## Kampo Medicine - Current Research

# *Three Cases of Severe Bradyarrhythmia in Elderly Dementia Patient Successfully Treated with Goreisan (Powder of Five Ingredients with Poria) Extract Formulation for Prescription*

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**Key words:**

bradyarrhythmia, bradycardia

*Goreisan* (五苓散, Wu-Ling-San, or Powder of Five Ingredients with Poria)

Kampo (漢方, the medicine traditionally practiced in Japan, based on ancient Chinese medicine)

Kampo extract formulation for prescription

sick sinus syndrome (SSS)

*sui-doku* (水毒, disorders of the body's fluid metabolism)

*Abstract*

***Introduction:*** Sick sinus syndrome (SSS), or sinus node dysfunction (SND), is a heterogeneous clinical syndrome of various etiologies, such as sinus bradyarrhythmia, sinus arrest, and sinoatrial (SA) block, with periods of bradyarrhythmia. In this paper we would like to describe three patients with elderly dementia who had severe bradyarrhythmia, and who have shown remarkable improvements with *Goreisan* (Powder of Five Ingredients with Poria, or *Wu-Ling-San*), which is a *Kampo* (traditional Japanese medicine) formula for *sui-doku* (disorders of the body's fluid metabolism).

***Case reports:*** All three patients had dementia, bradycardia and *sui-doku* (disorders of the body's fluid metabolism). Two of the patients had severe bradycardia with minimum pulse rate of less than 40 beats/min (bpm). All patients were treated with *Goreisan* extract formulation for prescription for *sui-doku*. All patients started recovering from bradycardia within a few days from the beginning of the treatment. Severe bradycardia associated with latent SSS (case 1), severe bradycardia associated with drug-induced bradycardia with SSS (case 2) and moderate bradycardia with infectious diarrhea (case 3) were controlled successfully with *Goreisan*.

***Discussion:*** There is little literature for treatment of SSS with *Kampo* formulation. For treatment of bradyarrhythmia and/or slow-pulse in *Kampo* formulation, on the other hand, some doctors take it for symptoms for cold and use drugs with Processed Aconitine Root (Processi Aconiti Tuber) or with Processed Ginger (Zingiberis Rhizoma). Ebe, et al. reported that *Keishi* (Cinnamomi Ramulus, or Cinnamon Twig, *Gui-Zhi*) and *Keihi* (Cinnamomi Cortex, Cassia Bark, *Gui-Pi* (*Rou-Gui*)) increase heart rate in his book: *Keihou-Igaku* (Theoretical Explanations and Assemblage of Prescriptions of "Cold Damage" and "Golden Chamber"). *Goreisan* contains Cinnamon which can increase pulse rate.

***Conclusions:*** This report suggests the possibility of using *Kampo* medicine for the treatment of severe bradyarrhythmia including SSS in elderly dementia patients. Our data and some reports suggest that *Goreisan* may be useful not only for the management of dizziness, edema, vomiting and diarrhea, but also for that of severe bradyarrhythmia in aged dementia. Further accumulation of the similar cases might be helpful for us to interpret the mechanism of rate control with *Goreisan* in future.

***Background:*** The sick sinus syndrome (SSS), or sinus node dysfunction (SND), is a combination of symptoms (dizziness, fatigue, syncope, pre-syncope, and palpitations) caused by sino-atrial (SA) node dysfunction and manifested by severe sinus bradyarrhythmia, SA block, or sinus arrest ([i]). Although the term SSS has been popular since the definition by Rubenstein ([ii]), the more comprehensive title SND is gaining prevalent. In this paper we would like to use the term SSS instead of SND. SSS is quite common, and its incidence increases with advancing age ([iii]). Symptomatic SSS patients are treated with implantable pacemakers. The degree of bradyarrhythmia at which to consider pacing is generally accepted to be "a rate of less than 40 beats/min (bpm) during waking hours" ([iv]). In SSS without absolute indications for pacemaker implantation, drug therapy approaches, occasionally, have been temporarily introduced ([v]).

On the other hand, there is no evidence-based guideline for treatment of SSS with *Kampo* formulation.

We report a patient suffering from severe bradyarrhythmia treated effectively with *Goreisan* (Powder of Five Ingredients with Poria, or Wu-Ling-San) extract formulation for prescription.

## Case Reports:

***Case one***: 82-year-old female.

[Chief complaint:] Dizziness.

[History:] The patient and her family consulted a local clinic due to dementia, just after death of her daughter, in the spring of 200X. Her family rejected nursing by themselves, so they consulted H hospital and admitted its old people's home (elder care facility: H-home) on June 15. On the second post-admission day, she had dizziness, vomit, and loose stools, therefore the nurse at H-home brought her to our department on June 18.

[Past history:]Hypertension, latent SSS (the family said, "A series of alphabet 'S' or something like that.")

[Western medical findings:]Height of 153cm. Weight of 54.5kg. Body temperature (BT) of 36.2℃. Blood pressure (BP) of 169/95 mmHg. Pulse rate (PR) of 38bpm (regular). Conscious level was clear: GCS15 (E4,V5,M6). Dementia-level was observed with MMSE (Mini-mental State Examination) scores, which were 19points.

Results of physical examination were normal except that the bowel sounds were slightly hyperactive. Schellong's test (head-up tilting test) was within normal limits (W.N.L.).

Blood chemistry findings were all within normal limits except the one-hour postprandial blood glucose was 111mg/dL. Thyroid function tests and CK-MB was within normal limit.

Electrocardiogram (ECG) marked sinus bradyarrhythmia at a heart rate of 38bpm, left axis deviation, inverted T-wave in V4-5, and minor ST-segment depressions in V6.

Chest X-ray films, computed tomographic (CT) scan of the brain and the neck: W.N.L. for her age, although there was mild brain atrophy in the subcortex.

Ultrasound study of the neck and the heart: W.N.L. for her age.

[*Kampo* findings:] On general diagnosis: Thirsty. Little urine. Pulse diagnosis: Superficial and slow. Tongue diagnosis: Light-red tongue with teeth indentation. Also, slightly dry, thin and white fur. Abdominal diagnosis: Slightly weak abdominal strength. Sound of fluctuating liquid.

Level of *sui-doku* (disorders of the body's fluid metabolism) : At least 32points with water retention scores ([vi]) (Table 1).

[Progress notes (Figure 1)]: Because of ECG findings, she should be admitted to another hospital with the cardiac care unit for arrhythmia monitoring, but the family selected palliative treatment. The patient did not meet the diagnostic criteria of orthostatic hypotension ([vii]). From physical examinations and roentgenological studies, there were little possibility of *orthopedic, oto*-rhino-laryngologic, *and* neurosurgeric

diseases. An ECG was characteristic of SSS (Rubenstein type I). The presumative diagnosis, therefore, was dizziness due to severe bradyarrhythmia.

Initially, atropine (0.5mg, intramuscularly) was given. However, the patient reported thirsty without pulse rate improvement. We did not continue injection of atropine enough to block parasympathetic nerve.

Her condition was diagnosed as *sui-doku* (disorders of the body's fluid metabolism) from *Kampo* findings. *Goreisan* (6g / day, b.i.d., Kracie Pharmaceutical, Ltd. (KB-17) was introduced orally. The dizziness and bradycaridia improved within 30 minutes. Before administration of *Goreisan*, although, minimum heart rate was 30bpm at night and 38bpm at daytime, after administration of *Goreisan* the minimum heart rate was about 55bpm at daytime for five month. The patient says, "This medicine (*Goreisan*) is very tasty and I always feels good by taking this medicine."

Table 1: Diagnostic score of water retention

| | | | |
|---|---|---|---|
| **Body feels heavy** | **3** | **Nausea, Vomitting** | **3** |
| **Pulsating headache** | **4** | **Increased gurgling** | **3** |
| **Dull headache** | **3** | **Morning stiffness** | **7** |
| **Getting motion sickness easily** | **5** | **Tendency toward edema, gastric clapotage** | **15** |
| **Lightheadedness, dizziness** | **5** | **Pleural effusion, cardiac water retention, ascites** | **15** |
| **Syncope** | **5** | **Epiumbilical palpitaion[1)]** | **5** |
| **Watery nasal discharge** | **3** | **Watery diarrhea** | **5** |
| **Hypersianosis** | **3** | **Decrease urinary volume** | **7** |
| **Foamy sputum** | **4** | **Diuresis** | **5** |

**Diagnostic criteria: A score of more than 13 points indicates water retetion.**

**Note 1: Epiumbilical palpitaion refers to an increased pulsation of the abdominal aorta that is felt during light massage of the umbilical area.**

Cf.: *The Journal of Kampo, Acupuncture and Integrative Medicine* 2005;1Special Edition:12

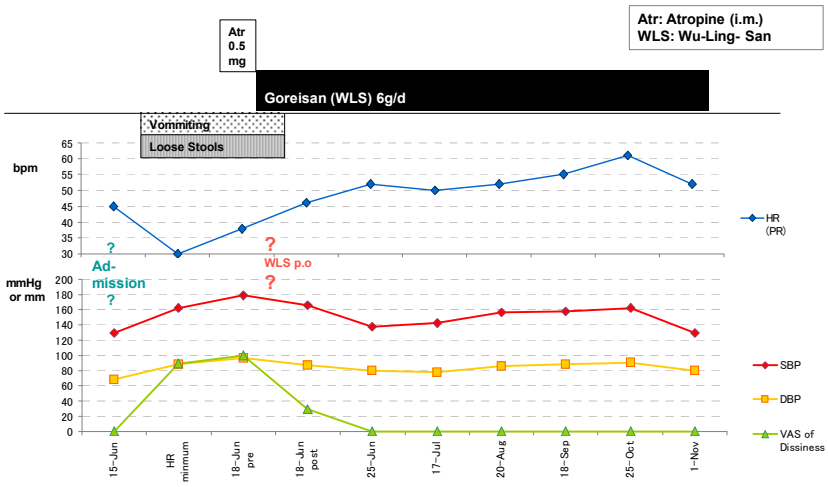


Figure 1: Clinical course of case 1

Change in BP, HR(PR),and VAS of dizziness measured before and after *Goreisan* administration

VAS:Visual Analogue Scale

***Case two:*** 87-year-old female.

[Chief complaints:] Loose stools, leg edema, excessive daytime somnolence, respiratory failure.

[Past History:] Cerebral infarction (76 y.o. in 1997), epilepsy (with carbamazepine 600mg/day t.i.d.), several contusions and fractures, behavioral and psychological symptoms of dementia (BPSD, in 2005)

[Present History:] The patient and her family consulted S-clinic and she admitted its old people's home (S-home) in September, 2005. On October 5, 2008, she had a cold and this preceded the onset of pneumonia (Pn).

The use of antibiotics (CTM, 2g/day, d.i.v.) and oxygen (Ox) therapy for four days showed good effectiveness for treatment of Pn, so antibiotics was switched from CTM to CEPN-PI (300mg/day, p.o.) and Ox therapy tapered off. On Oct.14, loose stools, leg edema and sleep disorders were shown, so she and the nurse consulted S-clinic and we made a house-call on the next day.

[Western medical findings:] Height of 151cm. Weight of 41.6kg. BT of 36.6℃, BP of 114 / 68 mmHg with a PR of 36bpm (regular). Conscious level was GCS10 (E3,V3,M4). Her dementia-level was 15points with MMSE. SpO2 : 98% ($O_2$ 3 l/min), Moist rale (coarse crackles) was heard at the right upper lung field. Her legs were slightly edematous.

Laboratory data on admission are shown in Figure 2.

An ECG performed in a comatose state (Oct.23) revealed episodes of severe bradyarrhythmia at a rate of 20bpm. A 12-lead ECG tracing on the next day showed episodes of sinus bradyarrhythmia with minimum heart rates of 37bpm.

[*Kampo* findings:] On general diagnosis: Thirst, sweat and little urine. Pulse diagnosis: Superficial and slow. Sometimes knotted pulse. Tongue diagnosis: Unknown. The patient rejected to open her mouth. Abdominal diagnosis by palpation: Slightly weak abdominal strength, sound of fluctuating liquid, epigastric discomfort slightly.

Level of *sui-doku* : At least 26points.

[Progress notes (Figure 2):] Although the family hoped palliative care at S-home, her condition was bad enough to be referred to the other hospital for immediate admission. As her condition was diagnosed as *sui-doku*, *Goreisan* (6g / day, b.i.d; KB-17) was introduced orally. CTM was reintroduced. Tulobuterol-tape 2mg/day and aspirin 100mg/day were continued and the other drugs (carbamazepine 600mg/day etc.) were discontinued. Within two days, her loose stools, leg edema, severe bradyarrhythmia, conscious level, and respiratory failure improved. Four days later, she did not need antibiotics (CTM) and oxygen therapy. Seven days later (Oct.22), her laboratory findings such as CRP were improved, and the drugs (carbamazepine etc.) were reintroduced and *Goreisan* was discontinued. Within one day, her bradycardia developed with decreased level of consciousness. Therefore, we changed the prescriptions as of Oct.15 immediately (*Goreisan*, tulobuterol-tape, and aspirin were reintroduced and carbamazepine was discontinued). On the next day, her status improved again. She had had no trouble with heart rate of 55 bpm until November 12, and subsequently the *Goreisan* was tapered off.

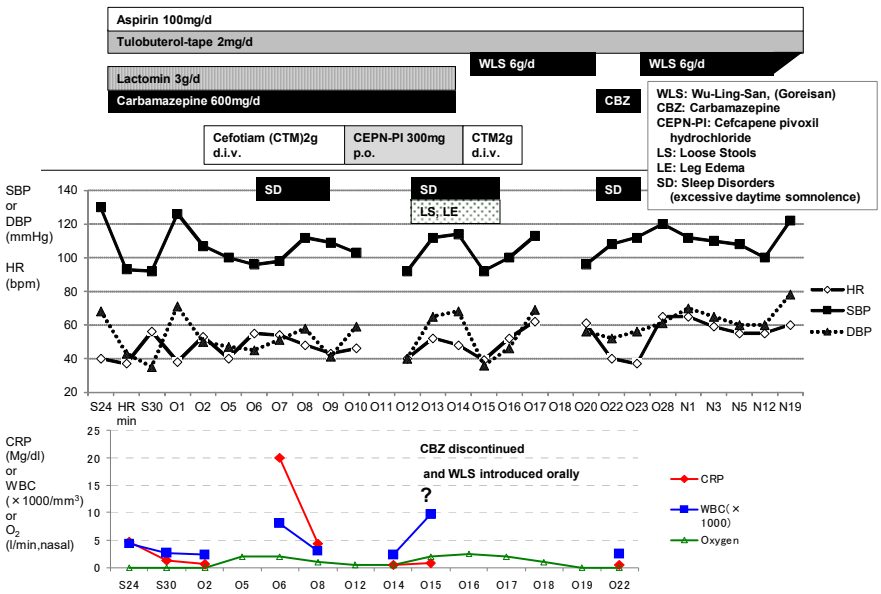


Figure 2: Clinical course of case 2
: (Top), Change in BP and HR(PR) measured before and after Gorei-san administration.
: (Bottom), Change in CRP, WBC, and Oxygen.

***Case three:*** The third case was a 72-year-old female.

[Chief complaints:] Watery diarrhea, vomiting.

[Past History:] Cerebral infarction.

[Present History:] The patient and her family consulted S-clinic and she entered its old people's home in October, 2001. On February 21, 2008, she noted the onset of nausea and vomiting. And for the following several days she had had recurrent watery diarrhea, which remained unresponsive despite lactomin and domperidone, accompanied by vomiting and sweating.

[Western medical findings:] Height ;145cm, Weight ; 54kg, BT; 37.3℃, BP; 127/ 71 mmHg, PR; 48bpm (regular). Conscious level; clear. Dementia-level; 16points (MMSE). There were no resistance and no tenderness, but the bowel sounds are hyperactive.

ECG findings: Sinus bradycardia, abnormal Q waves in III and aVF.

[Kampo findings:] On general diagnosis; thirst, sweat, little urine, slight cold sensitivity. Pulse diagnosis: Superficial and slowed-down (Huan). Tongue diagnosis: Dark-red tongue with teeth indentation, slightly dry, thin and white fur. Abdominal diagnosis: Slightly weak abdominal strength, sound of fluctuating liquid.

Level of *sui-doku* : At least 33points.

[Progress notes:] Examination disclosed infectious diarrhea due to norovirus-related gastroenteritis. Her condition was diagnosed as *sui-doku*. On February 25, *Goreisan* (6g / day, b.i.d; KB-17) were introduced orally for *sui-doku*. By the next day, abdominal symptoms subsided and besides her moderate bradyarrhythmia improved. She had had no trouble with heart rate of 50-60 bpm until March 4, when *Goreisan* were discontinued. Since then, the heart rate has been decreased gradually to 45-50bpm.

***Summary of three cases:*** All three patients had dementia, bradycardia and *sui-doku*. Two of the patients had severe bradycardia with minimum PR of less than 40 bpm. All patients were treated with *Goreisan* for *sui-doku*. Severe bradycardia associated with SSS (case 1), severe bradycardia associated with drug-induced bradycardia with SSS (case 2) and moderate bradycardia with infectious diarrhea (case 3) were controlled successfully with *Goreisan* (Table 2). All patients started recovering from bradycardia within a few days from the start of the treatment without any adverse reaction.

## *Discussion*

**Standard treatment of bradyarrythmias including SSS**: The indications for pacemaker implantation in patients with SSS are listed in the ACC/AHA/NASPE 2002 guideline ([viii]). Due to limitations of space, a detailed discussion on the indications for pacemaker implantation is not possible here. Please refer the guideline for more information.

In SSS without absolute indications for pacemaker implantation, drug therapy, occasionally, have been temporarily introduced ([ix]). Drug treatment of sinus bradyarrythmia is usually not indicated for asymptomatic patients. While intravenous atropine has aided some patients transiently, most patients ultimately require placement of a pacemaker. Although in the past, isoproterenol was used quite commonly in patients with bradyarrhythmia, further appreciation of its substantial risks of the increase in myocardial oxygen demand has diminished its role. Some physicians use theophylline or cilostazol for bradyarrythmia, though these are drugs of off-label use under health insurance in Japan. In patients with sinus bradyarrhythmia secondary to therapeutic use of digitalis, beta-blockers, carbamazepine or calcium channel blockers, simple discontinuation of the drug are often all that is necessary.

Table 2: Baseline characteristics of three patients

| No. | case1 | case2 | case3 |
|---|---|---|---|
| Age, Gender | 82、Female | 87、Female | 72、Female |
| Diseases other than bradycardia | Dementia(AD)、HT | Dementia+Brain infarction, knee-OA, Asthma | Dementia+Brain infarction, Fx at Lumbar discs, HT |
| Level of the Dementia | MMSE 19/30<br>HDS-R 18/30 | MMSE 15/30<br>HDS-R 16/30 | MMSE 16/30<br>HDS-R 16/30 |
| (Active) Symptoms | Dizziness, Thirst, Oliguria | Loose stools, slight leg edema and sleep disorders | Diarrhea (norovirus-related gastroenteritis) |
| ADL (Barthel Index) | 95/100 ? 100/100 | 0/100 ? 45/100 | 20/100 ? 55/100 |
| Water Retention Score (Terasawa) | 32/100 | At least 26/100 | At least 33/100 |
| WLS(Gorei-san) | 6g/day b.i.d. | 6g/day b.i.d. | 6g/day b.i.d. |
| ECG | Sinus bradyarrhythmia at a heart rate of 38bpm. Rubenstein type I . | Sinus bradyarrhythmia with minimum heart rates of 37bpm . | Sinus bradyarrhythmia at a heart rate of 38bpm. |
| Change in HR(PR) HR(PR) of pre-administration ? HR(PR) of post-administration | 30bpm at night, 38bpm at daytime ?<br>about 55bpm at daytime | 20bpm at night(with CBZ), 37bpm at daytime ?<br>about 55 bpm at daytime | 48 bpm ? 50-60 bpm (with WLS) ? 45-50 bpm (without WLS) |

Abbreviations:
MMSE, Mini-Mental State Examination; HDS-R,Hasegawa Dementia Scale-Revised ; AD, Alzheimer's disease. HT, Hypertension; ADL;Activities of Daily Living, WLS;Wu-Ling-San,or *Goreisan*（Kracie Pharmaceutical, Ltd., (KB-17)）, OA; Osteoarthrities, DM; diabetes mellitus, Fx;fracture

**Treatment of bradyarrythmias including SSS with *Kampo* formulation:** On the other hand, there is little literature for treatment of SSS with *Kampo* formulation. For treatment of bradyarrhythmia and/or slow-pulse with *Kampo* formulation, on the other hand, some doctors take these symptoms for *kan-sho* (cold pattern) and use drugs with *bushi* (Aconiti Later Radix, Processed Aconitine accessory root, or *Fu-Zi*) or with *kankyo* (Zingiberis Rhizoma, Dried Ginger Rhizome, or *Gan-Jiang*) ([x]). Some Japanese doctors have used *Kampo* drugs for treatment of bradyarrhythmia and/or slow-pulse as Table 3 shows.

Table 3 : Cases with Kampo formula for bradycardia

| Author | Literature | Organisation | Cardiac diseases | Age Sex | Pulse Diagnosis | HR change | Kampo fomula |
|---|---|---|---|---|---|---|---|
| Tauchi N. et al. | The Japan Pediatric society for Oriental Medicine 2003 Vol.19 pp.5-12 | Dept. of Pediatric Cardiology and NICU, Ogaki Municipal Hospital, Japan | Advanced atrioventricular (AV) block(2:1) | 5y.o. male | Not commented | 63bpm ? improvement of AV block (HR: unknown) | Ling-Gui-Zhu-Gan- Tang (Extract Granules) 2.0g/day t.i.d. (Pharmaceutical Manufacturers unknown) |
| Watanabe Y. | Kampo-no-Rinsho, 46(5)(1999) | Watanabe OB/OG, Fujieda-city, Japan | Left Ventricular Hypertrophy (LVH), extrasystolic arrhythmia, Mitral Stenosis (MS) susp. | 66y.o. female | Deep and Slow ? Big and Slowed Down | 45bpm ? 59bpm | Ren-Shen-Tang (Extract Granules) 4.0g/day(OHSUGI PHARMACEUTICAL Co.,LTD.), Da-Jian-Zhong-Tang (Extract Granules) 5.0g/day(Tsumura & Co.) |
| Sakamoto T. | Kampo-Kenkyu No.444, pp.3 68-369 (2008) | Sakamoto Clinic, Hirosaki-city, Aomori, Japan | Unknown Origin | 88y.o. female | Deep, Weak, Fine, and Slow ? Not commented | 30bpm ? 70bpm | San-Huang-Xie-Xin-Tang (Extract Capsules) 6g/day t.i.d (for 2 weeks) (Kotaro Kampo Pharmaceutical Co., Ltd. ) |

**How dose they describe *Goreisan* in classics:** *Goreisan* comes from the "*Shan-Han-Lun* (On Cold Damage)" and "*Jin-Kui-Yao-Lue* (Synopsis of Golden Chamber)", which classical textbooks written by Zhang-Zhong-Jing during the Latter (East) Hun era. The "*Shan-Han-Lun*" says, "When in Greater-Yang disease, after sweating is promoted and great sweat issues, if there is dryness in the stomach, vexation and agitation with insomnia, and a desire to drink water, giving a small amount of water will harmonize the stomach-Qi so that recovery will lead to ensue. If the pulse is floating and there is inhibited urination, slight heat, and dispersion-thirst. *Goreisan* governs. ([xi])"And the "*Jin-Kui-Yao-Lue*" says "When a thin person presents with palpitation below the umbilicus, drooling and foaming at the mouth, withdrawal, and dizziness, this indicates water. *Goreisan* governs. ([xii])" Indications for *Goreisan* is acute and chronic diseases due to *sui-doku*, such as headache, severe thirst with vomiting after drinking, urinary difficulty, edema, general fatigue, diarrhea, fluctuating liquid in the epigastric region, vomiting frothy saliva, and vertigo.

**Medicinal Constituents of *Goreisan*:** *Goreisan* is not a simple preparation of medicine, but contains multiple herbal medicines such as

(1) *Bukuryo* (茯苓, Poria, Hoelen, or *Fu-Ling*) 3g :For drain dampness and tonify spleen Qi.

(2) *Chorei* (猪苓, Polyporus, polyporus, or *Zhu-Ling*) 3g. For eliminate dampness and promote urination.

(3) *Byakujutu* (白朮, Atractylodis Macrocephalae Rhizoma, White Atractylodes Rhizome, or *Bai-Zhu*) 3g: For tonify spleen-Qi and promotes transformation and transportation of the spleen-Qi.

(4) *Takusha* (沢瀉, Alismatis Rhizoma, Water Plantain Rhizome, or *Ze-Xie*) 5g: For drains dampness and promotes urination.

(5) *Keishi* (桂枝, Cinnamomi Ramulus, Cinnamon Twig, or *Gui-Zhi*) and *Keihi* (桂皮, Cinnamomi Cortex, Cassia Bark, or *Gui-Pi* (*Rou-Gui*)) 2g: For warm vitality gate and tonify yang.

**The presumable reasons for successful treatment for this case of bradyarrhythmia with *Goreisan* were:**

1: Cardiologically, *Goreisan*, which is ***diuretics*** for eliminating dampness, made an improvement of the extravascular volume overload. This improvement in the extravascular volume overload led to an improvement of bradyarrhythmia.

2: From the pharmacologic point of view, withdrawal and discontinuation of the medicine that induces bradyarrhythmia can contribute to improvement of bradyarrhythmia. In second case, discontinuation of carbamazepine can be effective for improvement of bradyarrhythmia. serum half-life

From *Keihou-Igaku* point of view, *Keishi* moves the Qi from Stomach and increases amount of Qi to outside-tract and this leads to increase of heart rate. According to Ebe, et al.([xiii]), the Qi runs from Stomach to outside-tract through Epigastric region (*Xin-Xia*), Chest, Lung and Pericardium (*Xin-Bao*: connecting channel of the envelope of the Heart). If the Qi from Lung to Pericardium is difficult to be dispersed (*sen-san*), the amount of Qi to Pericardium decreases, this leads to "slow-pulse". According to "*Keihou-Igaku* (six-channel pattern indication)", the factor which decides pulse rate is the amount of Lung-Qi, which runs from Lung to Pericardium. *Goreisan* contains *Gui-Zhi* which can increase pulse rate. *Gui-Zhi* moves the Qi and increases amount of Qi, from Stomach to Pericardium and this makes the pulse increased.

3: From a viewpoint of traditional Chinese medicine (TCM), *Goreisan* contains *Gui-Zhi*, which is an acrid, warm medicinal which enters and warms the channels and network vessels, dissipates cold and moves the Qi and blood ([xiv]). Furthermore, *Gui-Zhi* warms the yang specifically of the Heart, Spleen, and Kidneys. If Qi is plentiful, then Yang is warm and energetic enough. If Qi is weak and empty, Yang is lacking and the systemic body and extremities become cold. If Heart-Qi and/or Heart-Yang are weak and empty, the pulse rates become slow and sometimes irregular, and also Blood and Qi are not circulated throughout the whole body. *Gui-Zhi*, which is contained in *Gorei-san*, moves the Qi and increases amount of Qi and this leads to increase of heart rate.

In Japan, although, some researches on *Kampo* formulation have been carried out from the viewpoint of the *Koho-ha* School (the classical school), they use *Keishito*-group (Ramulus Cinnamoni Decoction group) for treatment of reversed-Qi (*Ki-gyaku* or rising of Qi), which is manifested by so-called hot flush. There are two types of hot flush as follows ([xv]): Active-type hot flush that observed when individuals feel nervous, disappearing when the stress is removed. And fixed-type hot flush is always observed, increasing in the face due to tension as well as blood engorgement. The patients with active-type reversed-Qi normally experience "palpitation" or "tachycardia".

At first glance, the usage of *Keishito*-group for treatment of reversed-Qi, which usually contains palpitation or tachycardia, seems to be inconsistent with that of *Gui-Zhi* for treatment of bradyarrhythmia or for augmentation of Qi. Where this contradiction comes from?

One possible reason for this contradiction comes from our intention to discuss has not been on *Ketsu* (Blood) and *Sui* (all bodily fluids other than *Ketsu*) but on *Ki* (Qi) in this argument. Now, we must think of *Ki* (Qi), *Ketsu*, and *Sui*, because a balance of these three concepts is, like three wheels in tricycle, indispensable in order to take full advantage of the bradyarrhythmia-relieving aspect of the treatment. If the increase in pulse rate by an improvement of the extravascular volume overload with *Goreisan* is much greater than the decrease in pulse rate by an improvement of the active-type reversed-Qi with *Gui-Zhi*, *Goreisan*, which contains *Gui-Zhi*, may have effect of increase in pulse rate or improvement of bradycaridia in the total amount.

Another possible reason for this contradiction comes from "Our argument has been done with the concept of Qi." This may be said, "Are both *Kampo*, traditional Chinese medicine (TCM), and *Keihou-Igaku* based on metaphysical consepts of which there

are no plausible scientific rationale for understanding Qi?" Or "Are there any effects of *Gui-Zhi* or its ingredients on the improvement or decrease of pulse rate pharmacologically?" To the best of our knowledge, there has not been any report on the in vitro cardiotonic action of *Gui-Zhi* like that of *Fu-Zi*. But, it may be said that "A drug may have two opposite effects on the disease", like the efficacy of low-dose dopamine as a renal-protective agent during vigorous diuresis for CHF associated with moderate renal insufficiency and that of high-dose dopamine without diuretic effect for CHF[xvi]. According to some reports, cinnamaldehyde in *Gui-Zhi* is a *central nervous system (CNS)* stimulant at low-doses and a *sedative* at high-doses [xvii], [xviii], [xix]. *And we may* attribute *such CNS stimulation* (*low-dose*) and *sedation* (*high-dose*) to acceleration and suppression of catecholamine (mainly adrenaline) release from the adrenal glands. Briefly, it may be said that, on the one hand low-dose *Gui-Zhi* accelerates pulse rate through CNS stimulation directly and through promotion of urination by warming yang for dieresis or by eliminating dampness and diuresis indirectly. On the other hand, high-dose *Gui-Zhi* suppresses pulse rate through CNS ***sedation*** directly and through, indirectly, promotion of harmonizing yingfen and weifen by relieving exterior syndrome with pungent and warm natured drugs like *Keishito* (Ramulus Cinnamoni Decoction, or *Gui-Zhi-Tang*).

So far we have outlined on the presumable reasons for successful treatment for bradyarrhythmia in aged dementia with *Goreisan*. Briefly, functions of *Goreisan* are not only to promote urination and to drain damp accumulation, but also to warm yang Qi. Our data and some reports suggest that *Goreisan* may be useful not only for the management of dizziness, edema, vomiting and diarrhea, but also for that of severe bradyarrhythmia in aged dementia. *Goreisan* is thought to be effective for the treatment of bradyarrhythmia in elderly patients whose sinus node and heart function are aggravated with advancing age.

We are facing a prominent aging society in Japan, where the idea that "the care of the elderly is the responsibility of the family" has long been strongly held. Sometimes we encounter patients who are within indications for aggressive treatment in medically, but are out of curative indications of aggressive treatment in socially. For example, a super-aged dementia patient, whose family rejected nursing by themselves, is within indications for aggressive treatment in medically. In this case, the patient and one's family might choose palliative care instead of aggressive treatment. And this may lead to worse prognosis of the patient compare to that of the patient who took aggressive treatment. In those cases, through *Kampo* medical diagnosis and treatment, medical teams can develop comprehensive geriatric assessment (CGA) and offer true whole-person medicine, and this will lead to improvement of the patients' quality of life (QOL).

## *Conclusions:*

This report suggests the possibility of using *Kampo* medicine for the treatment of severe bradyarrhythmia including SSS in elderly dementia patients. Further accumulation of the similar cases from patients in clinical settings and extensive molecular and cellular research into these syndromes are required to gain insight into severe bradyarrhythmia, including SSS, and to develop new target therapies and preventive strategies.

## *Additional remark (Acknowledgements):*

(OZAKI K., et al. have been *reported as "Three cases of severe bradycardia including Sick Sinus Syndrome in Elderly Dementia Patients Successfully Treated with Herbal Medicine* Gorei-san *(Wu-Ling-San, or Poria Powder with Five Herbs)." at t*he 6th World Congress of Chinese Medicine 2009 Melbourne, Australia, Dec. 2009.

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## References


[1] Kasper D. L., Braunwald E., Hauser S., Longo D., Jameson J. L., Fauci A.S. : *Harrison's* Principles of *Internal Medicine*, *16t*e, n.p. : McGraw-Hill Professional, 2004. p.1335.

[2] Rubenstein J.J., Schulman C.L., Yurchak P.M.,. DeSanctis R.W. : Clinical spectrum of the sinus syndrome. *Circulation*,. 1972; 46 : 5-13.

[3] Peters R. W., Vijayaraman P., Ellenbogen K.A. : Indications for permanent and temporary cardiac pacing. (Edited by Ellenbogen K.A. and Wood M. A. : *Cardiac Pacing and ICDs*, 5th edition.), n.p. : Blackwell Publishing, 2008. 17-21.

[4] Libby P., Bonow R.O., Mann D. L., Zipes D. P. : Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th Edition: n.p. : Saunders, 2007. 831-835. (CHAPTER 34 – Cardiac Pacemakers and Cardioverter-Defibrillators(Hayes D. L., Zipes D. P.) Indications for Cardiac Pacing)

[5] Kodama I, Aizawa Y, Inoue H, et al. : Guidelines for Drug Treatment of Arrhythmias (JCS 2004) *Circulation Journal* 2004; 68(Suppl IV): 981-1053.)

[6] *The Journal of Kampo, Acupuncture and Integrative Medicine* 2005;1Special Edition:12 (Originally Terasawa Katsutoshi :*Shorei-kara-manabu, Wakan-shinryo-gaku,* 1st edition. Igaku-shoin, Tokyo, Japan. 1990,1-300. [寺澤捷年:症例から学ぶ和漢診療学, 医学書院, 東京, 日本1998;1-300])

[7] The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. : Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.

[8] ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Summary Article A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines) This document was approved by the American College of Cardiology Foundation Board of Trustees in September 2002, the American Heart Association Science Advisory and Coordinating Committee in August 2002, and the North American Society for Pacing and Electrophysiology in August 2002. Committee Members: Gabriel Gregoratos, Jonathan Abrams, Andrew E. Epstein, Roger A. Freedman, David L. Hayes, Mark A. Hlatky, Richard E. Kerber, Gerald V. Naccarelli, Mark H. Schoenfeld, Michael J. Silka, Stephen L. Winters, (Circulation. 2002;106:2145.)

[9] *Circulation Journal* 68(Suppl IV): 981-1053, 2004. (Kodama I, Aizawa Y, Inoue H, et al. : Guidelines for Drug Treatment of Arrhythmias (JCS 2004) *Circulation Journal* 68(Suppl IV): 981-1053, 2004.)

[10] Li-Zhong-Zi "Yi-Zong-Bi-Du(Essential Readings from the Medical Tradition)"(Mai-Fa-Xin-Can), Beijing : People's Medical Publishing House, 2006, 1-464. [李中梓:醫宗必讀, 人民衛生出版社, 北京,中国 2006. 1-464.) 「脈遲為寒當用乾薑附子溫之矣(p.66)」

[11] Mitchell C., Feng Ye, Wiseman N.: Shang-Han-Lun: On Cold Damage. Brookline, Massachusetts, USA:Paradigm Publications,1999, 1-800.

[12] Sung Yuk-ming.: Understanding the Jin-Gui-Yao-Lue. Beijing, China:,2009, 1-726.

[13] Ebe Y. , Yokota S. : Keihou-igaku; six-channel pattern indication (1), Toyo Gakujutsu Shuppansha, Tokyo, Japan, 2000, 1-212. [江部洋一郎、横田静夫 :『経方医学〈1〉「傷寒・金匱」の理論と処方解説 第2版』東洋学術出版社, 2000, 1-212. ]

[14] Becker S., Flaws B., Casañas R. : The treatment of cardiovascular diseases with Chinese medicine. Boulder, Colorado: Blue Poppy Press, 2005. 1-638.

[15] Sato Y., Hanawa T., Arai M., *et al.* (eds.):. Introduction to Kampo : Japanese traditional medicine / [by] the Japan Society for Oriental Medicine. Tokyo : Elsevier Japan, 2005. 1-286.

[16] Varriale P., Mossavi A.: The benefit of low-dose dopamine during vigorous diuresis for congestive heart failure associated with renal insufficiency : Does it protect renal function? *Clinical Cardiology* 1997; 20(7):627-630.

[17] Natural Medicines Comprehensive Database, 1999(www.naturaldatabase.com/)[the last date of access Mar.31, 2011]

[18] Natural Medicines Comprehensive Database, 2007(www.naturaldatabase.com/)[the last date of access Mar.31, 2011]

[19] Khare C.P. (ed.): Indian Medicinal Plants:An illustrated Dictionary, Berlin/Hidelberg : Springer-Verlag, 2007. 1-900.