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Effects of the oriental herbal medicine Bofu-tsusho-san in obesity hypertension: A multicenter, randomized, parallel-group controlled trial (ATH-D-14-01021.R2)

Kengo Azushima [a], Kouichi Tamura [a, *], Sona Haku [a], Hiromichi Wakui [a], Tomohiko Kanaoka [a], Masato Ohsawa [a], Kazushi Uneda [a], Ryu Kobayashi [a], Kohji Ohki [a], Toru Dejima [a], Akinobu Maeda [a], Tatsuo Hashimoto [a], Jin Oshikawa [a], Yusuke Kobayashi [a], Koichiro Nomura [a], Chieko Azushima [b], Yasuyo Takeshita [c], Ryota Fujino [d], Ken Uchida [d], Ken Shibuya [d], Daisaku Ando [e], Yasuo Tokita [e], Tetsuya Fujikawa [a], Yoshiyuki Toya [a], Satoshi Umemura [a]

[a] Department of Medical Science and Cardiorenal Medicine, Yokohama City University, Graduate School of Medicine, Yokohama, Japan
[b] Azushima Medical Clinic, Tokyo, Japan
[c] Renal Division, Department of Medicine, Yamato Municipal Hospital, Yamato, Japan
[d] Renal Division, Department of Medicine, Omori Red Cross Hospital, Tokyo, Japan
[e] Renal Division, Department of Medicine, Fujisawa Municipal Hospital, Fujisawa, Japan

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ABSTRACT

Objective: There is no clinical evidence that supports the benefit of integrative medicine, defined as combination therapy of oriental and western medicine, on obesity-related hypertension. This study evaluates the efficacy of Bofu-tsusho-san (BOF), an oriental herbal medicine, on the ambulatory blood pressure (BP) profile in hypertensive patients with obesity.
Methods: The study design was a multicenter, randomized, open-label, parallel-group controlled trial in 107 hypertensive patients with obesity. Participants were randomly assigned to receive either the conventional control therapy or BOF add-on therapy. In both groups antihypertensive therapy was aimed at achieving the target clinic BP. The primary outcome was change in the ambulatory BP profile from baseline to 24 weeks after randomization.
Results: Daytime systolic BP variability, an important parameter of ambulatory BP profile, was decreased in the BOF group, and the difference in the changes in daytime systolic BP variability was significant between the BOF and control group (Control vs BOF; the change from baseline in daytime systolic BP variability, 1.0 ± 3.3 vs $-1.0 \pm 3.3\%$; $p = 0.006$).
Conclusion: The BOF add-on therapy effectively improved the ambulatory BP variability. This is the first report suggesting that an integrative medicine approach may exert favorable effects on obesity-related hypertension compared with conventional pharmaceutical treatment.
Clinical trial registration: UMIN000003878.

1. Introduction

Obesity-related disease patients are increasing and obesity is a major medical problem associated with the development of hypertension, type 2 diabetes (T2DM) and dyslipidemia, and ultimately life-threatening cardiovascular disease (CVD) [1]. Obesity is reportedly often accompanied by hypertension and obesity-related hypertension is closely associated with the development of systemic atherosclerosis along with T2DM and dyslipidemia, resulting in increased CVD morbidity [2]. Therefore, there is a need for new treatment strategies for the management of both obesity and

* Corresponding author. Department of Medical Science and Cardiorenal Medicine, Yokohama City University, Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.
E-mail address: tamukou@med.yokohama-cu.ac.jp (K. Tamura).

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hypertension. In the face of widespread and still increasing obesity, a variety of anti-obesity drugs and procedures, such as bariatric surgery, have been developed as treatments under the approach of western medicine that have helped a number of severely obese patients, but these treatment modalities are limited due to both adverse effects and the degree of invasiveness [3,4].

Bofu-tsusho-san (BOF), an oriental herbal medicine, has been used for obese patients in Japan. BOF, composed of 18 crude herbal drugs (Supplemental Table 1), has been reported to exert various anti-obesity effects by stimulating adipose tissue in rodents [5,6]. With respect to active ingredients of BOF, a previous study reported that main effective components of BOF were *shizonepetae spica*, *glycyrrhizae radix*, *forsythiae fructus* and *ephedra herba*. Ephedrine contained in *ephedra herba* acts on sympathetic nerve terminal and promotes the release of norepinephrine. Increased norepinephrine stimulates β-receptor in adipose tissue, and induces thermogenesis in brown adipose tissue and lipolysis in white adipose tissue through increases the synthesis of cAMP. Additionally, since *glycyrrhizae radix*, *forsythiae fructus* and *schizonepetae spica* have a potent inhibiting effect of phosphodiesterase, degradation of cAMP is inhibited to exert more powerful anti-obesity effect described above [5]. In addition, we recently reported that BOF exerted a favorable effect on metabolism, including an antihypertensive effect, not only via its beneficial effect on adipose tissue function, but also its appetite inhibitory effect in a mouse model of human metabolic disorders with obesity [7]. The development of highly efficient antihypertensive drugs with fewer adverse effects based on oriental herbal medicine is an attractive research subject, and randomized controlled trials are needed to reasonably evaluate the efficacy and safety of oriental herbal medicine for treating hypertension [8]. However, there have been no randomized clinical trials investigating possible effects of BOF on blood pressure (BP) profiles in hypertensive patients with obesity.

Concerning the BP management, accumulating evidence supports that the “out-of-clinic” BP, particularly the ambulatory BP profile, is important for a proper diagnosis of hypertension and estimation of BP control [9]. Ambulatory BP monitoring allows the acquisition of critical information not only at the level of the 24-h BP but also the BP variations that occur in the course of daily activities. Among the several parameters obtained by ambulatory BP monitoring, ambulatory BP variability reflects a complex phenomenon that involves both short- and long-lasting changes [10]. The 24-h BP varies not only because of a reduction in BP during nighttime sleep and an increase in the morning, but also because of sudden, quick and short-term changes that occur both during the day and, to a lesser extent, at night. This phenomenon, ambulatory short-term BP variability, has been shown to depend on sympathetic vascular modulation and on atherosclerotic vascular changes [10]. Recently ambulatory short-term BP variability is highlighted as an emerging parameter to assess “quality of BP control” by accumulated findings showing that hypertensive patients with similar 24-h average BP values exhibited more severe organ damage when the short-term BP variability was greater [11–13]. Thus, short-term BP variability is associated with cardiovascular injury and is one of important prognostic factors for CVD [14].

In this Yokohama Combined Treatment with Oriental Herb Randomized Efficacy on Obesity Hypertension (Y-CORE) Study, we aimed to investigate whether an integrative medicine approach which combined an oriental medicine (BOF) and western medicine (dietary therapy and antihypertensive drug administration) would exerts favorable effects on the ambulatory BP profile including BP variability in hypertensive patients with obesity more efficiently than the western approach alone.

2. Methods

2.1. Study design

The Y-CORE study was a multicenter, prospective, randomized, open-label, parallel-group controlled trial investigating the effects of an integrative medicine approach on hypertensive patients with obesity. It was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the independent ethics committee for each center. The Y-CORE study was registered at the Clinical Trial Registry of University Hospital Information Network (registration no. UMIN000003878).

2.2. Inclusion criteria

Hypertensive patients with obesity who had a history of antihypertensive treatment, including diet and exercise therapies for a period of more than 4 weeks, were eligible and recruited for the study if they were 20–79 years of age. Obesity was defined as a body mass index (BMI) of more than 25 kg/m^2. Exclusion criteria included severe hypertension (clinic systolic BP > 180 mmHg and/or diastolic BP > 110 mmHg), secondary hypertension, a history of CVD including stroke in the past 6 months, uncontrolled type 1 or type 2 diabetes ($HbA_{1c} \geq 9.0\%$), women who were nursing or pregnant, or treatment with other oriental herbal medicines.

All of the patients provided written informed consent before participation in the study, and follow-up was undertaken by each investigator.

2.3. Procedures

This multicenter, prospective, randomized, open-label, parallel-group controlled trial was conducted at five hospitals in Japan, and a central source allocated randomization using a computer-generated, stratified, permuted block method was applied. The block size was 4, and the stratification factors were sex and BMI. After the run-in period, eligible patients were randomly assigned (in a 1:1 allocation ratio) either to the BOF add-on therapy group (the BOF group) or the conventional control therapy group (the control group). The core study center was located at Yokohama City University.

In both groups, each patient received lifestyle education, including dietary guidance by a nutritionist for obesity related hypertension in order to restrict the energy intake according to their pathological conditions and needs (25–30 kcal/kg-standard body weight/day), and antihypertensive therapy was aimed at achieving the BP goal recommended in the guideline of the Japanese society of hypertension [15]. Patients in the BOF group were initially given 2.5 g of BOF once daily; the dose of BOF was titrated up to 7.5 g daily, as long as adverse effects appeared, during the 24-week active treatment period. Body weight, clinic BP, ambulatory BP, brachial-ankle pulse wave velocity (baPWV), laboratory measurements, adverse events, and patient's adherence to treatment regimens were estimated at baseline, and after 12 and 24 weeks of treatment.

2.4. Measurements

The clinic BP was measured in a sitting position using a calibrated standard mercury sphygmomanometer and the recommended cuff size. Two measurements were taken at 1–2 min intervals, and their average was regarded as the clinic BP.

The ambulatory BP and heart rate (HR) were measured every 30 min with a fully automated device (TM-2431; A&D, RAC-3502; NIHON KOHDEN, FB-270; FUKUDA DENSHI, Tokyo, Japan),

essentially as described previously [16–19]. The participants were instructed to fill out a diary to record the times of sleeping, rising and other daytime activities. Therefore, the terms “daytime” and “nighttime” in the present study reflect the average period during which the subjects were awake/upright and asleep/supine, respectively.

Short-term BP variability is estimated as the coefficients of variation (CV) of the BP values obtained from ambulatory BP monitoring, and is calculated as the within-subject standard deviation (SD) of all the systolic and diastolic readings divided by the average BP during the course of the measurement period. HR variability, which is composed of the CV of the HR values, is also calculated as the within-subject SD of all the HR values divided by the average HR. BP and HR artifacts during monitoring were defined according to the criteria reported in our previous studies and were omitted from the analysis [18,19].

The baPWV values were determined with a PP analyzer (model: BP-203RPE2; Omron Healthcare, Kyoto, Japan), as described previously [17,20]. Pulse volume waveforms were recorded with sensors placed over the right brachial artery and both tibial arteries. The baPWV values obtained by this method are reported to be significantly correlated with the aortic PWV determined by the catheter method [21].

2.5. Outcomes

The primary outcome was change in the ambulatory BP profile including short-term BP variability from baseline to 24 weeks after randomization. Changes in clinic BP, body weight, BMI, abdominal circumference, glucose-lipid metabolism, renal function, electrolytes, adipokine, oxidative stress, and baPWV from baseline to 24 weeks after randomization, and adverse events during the active treatment period were assessed as secondary outcomes.

2.6. Statistical analysis

The sample size was estimated with the following assumptions; α was set at 0.05, power at 80%, and the intergroup difference in changes of ambulatory short-term systolic BP variability (CV) at 1.7%. This value for the change in short-term systolic BP variability was calculated by multiplying the body weight reduction by the ratio of changes in short-term systolic BP variability to changes in body weight in our previous study [16]. Assuming a 20% dropout rate, a total sample size of n = 100 randomized participants was required.

An intention-to-treat analysis was performed, including 106 of the 107 randomized subjects while excluding one subject who did not meet the inclusion criteria (Supplemental Fig. 1). All of the analyses were performed using SPSS version 19.0 (IBM Corporation). To examine the effects of BOF treatment, the change values (absolute values after the 12 or 24 week study periods minus those at baseline) were used for analysis. Significant differences between the groups were assessed by unpaired *t*-test or nonparametric analysis using the Wilcoxon U test for variables that were normally distributed. Differences between the groups for categorical variables, such as medication or past medical history, were analyzed using the Chi-square test. Univariate and multivariate linear regression analyses were performed to identify the factors affecting changes in the daytime systolic BP variability. Age, gender, BOF usage and the variables, which were significantly associated in the univariate analysis or were significantly different between the groups after treatment, were entered into the multivariate model. The data are mean ± SD absolute values, changes from baseline at 12 and 24 weeks, or as a percentage, and a value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

A total of 107 hypertensive patients with obesity were screened for eligibility from June 2010 to March 2013. At the inclusion visit, one of them did not fulfill the selection criteria. 106 patients were thus enrolled and randomly assigned (54 to the BOF group, 52 to the control group; Supplemental Fig. 1). Of the enrolled participants, 5 patients in the control group and 8 patients in the BOF group dropped out after the 12-week treatment and, additionally, 1 patient in the control group and 6 patients in the BOF group dropped out after the 24 week treatment (Supplemental Fig. 1). Therefore, the data on 93 patients for the interim evaluation and 88 patients for the final evaluation were available for the analysis, respectively (Supplemental Fig. 1). The baseline characteristics of the patients are shown in Table 1. The mean age, BMI, and clinic BP of the 106 patients were 59.6 ± 13.7 years old, 30.9 ± 5.0 kg/m^2 and 143 ± 19/84 ± 13 mmHg, respectively. There were no significant differences in the baseline characteristics between the two groups (Table 1). Medication including the antihypertensive agents, oral glucose-lowering agents and lipid-lowering agents used at baseline and during the whole active treatment period were comparable in the two groups (Supplemental Table 2). The average dose of BOF was 6.8 ± 1.4 g per day after a period of 24 weeks of treatment.

3.2. Primary outcome

The effects on changes in ambulatory BP profile of BOF add-on therapy versus conventional therapy are shown in Table 2. At baseline, there were no significant differences in the ambulatory average BP level and ambulatory short-term BP variability, estimated as CV of the BP values obtained from ambulatory BP monitoring, between the two groups. In accord with the study protocol which was intended to achieve the same clinic BP goal in each group, the ambulatory average BP decreased to comparable levels in the two groups after a period of 24 weeks of treatment

Table 1
Baseline characteristics of the study groups.

	Control group	BOF group	*p*
Gender (male/female)	29/23	28/26	0.909
Age (year)	60.0 ± 12.9	59.2 ± 14.5	0.686
Height (cm)	160.9 ± 9.1	162.4 ± 8.6	0.546
Body weight (kg)	79.8 ± 17.3	82.5 ± 16.4	0.514
BMI (kg/m^2)	30.6 ± 4.9	31.3 ± 5.0	0.407
Abdominal circumference (cm)	101 ± 10	105 ± 12	0.063
Clinic systolic BP (mmHg)	144 ± 20	142 ± 19	0.733
Clinic diastolic BP (mmHg)	82 ± 15	85 ± 12	0.151
Smoke (%)	16	16	0.966
Alcohol (%)	48	31	0.088
Diabetes mellitus (%)	35	23	0.194
Lipid disorder (%)	69	71	0.830
Previous cardiovascular event (%)	2	6	0.317
Fasting plasma glucose (mg/dL)	124 ± 40	112 ± 27	0.129
HbA_{1c} (%)	6.1 ± 0.6	6.0 ± 0.6	0.212
Total cholesterol (mg/dL)	197 ± 32	203 ± 35	0.335
LDL-cholesterol (mg/dL)	113 ± 25	119 ± 31	0.309
HDL-cholesterol (mg/dL)	54 ± 15	57 ± 17	0.418
Triglycerides (mg/dL)	219 ± 213	185 ± 133	0.758
Serum creatinine (mg/dL)	0.85 ± 0.29	0.84 ± 0.31	0.810
eGFR (mL/min/1.73 m^2)	68.9 ± 17.9	71.4 ± 21.9	0.750
UACR (mg/g-Cr)	189.1 ± 437.2	153.4 ± 325.0	0.283

The values are presented as means ± SD or %. BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

Table 2
Comparison of ambulatory BP profile in the control and BOF groups.

	Baseline	12 weeks			24 weeks		
		After treatment	Change	*p*	After treatment	Change	*p*
Ambulatory BP and HR							
Daytime:							
Systolic BP (mmHg)							
Control group	143 ± 12	139 ± 13	−4 ± 12	0.870	136 ± 13	−7 ± 12	0.095
BOF group	140 ± 13	136 ± 12	−4 ± 15		136 ± 11	−3 ± 11	
Diastolic BP (mmHg)							
Control group	86 ± 8	83 ± 10	−2 ± 8	0.665	82 ± 9	−3 ± 7	0.045
BOF group	84 ± 10	81 ± 8	−3 ± 8		82 ± 8	−1 ± 6	
HR (beats/min)							
Control group	73 ± 9	73 ± 9	0 ± 6	0.737	72 ± 9	−1 ± 6	0.119
BOF group	75 ± 11	75 ± 13	0 ± 8		74 ± 13	1 ± 9	
Nighttime:							
Systolic BP (mmHg)							
Control group	128 ± 15	124 ± 16	−3 ± 13	0.692	122 ± 14	−6 ± 15	0.885
BOF group	128 ± 18	128 ± 13	−2 ± 21		123 ± 15	−6 ± 15	
Diastolic BP (mmHg)							
Control group	77 ± 10	73 ± 9	−3 ± 7	0.269	72 ± 9	−5 ± 8	0.195
BOF group	76 ± 10	75 ± 10	−1 ± 10		72 ± 9	−3 ± 7	
HR (beats/min)							
Control group	63 ± 8	63 ± 8	0 ± 5	0.878	63 ± 8	−1 ± 6	0.430
BOF group	64 ± 12	64 ± 12	0 ± 8		63 ± 12	1 ± 6	
Ambulatory BP and HR variability							
Daytime:							
Systolic BP variability (%)							
Control group	11.5 ± 3.4	13.0 ± 4.9	1.5 ± 4.6	0.226	12.3 ± 3.1	1.0 ± 3.3	0.006
BOF group	12.2 ± 3.3	12.7 ± 4.0	0.5 ± 3.7		11.4 ± 2.8	−1.0 ± 3.3	
Diastolic BP variability (%)							
Control group	13.8 ± 6.0	14.9 ± 6.1	1.4 ± 5.5	0.178	14.4 ± 4.5	0.9 ± 6.2	0.135
BOF group	15.4 ± 5.5	15.1 ± 5.6	−0.1 ± 5.2		14.8 ± 5.9	−1.1 ± 6.4	
HR variability (%)							
Control group	14.6 ± 6.6	13.3 ± 4.7	−1.2 ± 6.9	0.946	12.4 ± 4.4	−2.3 ± 7.7	0.386
BOF group	16.1 ± 6.8	14.7 ± 5.7	−1.3 ± 6.9		15.7 ± 5.2	−0.9 ± 6.7	
Nighttime:							
Systolic BP variability (%)							
Control group	10.7 ± 3.5	10.6 ± 3.6	−0.3 ± 4.1	0.249	10.8 ± 3.0	0.2 ± 4.6	0.885
BOF group	10.2 ± 4.0	10.5 ± 4.1	0.8 ± 4.2		10.8 ± 3.9	1.1 ± 4.7	
Diastolic BP variability (%)							
Control group	13.4 ± 5.3	12.5 ± 3.9	−0.8 ± 4.7	0.605	12.6 ± 4.3	−0.4 ± 5.6	0.199
BOF group	12.1 ± 4.3	11.5 ± 4.3	−0.2 ± 5.7		13.0 ± 4.6	1.1 ± 5.5	
HR variability (%)							
Control group	7.7 ± 3.1	7.1 ± 3.2	−0.3 ± 3.5	0.372	8.1 ± 2.7	0.6 ± 3.4	0.737
BOF group	8.1 ± 3.7	8.3 ± 3.0	0.3 ± 3.7		9.1 ± 4.9	0.9 ± 4.6	

The values are presented as means ± SD. BP, blood pressure; HR, heart rate.

(Control vs BOF; daytime ambulatory average BP, 136 ± 13/82 ± 9 vs 136 ± 11/82 ± 8 mmHg; nighttime ambulatory average BP, 122 ± 14/72 ± 9 vs 123 ± 15/72 ± 9 mmHg; Table 2). Concerning the changes from baseline in the ambulatory average BP level by the respective treatments, the magnitude of decrease in the daytime diastolic BP was significantly smaller in the BOF group than in the control group after a period of 24 weeks of treatment (Control vs BOF; change in daytime diastolic BP, −3 ± 7 vs −1 ± 6 mmHg, $p = 0.045$; Table 2).

However, with respect to the effects on changes in ambulatory short-term BP variability of BOF add-on therapy versus conventional therapy, the daytime systolic BP variability was decreased only in the BOF group at 24 weeks and the difference was statistically significant between the BOF and control groups (Control vs BOF; change from baseline in daytime systolic BP variability, 1.0 ± 3.3 vs −1.0 ± 3.3%, $p = 0.006$; Table 2). In addition, the daytime diastolic BP variability was similarly decreased only in the BOF group at 24 weeks, but the difference did not reach the significance between the BOF and control groups (Control vs BOF; change from baseline in daytime diastolic BP variability, 0.9 ± 6.2 vs −1.1 ± 6.4%, $p = 0.135$; Table 2).

3.3. Secondary outcomes

As shown in Supplemental Table 3, there were no significant differences in the clinic BP or baPWV between the two groups at baseline. Concerning the changes from baseline in the clinic BP or baPWV by the respective treatments as additional efficacy outcomes, there were also no significant differences in the changes from baseline in the clinic BP or baPWV between the two groups during the active treatment period (Supplemental Table 3).

Table 3 summarizes the differences in the anti-obesity effect between groups as the additional efficacy outcomes. Although each patient received lifestyle education, including dietary guidance by a nutritionist for obesity related hypertension in order to restrict the energy intake according to their pathological conditions and needs (25–30 kcal/kg-standard body weight/day) in both groups, the BOF add-on therapy efficiently reduced body weight and BMI at 12 and 24 weeks, and the differences were statistically significant between the BOF and control groups for both measures (Control vs BOF; change from baseline in body weight, −1.2 ± 2.6 vs −2.8 ± 3.5 kg, $p = 0.023$; change from baseline in BMI, −0.5 ± 1.0 vs −1.1 ± 1.3 kg/m^2, $p = 0.029$; Table 3). Although abdominal circumference exhibited a similar tendency of change at 24 weeks, the difference

Table 3
Comparison of body weight, BMI and abdominal circumference in the control and BOF groups.

	Baseline	12 weeks			24 weeks		
		After treatment	Change	*p*	After treatment	Change	*p*
Body weight (kg)							
Control group	79.8 ± 17.3	78.9 ± 17.4	−0.8 ± 2.5	0.007	78.3 ± 17.9	−1.2 ± 2.6	0.023
BOF group	82.5 ± 16.4	80.5 ± 15.6	−2.0 ± 2.7		79.6 ± 15.4	−2.8 ± 3.5	
BMI (kg/m^2)							
Control group	30.6 ± 4.9	30.1 ± 5.0	−0.3 ± 0.9	0.005	29.9 ± 5.2	−0.5 ± 1.0	0.029
BOF group	31.3 ± 5.0	30.3 ± 4.9	−0.8 ± 1.0		30.3 ± 4.9	−1.1 ± 1.3	
Abdominal circumference (cm)							
Control group	101 ± 10	100 ± 13	−3 ± 4	0.760	100 ± 12	−2 ± 6	0.053
BOF group	105 ± 12	103 ± 12	−3 ± 5		102 ± 11	−4 ± 6	

The values are presented as means ± SD. BMI, body mass index.

Table 4
Comparison of laboratory measurements in the control and BOF groups.

	Baseline	12 weeks			24 weeks		
		After treatment	Change	*p*	After treatment	Change	*p*
Glucose-lipid metabolism:							
Fasting plasma glucose (mg/dL)							
Control group	124 ± 4	118 ± 31	−3 ± 33	0.460	112 ± 27	−9 ± 33	0.161
BOF group	112 ± 27	108 ± 25	−5 ± 17		112 ± 28	−1 ± 14	
HbA_{1c} (%)							
Control group	6.1 ± 0.6	6.1 ± 0.6	0.0 ± 0.3	0.038	6.0 ± 0.7	−0.1 ± 0.4	0.103
BOF group	6.0 ± 0.6	5.9 ± 0.6	−0.1 ± 0.2		5.9 ± 0.6	−0.2 ± 0.3	
Total cholesterol (mg/dL)							
Control group	197 ± 32	192 ± 34	−4 ± 23	0.397	195 ± 31	−1 ± 28	0.556
BOF group	203 ± 35	203 ± 33	−1 ± 21		197 ± 32	−4 ± 28	
LDL-cholesterol (mg/dL)							
Control group	113 ± 25	113 ± 25	0 ± 18	0.794	110 ± 24	−2 ± 24	0.754
BOF group	119 ± 31	121 ± 31	2 ± 19		117 ± 27	−1 ± 23	
HDL-cholesterol (mg/dL)							
Control group	54 ± 15	53 ± 14	0 ± 6	0.587	56 ± 15	3 ± 7	0.776
BOF group	57 ± 17	58 ± 15	1 ± 8		61 ± 17	2 ± 7	
Triglycerides (mg/dL)							
Control group	219 ± 213	179 ± 141	−45 ± 208	0.818	193 ± 18	−32 ± 214	0.399
BOF group	185 ± 133	159 ± 79	−25 ± 128		137 ± 53	−31 ± 78	
Renal function:							
Serum creatinine (mg/dL)							
Control group	0.85 ± 0.29	0.84 ± 0.20	−0.02 ± 0.12	0.749	0.83 ± 0.28	−0.03 ± 0.13	0.920
BOF group	0.84 ± 0.31	0.81 ± 0.27	−0.02 ± 0.10		0.80 ± 0.27	−0.03 ± 0.12	
eGFR (mL/min/1.73 m^2)							
Control group	68.9 ± 17.9	73.5 ± 37.1	5.2 ± 32.1	0.517	70.5 ± 19.5	2.5 ± 9.6	0.825
BOF group	71.4 ± 21.9	69.3 ± 26.6	−2.7 ± 22.1		73.8 ± 24.3	2.8 ± 9.8	
UACR (mg/g-Cr)							
Control group	189.1 ± 437.2	138.5 ± 392.1	−25.2 ± 282.5	0.896	132.0 ± 362.8	−35.3 ± 312.5	0.524
BOF group	153.4 ± 325.0	159.8 ± 328.5	−7.0 ± 171.5		191.2 ± 408.9	25.4 ± 209.6	
Adipokine and oxidative stress:							
Adiponectin (μg/mL)							
Control group	3.3 ± 3.0	3.1 ± 2.2	0.0 ± 1.2	0.574	3.2 ± 2.1	−0.1 ± 1.6	0.546
BOF group	3.4 ± 2.0	3.7 ± 2.1	0.1 ± 0.8		4.0 ± 2.3	0.3 ± 1.0	
Resistin (ng/mL)							
Control group	6.4 ± 4.8	6.2 ± 4.4	−0.2 ± 2.3	0.146	5.8 ± 3.5	−0.5 ± 2.5	0.015
BOF group	5.6 ± 2.4	5.9 ± 2.7	0.4 ± 1.4		5.9 ± 2.9	0.6 ± 1.5	
MDA-LDL (U/l)							
Control group	124 ± 35	121 ± 33	−3 ± 33	0.311	119 ± 30	−6 ± 37	0.044
BOF group	126 ± 51	126 ± 46	−1 ± 43		129 ± 40	4 ± 43	
Pentosidine (ng/mL)							
Control group	24 ± 9	27 ± 10	3 ± 11	0.771	28 ± 13	5 ± 14	0.473
BOF group	30 ± 30	31 ± 19	0 ± 18		30 ± 16	−2 ± 31	
Urinary L-FABP (μg/g-Cr)							
Control group	10.6 ± 20.4	7.2 ± 9.5	−2.7 ± 20.7	0.870	7.6 ± 8.6	−2.4 ± 19.5	0.682
BOF group	6.7 ± 6.4	7.6 ± 6.9	0.3 ± 5.6		9.5 ± 13.8	2.2 ± 13.0	
Urinary 8-OHdG (μg/g-Cr)							
Control group	4.7 ± 2.6	4.0 ± 1.9	−0.6 ± 2.5	0.041	5.1 ± 3.5	0.4 ± 3.8	0.171
BOF group	4.5 ± 2.4	4.9 ± 2.3	0.3 ± 2.3		5.9 ± 3.1	1.3 ± 3.3	

The values are presented as means ± SD. Δ means the change from baseline. LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; MDA-LDL, malondialdehyde-modified low-density lipoprotein; L-FABP, liver-type fatty acid binding protein; 8-OHdG, 8-hydroxydeoxyguanosine.

between the BOF and control groups did not reach significance (Control vs BOF; change from baseline in abdominal circumference, −2 ± 6 vs −4 ± 6 cm, $p = 0.053$; Table 3).

The effects of BOF add-on therapy on glucose-lipid metabolism, renal function, adipokine level, and oxidative stress as additional efficacy outcomes are summarized in Table 4. At baseline, there were no significant differences in the laboratory measurements between the two groups. BOF add-on therapy reduced HbA_{1c} at 12 and 24 weeks, and the change at 12 weeks from baseline in HbA_{1c} was statistically significant (Control vs BOF; change from baseline in HbA_{1c}, 0.0 ± 0.3 vs −0.1 ± 0.2%, $p = 0.038$; Table 4), with a non-significant difference in the change at 24 weeks (Control vs BOF; change from baseline in HbA_{1c}, −0.1 ± 0.4 vs −0.2 ± 0.3%, $p = 0.103$; Table 4). However, BOF add-on therapy exerted no evident effects on serum insulin level and HOMA-IR (data not shown). On the other hand, BOF add on therapy did not affect the change in lipid metabolism. Also, the renal function parameters including serum creatinine, estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR) were comparable in the two groups during the entire active treatment period (Table 4).

With respect to adipokine and inflammatory markers, while there was no significant change in the adiponectin level between the two groups, the resistin level was significantly elevated in the BOF group compared with the control group after a period of 24 weeks of treatment (Control vs BOF; change from baseline in resistin, −0.5 ± 2.5 vs 0.6 ± 1.5 ng/mL, $p = 0.015$; Table 4). In addition, the BOF add on therapy significantly increased the malondialdehyde low-density lipoprotein (MDA-LDL) level, an oxidative stress marker, compared with the control group after 24 week treatment (Control vs BOF; change from baseline in MDA-LDL, −6 ± 37 vs 4 ± 43 U/l, $p = 0.044$; Table 4). Furthermore, the change in the urinary 8-hydroxydeoxyguanosine (8-OHdG) level in the BOF group was significantly higher than the control group after a period of 12 weeks of treatment (Control vs BOF; change from baseline in urinary 8-OHdG, −0.6 ± 2.5 vs 0.3 ± 2.3 μg/g-Cr, $p = 0.041$; Table 4).

3.4. Exploratory analysis of contributing factors to change in ambulatory short-term BP variability

To identify the factors affecting the beneficial change in ambulatory BP variability, we performed multivariate linear regression analysis. In the univariate analysis, BOF usage and the change in serum creatinine were significantly correlated with the change in daytime systolic BP variability (Table 5). Thus, we entered six variables, including age, sex, BOF usage, and the changes in serum creatinine, BMI, and daytime systolic BP level, into the multivariate analysis. The results of the multivariate linear regression analysis in all patients indicated a significant association between the change in daytime systolic BP variability and the BOF usage (Table 5). In addition, the change in serum creatinine was also significantly associated with the change in daytime systolic BP variability.

Table 5
Univariate and multivariate linear regression analysis of the change in daytime systolic BP variability.

Variables	Univariate		Multivariate	
	ρ	p	β	p
Age	−0.073	0.502	−0.094	0.373
Sex	0.056	0.606	−0.011	0.921
BOF add-on therapy group	−0.296	0.006	−0.298	0.008
Change in daytime systolic BP level	−0.092	0.400	−0.105	0.334
Change in BMI	0.088	0.424	0.062	0.572
Change in HbA_{1c}	0.035	0.746		
Change in serum creatinine	−0.275	0.010	−0.244	0.022
Change in resistin	−0.149	0.180		
Change in MDA-LDL	0.141	0.204		
Change in urinary 8-OHdG	0.067	0.545		
			$R^2 = 0.185$	

BP, blood pressure; BMI, body mass index; MDA-LDL, malondialdehyde-modified low-density lipoprotein; 8-OHdG, 8-hydroxydeoxyguanosine.

3.5. Tolerability

While there were no adverse events reported in the control group, 3 patients in the BOF group experienced minor adverse events (gastric irritation, constipation, and elevation of serum hepatic enzyme level). No electrolyte abnormality was observed in any of the patients during the active treatment period.

4. Discussion

This is the first report, to the best of our knowledge, suggesting that integrative medicine which is defined as a combination therapy of oriental medicine and western medicine (in this case, BOF add-on therapy) is able to exert greater beneficial effects than conventional western therapy alone, based on “out-of-clinic” ambulatory BP profile (i.e. ambulatory BP variability) in hypertensive patients with obesity (Table 2). In the present study, it was demonstrated that the BOF add-on therapy, compared with the conventional therapy, significantly improved short-term BP variability on ambulatory BP monitoring (Table 2), in addition to an anti-obesity effect (reduction in both body weight and BMI) (Table 3). Furthermore, on multivariate analysis, BOF usage was independently associated with the improvement in ambulatory BP variability, in spite of there being no significant relationship to the changes in the BP level or BMI (Table 5). These results suggest that, in obesity-related hypertension, BOF may exert a beneficial effect on short-term BP variability that is independent of the reductions in body weight and/or average BP level.

Previous studies have shown that the average BP level is the primary BP-related risk factor for CVD and an appropriate BP reduction is essential to both prevent target organ damage and reduce cardiovascular mortality in cases of hypertension [22]. With respect to direct BP lowering capacity of BOF, since the medication status of the antihypertensive agents used was comparable in the two treatment groups during the entire treatment period and antihypertensive agents were increased similarly in both groups to achieve the target clinic BP level (Supplemental Table 2), the direct effect of BOF on average BP lowering may be weak.

On the other hand, accumulating evidence has indicated that the adverse cardiovascular consequences of high BP not only depend on absolute BP values, but also on BP variability in the short- and long-term [23]. Indeed, observational studies have demonstrated that an increased short-term BP variability estimated by ambulatory BP monitoring is closely associated with the development, progression and severity of cardiac, vascular and renal organ damage [12,13,24–28]. The enhanced short-term BP variability was also shown to be associated with an increased risk of CVD and mortality independently adding to CVD risk, over and above the contribution of elevated mean BP levels [11,29,30]. Although the relative importance of short-term BP variability on ambulatory BP monitoring as an independent prognostic factor of CVD and mortality is still controversial [14,31,32], a recent longitudinal study reported that even small increase in short-term BP variability is significantly associated with enhanced risk of CVD and mortality in 7112 hypertensive patients [33]. From these results of accumulated evidence we would like to consider that antihypertensive treatment should target improvements in short-term BP variability on ambulatory BP monitoring, in addition to reducing

absolute BP levels, in order to achieve the highest cardiovascular protection in hypertensive patients, and BOF may be one of possible candidates to improve short-term BP variability in hypertension with obesity.

With respect to the mechanism of BOF-mediated improvement in short-term BP variability, it is widely reported that obesity is one of the contributing factors to increased short-term BP variability [34] and it is also reported that reduction in body weight associated with an improvement in BP profile in obese patients [35,36]. Therefore, the anti-obesity effects (reduction in body weight and BMI) by the BOF add-on therapy may have contributed to the improvement in ambulatory short-term BP variability in the present study. However, in the present study there was no significant relationship between the reduction in BMI and the improvement in short-term BP variability on univariate analysis (Table 5). Therefore, it is also possible that BOF further improved the effect on short-term BP variability, which is not mediated by its anti-obesity effect. Collectively, the BOF-mediated effect on ambulatory BP variability, rather than a direct BP lowering effect, appears to improve the "quality" of BP management of obesity-related hypertension.

In the present study, the BOF add-on therapy accelerated the body weight reduction (Table 3) and exerted a more favorable effect on glucose metabolism than the conventional therapy group (Table 4). These results are consistent with a previous clinical study demonstrating that treatment with BOF was effective in decreasing visceral fat and in improving glucose metabolism in obese Japanese women [37]. Since BOF add-on therapy reduced HbA1c level (Table 4) but exerted no evident effects on serum insulin level and HOMA-IR (data not shown), further study is needed to examine beneficial effects of BOF on insulin sensitivity and related parameters such as leptin in obesity hypertension.

On the other hand, there were several unexpected findings concerning the BOF-mediated changes in inflammatory adipokines and markers of oxidative stress. The inflammatory adipokine resistin and the oxidative stress markers MDA-LDL and urinary 8-OHdG have been reported to be associated with cardiovascular risk factors, including obesity and hypertension [38–41]. In the present study, resistin, MDA-LDL, and urinary 8-OHdG in the BOF add-on therapy group were significantly elevated compared with the conventional therapy group (Table 4), in spite of the efficient reduction in body weight and BMI in the BOF group. However, there are several interesting preceding studies showing that the body weight reduction exerted by dietary therapy and/or exercise guidance resulted in increases in the circulating resistin concentration and urinary 8-OHdG level [42–47]. Therefore, the causal relationship between body weight reduction and changes in the inflammatory adipokines and markers of oxidative stress remains to be determined in the pathophysiology of obesity related hypertension.

The limitations of the present study include the design not being a double-blinded placebo-controlled study. Also, further studies with a longer treatment period are needed to investigate whether the beneficial effects of BOF on ambulatory BP variability would be maintained with continued benefit for the cardiovascular function parameters without serious adverse events. In addition, the R^2 level in the multivariate analysis was relatively low ($R^2 = 0.185$) (Table 5) and the mechanism of the beneficial effect of BOF on ambulatory BP variability remains to be determined. Since the improvement in short-term BP variability conferred by BOF add-on therapy on short-term BP is independent of its anti-obesity effect and BP reduction, other factors such as its putative effects on vasoactive substance, endothelial function and/or renal sodium handling would be possible candidates involved [48,49]. We indeed reported that the BOF-mediated improvement in adipose tissue function by amelioration of adipokine dysregulation as well as the reduction of food intake by the appetite-inhibitory property of BOF through suppression on the ghrelin system contribute to the BP lowering effect and favorable metabolic modulation by BOF in a mouse model of human metabolic disorders with obesity [7]. Nevertheless, as a major limitation of the present study, the mechanism whereby BOF improved short-term BP variability is still not clear. Therefore, further experimental results and clinical trials that support the hypothesis and elucidate the mechanism whereby BOF improves short-term BP variability in hypertension with obesity.

Furthermore, the present study did not intend to examine the effects of the individual components of BOF on BP profile in the participants. A recent case report showed that ephedrine, a component of BOF, could induce pulmonary arterial hypertension [50] and it would be possible that BOF treatment may exert the adverse effects caused via the enhanced sympathetic nerve activity by ephedrine. However, no patients in the BOF group reported symptoms related to activation of sympathetic nerve activity, such as palpitation, and changes in BP and HR were comparable in the two groups after the treatment. These results suggest that the clinical dose of BOF may not exert the adverse effects caused by activation of sympathetic nerve due to relatively few contents of ephedrine in BOF. Nevertheless, the target mechanism of oriental herbal formulas at the level of each active ingredient for hypertension is an important issue for the development of antihypertensive drugs based on oriental herbal medicine. Therefore, further basic and clinical studies are warranted to investigate the role of each component of BOF in its clinical efficacy.

In conclusion, the BOF add-on therapy effectively improved the ambulatory short-term BP variability, concomitantly with its anti-obesity effects. Therefore, the integrative medicine approach used here, employing this oriental herbal medicine, appeared to improve the ambulatory BP variability in obesity related hypertension better than conventional therapy by western medicine alone.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.025.

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