that sympathetic nerve activity is inhibited in the group of patients belonging to the sympathetic nerve domination type. After the administration of Kososan, sympathetic nerve activity is stimulated in the group of patients belonging to the non-sympathetic nerve domination types. Thus, the regulatory actions of the Kampo medicines on the autonomic nervous system were confirmed. This method of using an Irisorder® was useful for evaluating the treatment effects of Kampo medicines.

Key words Kampo medicine, Hangekobokuto, Kososan, autonomic nervous system, pupillary dynamics, Irisorder.

Introduction

Hangekobokuto and Kososan are representative Kampo medicines for "Ki," which means vital energy. Hangekobokuto is a Kampo medicine mentioned in "Jin kui yao lue": a section of the Shang han lun (about 3rd century in China) devoted mainly to the treatment of chronic diseases. Hangekobokuto is composed of Pinelliae Tuber, Hoelen, Magnoliae Cortex, Perilla Herba, and Zingiberis Rhizoma. This Kampo medicine targets the sensation of a small item of food obstructing the throat and is used for depressive neurotic complaints (such as anxiety and insomnia) that are accompanied by digestive tract symptoms, respiratory symptoms, or cardiovascular symptoms such as palpitation. Kososan is a Kampo medicine mentioned in "Wazai-kyoku-ho," Formulations and Pharmacopoeia that was compiled in the 12th century during the Song Dynasty. Kososan is composed of Cyperi Rhizoma, Aurantii Nobilis Pericarpium, Perilla Herba, Glycyrrhizae Radix, and Zingiberis Rhizoma. This Kampo medicine is used for hypochondria associated with gastrointestinal impairment, depressive states, and allergic diseases. Both Hangekobokuto and Kososan are representative Kampo medicines that are used for autonomic abnormalities that manifest as neurosis and depressive symptoms, and have a wide range of applications. Nevertheless, the targets of the treatment by these Kampo medicines largely overlap, and experience is necessary to differentiate between the precise indications for which each is used. Based on considerable experience in the use of Hangekobokuto and Kososan, Hanawa specified that Hangekobokuto should be used in Ki stagnation accompanied by water stagnation and Kososan should be used in Ki stagnation accompanied by gastrointestinal impairment. He also reported that both the Kampo medicines essentially treated Ki stagnation that is manifested by symptoms of central nervous system; however, Kososan is used for Ki stagnation not producing localized symptoms while Hangekobokuto is used for Ki stagnation showing concrete peripheral symptoms.¹)

In order to clarify the relationship between the effects of treatment with Kampo medicines and the autonomic nervous system, we performed autonomic function tests. Of all the autonomic function tests, the pupillary test is the most noninvasive one and allows real-time diagnosis. In order to assess the effects of Kampo medicines, we performed studies to establish an objective method of evaluating the autonomic balance by using Irisorder®.

In our previous studies, we have confirmed that an analysis of the parameters of the Irisorder® by using radar charts allows the visual evaluation of the autonomic nervous balance and provides results that are highly consistent with the symptoms.²,³ To further increase the objectivity of this method of analysis, the radar charts were numerically

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expressed using the Mahalanobis-Taguchi System (MTS).

This study was performed to determine whether an objective differentiation between Hangekobokuto and Kososan is possible based on the pupillary dynamics in terms of autonomic nerve function.

**Methodology**

**Substances.** Hangekobokuto is composed of Pinelliae Tuber (6.0 g), Hoelen (5.0 g), Magnoliae Cortex (3.0 g), Perilla Herba (2.0 g), and Zingiberis Rhizoma (0.5 g). Kososan is composed of Cyperi Rhizoma (4.0 g), Aurantii Nobilis Pericarpium (3.0 g), Perilla Herba (2.0 g), Glycyrrhizae Radix (2.0 g), and Zingiberis Rhizoma (0.5 g).

**Subjects.** 38 patients who were administered Hangekobokuto (4 males and 34 females; mean age, 50.2 years), and 18 patients who were administered Kososan (3 males and 15 females; mean age, 49.8 years) were the subjects of our study. All these patients visited the Oriental Medicine Research Center of the Kitasato Institute between April 2003 and April 2006. Before the examination, the absence of ophthalmological diseases was confirmed. This study was performed in conformity with the Helsinki Declaration (2002), and informed consents was obtained from all the subjects.

**Method.** The pupillary dynamics of the patients were measured at the first consultation and reconsultation. Considering the intraday variation, these parameters were measured between 09:00 and 15:00 hours.

Eleven parameters are obtained from the Iriscreder®: initial diameter (D1), minimum diameter (D2), constriction ratio (CR), initial area before light stimulus (A1), time to constriction (t1), time to half constriction (t2), time to total constriction (t3), recovery time (t5), maximum velocity of constriction (vc), maximum velocity of dilatation (vd), and maximum acceleration of constriction (ac). CR is calculated by the formula CR = (D1-D2)/D1. Other parameters are illustrated in Fig.1. Ishikawa et al. have reported the normal values of each of the parameters after taking into consideration the gender and age of healthy subjects.\(^4\) Utsumi et al. have reported that the relative evaluation of pupillary light reflex parameters and not their individual evaluation is necessary.\(^5\) Therefore, we performed a radar chart analysis\(^2,3\) of the 11 parameters based on the standard values reported by Ishikawa et al.

Using the Iriscreder®, a pattern analysis of the autonomic nervous system was performed on the basis of the diagnostic criteria proposed by Utsumi et al.\(^5,6\) The blue areas in Fig. 2 indicate the standard values ± S.D. depending on the sex/age groups in keeping with the values reported by Ishikawa et al. When all the parameters were included in the blue area, as shown in Fig. 2a, the autonomic balance was considered to be normal. The sympathetic nerve domination type (Fig. 2b) was defined as that showing a long initial

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Fig. 1. Parameters obtained from the Iriscreder®
pupillary diameter (D1), a high maximum velocity of dilatation (vd), and a short pupillary recovery time (t5). The parasympathetic nerve domination type (Fig. 2c) was defined as that showing a short D1 and a long t5. We also observed the presence of a sympathetic nerve overtension type (Fig. 2d) that was not included in the diagnostic criteria proposed by Utsumi et al. This type showed a long D1, long D2 and weak pupil constriction in response to light. In this study, these four types were grouped into two. Fig. 2b and Fig. 2d were grouped together as the sympathetic nerve domination type, and Fig. 2a and Fig. 2c as the non-sympathetic nerve domination type.

For further objective evaluation, the data on the 11 parameters obtained from the Iriscriptor® were analyzed using the MTS. In addition, the Mahalanobis distance was calculated, and the radar charts were numerically expressed.

The MTS7 was developed by Dr. Genichi Taguchi, who incorporated the statistical concepts of Dr. Mahalanobis-an Indian mathematician-in quality engineering. This system is based on the theory of pattern recognition and information processing; it has been applied for the evaluation of the reliability of health diagnoses and the results of treatments.8,9 The MTS is a diagnostic and forecasting tool used for the identification of the degree of abnormality of the observations; it is based on the multivariate variables of the "normal" group of observations. In order to use this method, we defined a reference space for the standard values reported by Ishikawa et al.; this space is also referred to as the Mahalanobis Space. The Mahalanobis Space is compared with the data of the subjects, and the degree of similarity is calculated. The results are expressed as the "Mahalanobis distance." This distance represents the degree of similarity. In this study, the longer Mahalanobis distances were considered to be indicative of poor autonomic balancing, while the shorter ones were deemed to be in proximity with the standard autonomic balancing. The calculation of the Mahalanobis distance is summarized in Fig. 3.

A comparative study was performed for the following three items. The subjects who were prescribed Hangekobokuto were denoted as the HK group; and those who were prescribed Kososan, the KS group. The sympathetic nerve domination type was denoted as S-type and non-sympathetic nerve domination type was denoted as non-S-type. The difference in the Mahalanobis distance before and after the subjects were administered the Kampo medicines was denoted by Δ-MD, and each parameter was denoted by Δ-D1, Δ-D2, Δ-CR, Δ-A1, Δ-t1, Δ-t2, Δ-t3, Δ-t5, Δ-vc, Δ-vd, and Δ-ac.

1) The Mahalanobis distances obtained during the initial consultation were compared between the HK and KS groups.

Fig. 2. Radar charts
Blue areas indicate the standard values ± S.D. on the basis of age and sex groups
2) The Mahalanobis distances before and after the administration of Hangekobokuto or Kososan were compared (S-type and non-S-type).

3) \( \Delta \text{-MD}, \Delta \text{-D1}, \Delta \text{-D2}, \Delta \text{-CR}, \Delta \text{-A1}, \Delta \text{-t1}, \Delta \text{-t2}, \Delta \text{-t3}, \Delta \text{-t5}, \Delta \text{-vc}, \Delta \text{-vd}, \) and \( \Delta \text{-ac} \) were compared between the HK and the KS groups (S-type and non-S-type).

**Statistical analysis.** The statistical significance of the differences observed in the values before and after the administration of Hangekobokuto or Kososan was determined using Wilcoxon's signed rank test, and the differences between the HK and KS groups were analyzed using the Mann-Whitney test. A value of \( P < 0.05 \) was considered to be statistically significant.

## Results

The average duration between the first consultation and reconsultation was 94.5 days.

The subjects were classified on the basis of the autonomic nerve balance at the initial consultation. Of the patients who were treated with Hangekobokuto, 18 (47.4\%) were classified under the S-type and 20 (52.6\%) under the non-S-type. Of the patients who were treated with Kososan, 9 (50\%) were classified under the S-type and 9 (50\%) under the non-S-type. Table 1 shows the averages of Mahalanobis distances and the averages of each parameter at the initial consultation.

1) The comparison of the Mahalanobis distances of the HK group and the KS group calculated at the initial consultation revealed no significant difference (\( P = 0.709 \)) (Fig. 4).

2) The comparison of the Mahalanobis distances calculated before and after the administration of Hangekobokuto revealed a significant difference in the S-type (\( P = 0.012 \)) but not in the non-S-type (\( P = 0.759 \)) (Fig. 5). Since a significant change was observed in the S-type after the Hangekobokuto administration, the values for each parameter before and after the administration were compared. D1 (\( P = 0.042 \)), D2 (\( P = 0.009 \)), CR (\( P = 0.033 \)), and t5 (\( P = 0.007 \)) significantly approached the standard values after the Hangekobokuto administration (Fig. 6). The comparison of

<table>
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<th>group</th>
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<th>D1(mm)</th>
<th>D2(mm)</th>
<th>CR</th>
<th>A1(mm²)</th>
<th>t1(ms)</th>
<th>t2(ms)</th>
<th>t3(ms)</th>
<th>t5(ms)</th>
<th>vc(mm/s)</th>
<th>vd(mm/s)</th>
<th>ac(mm²/s²)</th>
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<td>4.30</td>
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<td>277.7</td>
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<td>49.76</td>
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<td></td>
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<td>25.01</td>
<td>305.8</td>
<td>284.8</td>
<td>964.1</td>
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<tr>
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Fig. 4. Mahalanobis distances observed in patients administered Hangebokuto and Kososan at the initial consultation

Fig. 5. Mahalanobis distances before and after the administration of Hangebokuto

Fig. 6. D1, D2, CR, and t5 before and after the administration of Hangebokuto (sympathetic nerve domination type)
The vertical axis represents the percentage of the standard value.

3) The comparison of the changes in the values of each parameter after the administration of Hangebokuto and Kososan revealed no significant difference in the S-type. In the non-S-type, CR ($P = 0.028$) and vd ($P = 0.032$) were significantly changed by the administration of Kososan than by that of Hangebokuto (Fig. 8).

**Discussion**
The purpose of this study is to determine whether an
objective differentiation between Hangekobokuto and Kososan is possible based on the pupillary dynamics in terms of autonomic nerve function. A comparison between the values observed before and after the administration of Hangekobokuto revealed that the parameters involved in the mydriatic phase approached the standard values in the sympathetic nerve domination type. Correspondingly, the values observed after the administration of Kososan approach the standard values in the non-sympathetic nerve domination type.

The pupil is an aperture located at the center of the iris, and the normal pupillary diameter is the same for both the right and left eyes—approximately 3–4 mm in an illuminated room and 8 mm in a dark room; however, pupillary diameter differs according to the age and sex of the subject under consideration. The size of the pupil is regulated by two types of smooth muscle fibers of the iris: radial fibers that form the dilator pupillae and circular fibers that form the sphincter pupillae (Fig. 9). The dilator pupillae are primarily controlled by the sympathetic nervous system. When this muscle contracts, the pupil dilates. The sphincter pupillae are supplied by the parasympathetic fibers of the oculomotor nerve that arise from the parasympathetic nucleus (Edinger-Westphal nucleus). When this muscle contracts, the pupil
constricts. Thus, the pupil size is controlled antagonistically by the sympathetic and the parasympathetic nervous systems, which together comprise the autonomic nervous system.

The most important function of the pupil is the light reflex. This is an instantaneous event; however, the reflex pathway is complicated. When the retina is stimulated by light, neural signals are transmitted along the following route: the retina, optic nerve, optic tract, Edinger-Westphal nucleus, oculomotor nerve, and the ciliary ganglion. This results in the contraction of the sphincter pupillae, which, in turn, causes pupillary constriction. Subsequently, the hypothalamus regulates the contraction of the dilator pupillae through the ciliospinal center and the ganglion cervicale superior, resulting in the dilatation of the pupil. Since the velocity and duration of this reflex differs depending on the state of the autonomic nervous system, this reflex is an attractive option as an autonomic nerve function test.

Recently, studies on various diseases have focused on pupillary dynamics, including those in Horner’s syndrome, Alzheimer’s disease, migraine, diabetic autonomic neuropathy, and depression. Patients suffering from depression have been reported to manifest a shorter time for pupillary constriction and a low constriction ratio as compared to healthy subjects. A study on patients suffering from anxiety showed a low constriction ratio and no difference in the recovery time as compared to healthy subjects, suggesting a greater supranuclear inhibition of the parasympathetic oculomotor reflex arc in the anxious patients. The syndrome that is treated with Hangekobokuto is expected anxiety, i.e., a marked tendency toward anxiety neurosis. In this study, some patients showed pupillary light reflex similar to those shown by patients studied by Bakes et al.

We have previously evaluated the use of the Irisometer® as an objective method for assessing the autonomic nerve balance in order to evaluate Kampo medicines. In this study, we attempted to differentiate between Hangekobokuto and Kososan by this method. Differentiating between the two Kampo medicines was impossible based on the data gathered at the initial consultation.

However, after the administration of Hangekobokuto, significant changes were observed in the sympathetic nerve domination type, and especially the values of the parameters involved in the mydriatic phase approached the standard values. After the administration of Kososan, no significant differences in either the sympathetic nerve domination type or the non-sympathetic nerve domination type were observed. The Mahalanobis distances observed in two patients belonging to the sympathetic nerve domination type group, in particular, approached the standard values after the administration of Kososan. The radar charts of these two patients are shown in Fig. 10. We have previously reported the cases of these two patients. From these radar charts, we inferred that the values observed in the patients belonging to the sympathetic nerve domination type group approached the standard values after the administration of Kososan. The results for these two patients were obtained while evaluating the effects of the Kampo medicines in various individuals.

To check which parameters are the most effective for distinguishing between Hangekobokuto and Kososan, we compared the changes in each parameter after the administration of Hangekobokuto or Kososan. The parameters showed no significant differences in the sympathetic nerve domination type. However, CR and vd were significantly different between Kososan and Hangekobokuto in the non-sympathetic nerve domination type. Kososan acts to

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Fig. 10. Radar charts of two patients belonging to the sympathetic nerve domination type after the administration of Kososan
increase the values of both these parameters while Hangekobokuto functions to decrease them. The mean increase in CR and vd in the non-sympathetic nerve domination type is the resultant of the activation of the movement of the muscle in the dilator pupillae, which is primarily controlled by the sympathetic nervous system.

These results suggest that, based on pupillary dynamics, Hangekobokuto inhibits sympathetic nerve activity in the sympathetic nerve domination types, and Kososan stimulates sympathetic nerve activity in the non-sympathetic nerve domination types (Fig. 11). There are two states prevalent in the non-sympathetic nerve domination types: one is the state of relaxation and the other is the state of paralysis. Kososan stimulates the latter state. In this respect, further studies on individual subjects are likely to confirm the mechanism of action of Kampo medicines.

In conclusion, Kampo medicines, which are essentially multi-component crude drugs, are considered to act on the sympathetic and parasympathetic nerve systems for restoring their balance. In this study, this alteration was confirmed, and valuable results were obtained.

Acknowledgments

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References

半夏厚朴湯および香蘇散は、神経症・うつ状態をともなう氣鬱に使用される自律神経疾患の代表処方であるが、両処方の使用目標は重複する部分が多く、鑑別が容易ではない。我々は、漢方薬の治療効果と自律神経との関係を明らかにすることを目的に浜松ホトニックス社製の赤外線電子瞳孔計Irisorder® C-7364（以下、Irisorder®）を用いて検討してきた。

瞳孔反応における自律神経機能の観点より半夏厚朴湯および香蘇散の客観的な鑑別が可能であるか検討した。その結果、半夏厚朴湯は交感神経が亢進している症例の交感神経活動を抑制し、香蘇散は副交感神経が亢進している症例の交感神経活動を促進する作用があることが示唆された。漢方薬が自律神経系に調節的に働く様子を客観的に証明することができたことより、Irisorder®を用いた評価方法は漢方薬の効果判定法に適していると思われた。

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