



Waon Therapy for Managing Chronic Heart Failure – Results From a Multicenter Prospective Randomized WAON-CHF Study –

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Background: Waon therapy improves heart failure (HF) symptoms, but further evidence in patients with advanced HF remains uncertain.

Methods and Results: In 19 institutes, we prospectively enrolled hospitalized patients with advanced HF, who had plasma levels of B-type natriuretic peptide (BNP) >500 pg/ml on admission and BNP >300 pg/ml regardless of more than 1 week of medical therapy. Enrolled patients were randomized into Waon therapy or control groups. Waon therapy was performed once daily for 10 days with a far infrared-ray dry sauna maintained at 60°C for 15 min, followed by bed rest for 30 min covered with a blanket. The primary endpoint was the ratio of BNP before and after treatment. In total, 76 Waon therapy and 73 control patients (mean age 66 years, men 61%, mean plasma BNP 777 pg/ml) were studied. The groups differed only in body mass index and the frequency of diabetes. The plasma BNP, NYHA classification, 6-min walk distance (6MWD), and cardiothoracic ratio significantly improved only in the Waon therapy group. Improvements in NYHA classification, 6MWD, and cardiothoracic ratio were significant in the Waon therapy group, although the change in plasma BNP did not reach statistical significance. No serious adverse events were observed in either group.

Conclusions: Waon therapy, a holistic soothing warmth therapy, showed clinical advantages in safety and efficacy among patients with advanced HF. (*Circ J* 2016; **80**: 827–834)

Key Words: Advanced heart failure; B-type natriuretic peptide; Nitric oxide; Vascular failure; Waon therapy

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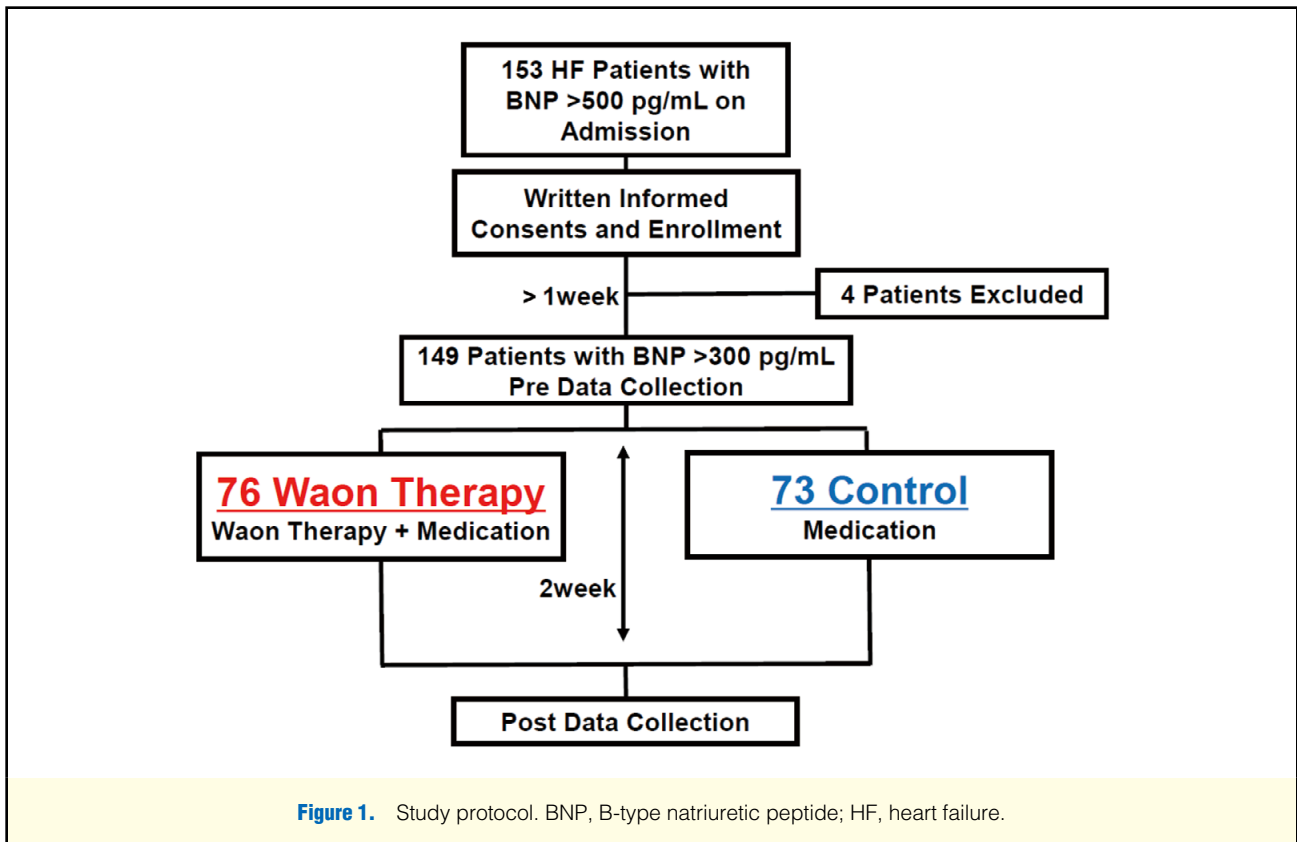
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The full list of WAON-CHF study investigators is provided in the [Appendix](#).

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Despite the development of pharmacological and surgical treatments, in the 21st century the number of patients with advanced heart failure (HF) is constantly increasing.^{1,2} However, these treatments are often painful and stressful and can depress patients.^{3,4}

In Japan, Waon therapy^{5–7} has been commonly used to treat such patients for >20 years. It is indicated as Class I for patients with chronic HF in the Japanese guideline.⁸ In Japanese, Waon means “soothing warmth or comfortable warmth that refreshes the patients’ mind and body”.⁶ In Waon therapy, the body is warmed in an evenly heated chamber for 15 min at 60°C. After the core body temperature has increased by approximately 1.0–1.2°C, the warmth is retained by covering the patient for an additional 30 min, and finally, the patient drinks cold water corresponding to the amount of perspiration.⁹

Data for Waon therapy have accumulated. It has been shown to reduce preload and afterload through peripheral vasodilation,^{9–12} to improve the autonomic nervous system,¹³ to reduce oxidative stress,¹⁴ and to improve endothelial function through increases in endothelial nitric oxide (NO) synthase and NO production.^{9–15} Cardiac event rate, ventricular arrhythmias,¹⁶ HF symptoms, quality of life,¹⁷ and exercise tolerance¹⁵ can all be improved with Waon therapy.^{14–20}

We have previously demonstrated the safety and efficacy of Waon therapy through a prospective case-control study of patients with mild to moderate HF,²¹ but a randomized study has been required. We therefore conducted a multi-center prospective randomized control study in patients with advanced HF.

Methods

Patient Selection

We enrolled 153 in-hospital patients with advanced HF with New York Heart Association (NYHA) classification II–IV, who had plasma levels of B-type natriuretic peptide (BNP) >500 pg/ml on admission in 19 noted Japanese institutes between 2011 and 2014. Patients fulfilling the following criteria were excluded: (1) serum creatinine level >2.0 mg/dl, (2) macroproteinuria, (3) de novo HF (no history of hospitalization for HF), (4) aortic valve stenosis or obstructive hypertrophic cardiomyopathy with pressure gradient ≥50 mmHg, (5) active infection, (6) history of myocardial infarction or stroke within previous 6 months, (7) malignancy within 5 years, (8) hemodialysis, and (9) body weight ≥135 kg.

Written informed consent was given by all participants before the enrollment and the ethics committee of each institute approved the study protocol beforehand.

Patients with BNP >300 pg/ml for at least >1 week with in-hospital medical therapy were randomly assigned to the Waon therapy or control group in each institutes. Patients in the control group continued the optimal medical therapy during the 2-week study period. All randomization was performed by the minimization method considering adjustment factors, including institutions, sex (male or female), and NYHA class (II and III vs. IV), at the Japan Clinical Research Support Unit.

The following therapies were prohibited during the study period: cardiac rehabilitation and mechanical support (including respirator, intra-aortic balloon pumping, percutaneous cardiopulmonary support, and ventricular assist device). The

Table 1. Baseline Characteristics of Patients With Chronic Heart Failure

	Total (n=149)	Waon therapy (n=76)	Control (n=73)	P value
Demographics				
Male, n (%)	91 (61)	47 (62)	44 (60)	0.8679
Age, years	66±16	66±16	66±15	0.9231
BMI	21.4±4.1	20.6±3.9	22.1±4.7	0.0346*
Ischemic etiology, n (%)	42 (28)	20 (26)	22 (30)	0.757
Atrial fibrillation, n (%)	36 (24)	18 (26)	18 (26)	0.986
NYHA class				0.817
II, n (%)	63 (42)	33 (43)	30 (41)	–
III, n (%)	68 (46)	35 (46)	33 (45)	–
IV, n (%)	18 (12)	8 (11)	10 (14)	–
Concomitant diseases				
Diabetes, n (%)	50 (34)	19 (25)	31 (43)	0.0257†
Hypertension, n (%)	62 (42)	33 (43)	29 (40)	0.7399
Dyslipidemia, n (%)	59 (40)	28 (37)	31 (43)	0.5068
Concomitant medications				
ACEI, n (%)	84 (56)	44 (58)	40 (55)	0.876
ARB, n (%)	38 (26)	18 (24)	20 (27)	0.756
CCB, n (%)	20 (13)	10 (13)	10 (14)	0.768
PDE III inhibitor, n (%)	42 (28)	23 (30)	19 (26)	0.875
β-blocker, n (%)	129 (87)	65 (86)	64 (88)	0.934
Diuretics, n (%)	146 (98)	74 (97)	72 (99)	0.934
Intravenous Inotropes (%)	25 (17)	11 (15)	14 (19)	0.897
Duration of heart failure				
<3 months	13 (9)	5 (8)	8 (13)	–
3–6 months	9 (6)	6 (9)	3 (5)	–
6–12 months	10 (7)	6 (9)	4 (6)	–
1–2 years	6 (4)	3 (5)	3 (5)	–
2–3 years	13 (9)	6 (9)	7 (11)	–
3–5 years	16 (11)	9 (14)	7 (11)	–
>5 years	61 (41)	29 (45)	32 (50)	–
Concomitant device therapy				
ASV, n (%)	2 (1)	1 (1)	1 (1)	0.999
CRT-P, n (%)	4 (3)	1 (1)	3 (4)	0.925
CRT-D, n (%)	30 (20)	14 (18)	16 (22)	0.966
ICD, n (%)	5 (3)	2 (2)	3 (4)	0.754
Pacemaker, n (%)	14 (9)	7 (9)	7 (10)	0.879

*P<0.05 with unpaired t-test; †P<0.05 with chi-square test. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ASV, adaptive servo-ventilator; BMI, body mass index; CCB, calcium-channel blocker; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacing; ICD, intracardiac defibrillator; NYHA, New York Heart Association; PDE, phosphodiesterate.

doses of anti-HF agents were fixed during the study period in both groups.

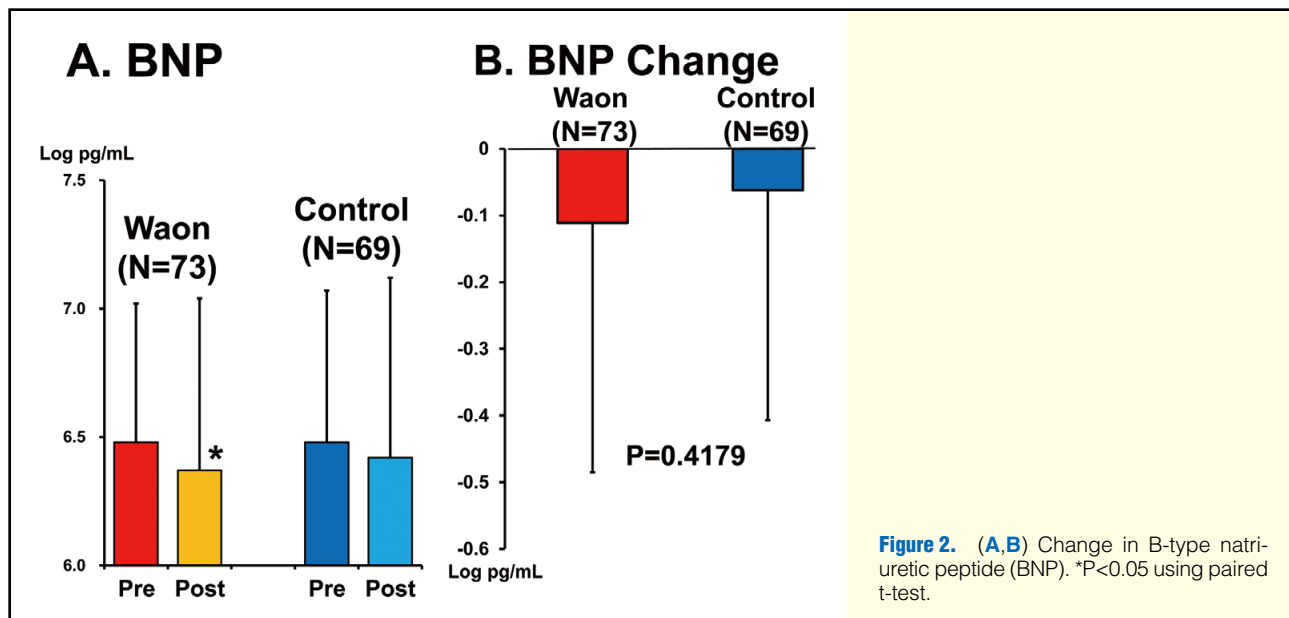
Waon Therapy

Waon therapy uses a far infrared-ray dry sauna (Waon therapy equipment), which is uniformly maintained at 60°C, and was performed as previously reported.²¹ Patients remained seated for 15 min, and then rested supine while covered with a warm blanket for an additional 30 min. All participants were weighed before and after the Waon therapy, and oral hydration with cold water was provided to compensate for the weight loss from perspiration. Waon therapy was performed once daily, 5 days each week for 2 weeks, for a total of 10 sessions. The endpoints were assessed at 2 weeks after the initiation of Waon therapy.

Baseline Variables and Endpoints

Patient data, blood test results, urinalysis results, ECGs, chest radiographic, and echocardiographic data as well as the 6-min walk distance (6MWD) were obtained <24h before the randomization.

The primary endpoint was changes in the logarithm of BNP before and after the study period, which was compared between groups. The secondary endpoints were changes in NYHA class, 6MWD, cardiothoracic ratio, left ventricular ejection fraction (LVEF), heart rate, existence of arrhythmia and bundle branch block, and the rate of adverse events. LVEF was calculated by the modified Simpson method. All endpoints were assessed at 2 weeks after the randomization.



Statistical Analysis

Analysis of the study population was performed by intention-to-treatment. The summary statistics of the continuous parameters are shown as mean±SD. If the data showed skewed distribution, they were logarithmically transformed. Statistical comparison was performed within the data: in continuous data with the paired t-test, in categorical data with the Wilcoxon signed rank test, and in 2*2 data with the Fisher's exact test. For between-group comparisons, continuous data used Student's t-test, and categorical data used the Wilcoxon test. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). Statistical tests were 2-tailed, and P<0.05 was considered significant.

Results

Baseline Characteristics

Among 153 patients, 4 were excluded based on the predetermined criteria (macroproteinuria, 1; undergoing cardiac rehabilitation, 1; active malignancy, 2). Finally, 76 patients were assigned to the Waon therapy group, and the remaining 73 were assigned to the control group (Figure 1).

Patients' baseline characteristics are shown in Table 1. Of these 149 patients, 91 (61%) were male, and the mean age was 66±16 years. Most of patients (88%) were NYHA class II or III, and all patients had received optimal medical or device therapy. Many of the patients (75%) had been suffering from HF for >1 year (ischemic cardiomyopathy, 42; hypertrophic cardiomyopathy, 9; dilated cardiomyopathy, 65; other, 33).

There were no significant differences in the background data between the Waon therapy group and the control group except for body mass index and the complication of diabetes (Table 1).

Efficacy of Waon Therapy

As for the primary endpoint, the logarithmic value of plasma BNP level decreased significantly in the Waon therapy group (P=0.0135), but remained unchanged in the control group during the 2-week study period (P=0.1422) (Figure 2A). However, there were no significant differences in the changes

in the logarithm of BNP between the 2 groups (Figure 2B, P=0.4179).

NYHA class remained unchanged in the control group, but improved significantly in the Waon therapy group (Figure 3A). NYHA class significantly improved in the Waon therapy group compared with the control group (Figure 3B). The 6MWD and cardiothoracic ratio did not improve after 2 weeks of medication in the control group, but both improved significantly after 2 weeks of Waon therapy with medication (Figures 4,5). Furthermore, the improvement in 6MWD and cardiothoracic ratio was greater in the Waon therapy group compared with the control group (Table 2).

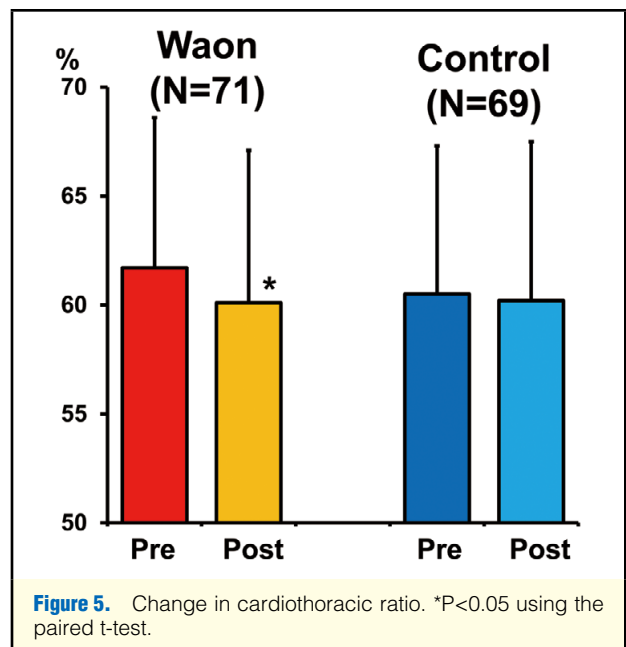
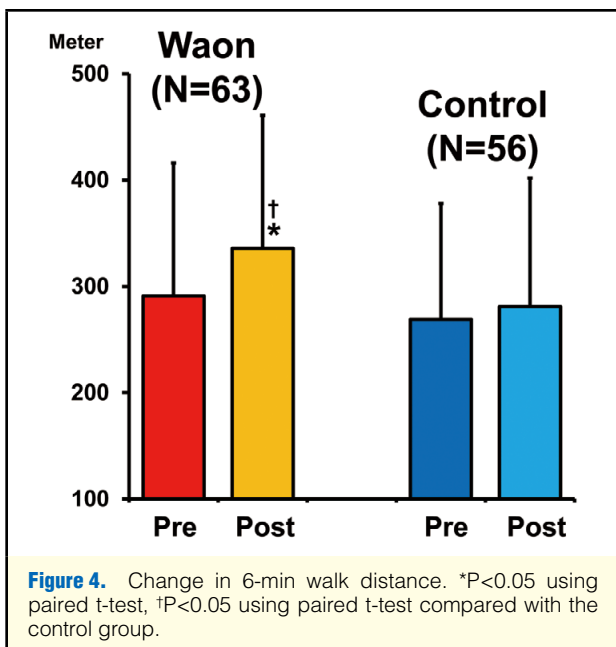
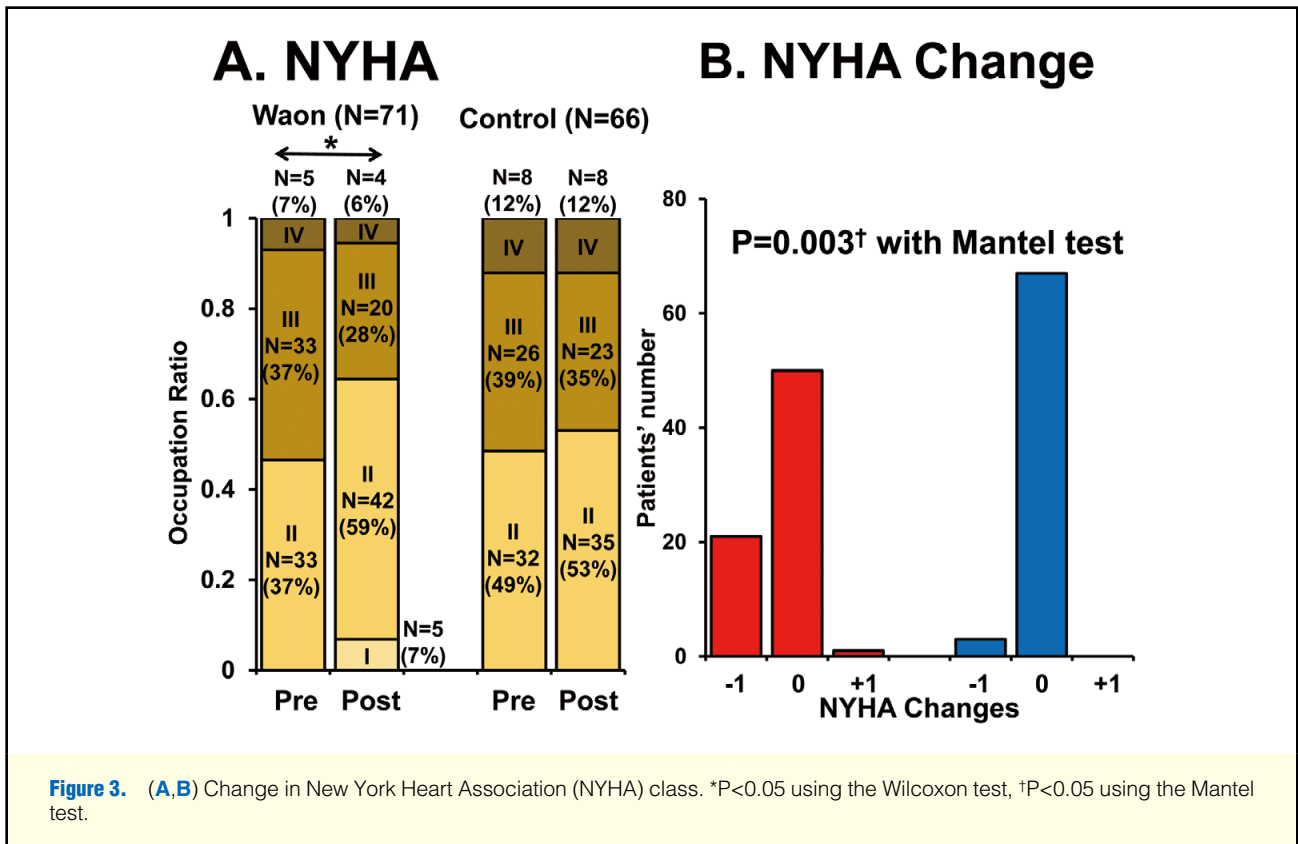
Safety of Waon Therapy

No fatal events or deaths occurred during the study period in either group. Paroxysmal atrial fibrillation occurred in a patient in the Waon therapy group. No patient in either group suffered de novo bundle branch block during the study period.

There were no significant differences in the prevalence of adverse events between the Waon therapy group and the control group (17 [22%] vs. 11 [15%], P=0.2962). Among them, 7 patients experienced Waon therapy-related adverse events: decrease in blood pressure (2); hypovolemia (2); increase in urine volume (1); decrease in body weight (1); bleeding after tooth extraction (1).

Discussion

We performed for the first time a multicenter prospective randomized control study consisting of a Waon therapy group (n=76) and a control group (n=73) of patients with advanced HF. Although the primary endpoint did not meet statistical significance, plasma BNP levels decreased significantly in the Waon therapy group, and the secondary endpoints, including NYHA class, 6MWD, and cardiothoracic ratio, also improved significantly in the Waon therapy group. Furthermore, these secondary endpoints showed a statistically significant improvement in the Waon therapy group compared with the control group. In contrast, none of clinical data improved in the control group, suggesting severity of the background HF. The



prevalence of adverse events was comparable between groups, and no serious events occurred during Waon therapy.

Safety of Waon Therapy in Patients With Advanced HF

Although we have previously demonstrated the safety of Waon therapy in a prospective case-control study⁸ and a cross-

over trial,²² the safety in patients with advanced HF has been hitherto unknown. We demonstrated in the present study that Waon therapy could be performed as safely as the prevalent optimal medical therapy. Patients with advanced HF are at high risk of adverse events because of unstable hemodynamics and cardiac cachexia.¹ Many invasive treatments, including

Table 2. Changes in the Study Endpoints During 2-Week Period			
	Waon therapy (n=76)	Control (n=73)	P value
sBP, mmHg			
Pre	98.2±14.9	99.9±15.9	
Post	97.8±15.6	98.6±15.7	
Change	-0.3±11.9	-1.3±10.3	0.5969
P value	0.8133	0.2889	
HR, bpm			
Pre	70.5±12.6	73.5±12.0	
Post	71.2±13.2	72.6±12.6	
Change	0.7±10.7	-0.9±10.7	0.3741
P value	0.5772	0.4860	
S-Cre, mg/dl			
Pre	1.23±0.40	1.15±0.38	
Post	1.28±0.47	1.19±0.37	
Change	0.05±0.21	0.05±0.16	0.9406
P value	0.0593	0.0246*	
LVDd, mm			
Pre	61.7±10.5	62.2±11.8	
Post	61.3±10.6	61.8±12.8	
Change	-0.40±3.51	-0.35±2.70	0.9285
P value	0.3441	0.2906	
LVEF, %			
Pre	30.2±15.1	30.9±16.3	
Post	31.0±14.4	31.3±16.2	
Change	0.87±4.95	0.39±4.95	0.5765
P value	0.1487	0.5199	
LAD, mm			
Pre	46.9±9.5	48.4±8.2	
Post	47.6±9.4	48.2±8.1	
Change	0.75±4.88	-0.15±4.31	0.2610
P value	0.2047	0.7839	
6MWD, m			
Pre	291±125	269±109	
Post	336±125	281±121	
Change	44.9±49.3	12.7±72.4	0.0062*
P value	<0.0001*	0.1948	
CTR, %			
Pre	61.7±6.9	60.5±0.8	
Post	60.1±7.0	60.2±7.3	
Change	-1.58±2.81	-0.28±2.97	0.0086*
P value	<0.0001*	0.4300	

*P<0.05 with unpaired t-test. CTR, cardiothoracic ratio; HR, heart rate; LAD, left atrial diameter; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; sBP, systolic blood pressure; S-Cre, serum creatinine level; 6MWD, 6-min walk distance.

cardiac replacement therapy, have high mortality and morbidity, and are stressful and painful for debilitated patients.²³ In contrast, Waon therapy is a comfortable and non-invasive treatment for patients with advanced HF.

In the present study, we noted 7 Waon therapy-related minor adverse events: decrease in blood pressure, hypovolemia, increase in urine volume, decrease in body weight, and bleeding after tooth extraction. However, we believe that these results indicate the effect of Waon therapy; that is, diuresis and improved peripheral perfusion. Adequate post-treatment management, such as providing water for the patients after the therapy or adjusting the doses of daily diuretics and antihyper-

tensive agents, is essential. There was no new onset of arrhythmia during Waon therapy, except for the patient who suffered atrial fibrillation. He had a history of paroxysmal atrial fibrillation, and the arrhythmia recovered soon after β -blockers were titrated.

Efficacy of Waon Therapy in Patients With Advanced HF

BNP and other secondary endpoints such as 6MWD, NYHA class, and cardiothoracic ratio improved significantly in the Waon therapy group. Optimal medical therapy alone did not improve the clinical course in the control group, which indicates refractoriness of HF in the enrolled population. Considering

the severity of HF, we believe that the additive effect of Waon therapy on the optimal medical therapy without any invasive therapy is relevant.

The mechanism of Waon therapy has been discussed in various studies. Waon therapy stimulates endothelial function through stimulating the expression of NO, resulting in dilatation of the systemic vasculature.^{9,10} Patients with advanced HF are often complicated with reduced cardiac output and pulmonary congestion. Waon therapy increases cardiac output and ameliorates pulmonary congestion by reducing preload and afterload through dilatation of the systemic vasculature, and consequently decreasing functional mitral regurgitation.⁷ Improvement in vascular failure with Waon therapy eventually result in amelioration of ventricular failure. Patients with advanced HF often have right-sided HF as well as left-sided HF. Waon therapy is especially effective for right-sided HF because of the significant decrease in preload as well as in functional tricuspid regurgitation.⁷ Consistently, considering that left ventricular diastolic diameter and left atrial diameter remained unchanged during Waon therapy, the reduction in cardiothoracic ratio may result from unloading of the right atrium and right ventricle (ie, recovery of right-sided HF). Repeated Waon therapy might have reduced the size of an excessively remodeled left atrium. Furthermore, Waon therapy has a pleiotropic effect, including improvement in the autonomic nervous system, correction of neurohormonal factors, and promotion of mental and physical relaxation.^{24,25}

Patients with advanced HF often have a fear of death, mental stress, and pain.²⁶ Waon therapy provides comfort and relaxation for such patients.⁶ The therapy also improves the bond between patients and healthcare providers. Quantitative assessment of Waon therapy for the mental well-being of such patients would be promising.

Future Direction of Waon Therapy

The scope of Waon therapy may expand in the near future.²⁷ Although cardiac replacement therapy has revolutionized the therapeutic strategy for advanced HF, it can be applied only in limited patients and is not indicated for elderly patients or patients with end-organ dysfunction or malignancy.²⁸ Moreover, cardiac replacement therapy is an extremely expensive procedure. In contrast, Waon therapy is inexpensive and has few contraindications.⁶

Systemic treatment is essential for patients with advanced HF, because HF progresses through a vicious cycle between the cardiac and peripheral circulations. However, there are few therapeutic tools targeting the whole body, including the cardiac and systemic vasculature. Although cardiac rehabilitation is an excellent tool for improving the peripheral circulation,²⁹ Waon therapy has wider indications, including patients with movement disorders such as stage D HF, osteoarthritis, or limb ischemia. Although we prohibited cardiac rehabilitation to assess the pure efficacy of Waon therapy, the combination of Waon therapy and cardiac rehabilitation would have strengthened the improvement in patients' activity assessed by 6MWD when patients can tolerate cardiac rehabilitation. In addition, Waon therapy does not contraindicate other heart-specific treatments. To enable holistic treatment of patients, combination therapy including multidisciplinary treatment for the heart and Waon therapy for the peripheral circulation is a likely strategy in the future.²³

Other uses for Waon therapy, including peripheral artery disease,^{5,28} chronic fatigue syndrome, fibromyalgia, and Sjögren syndrome, also need to be explored in the future.^{5,27,30–32}

Study Limitations

The primary endpoint of this study (ie, changes in the logarithm of BNP before and after the study period) did not reach statistical significance, although the BNP decreased significantly only in the Waon group. In other words, the baseline HF of the enrolled patients was severe. We have already demonstrated significant efficacy of 10–15 sessions of Waon therapy for patients with milder HF.^{8,14–17,21} However, in patients with more advanced HF, such as those enrolled in the present study, more sessions (eg, 20–40 times) of Waon therapy are likely needed to achieve apparent clinical benefits such as left ventricular reverse remodeling. Evidence supporting long-term Waon therapy in patients with advanced HF is a future concern. However, longer term Waon therapy assessed in a randomized fashion may be difficult in patients with advanced HF, considering their poor prognosis.

We assessed the improvement in quality of life during Waon therapy, because that is a therapeutic goal for patients with advanced HF. We have previously demonstrated that Waon therapy improved patients' quality of life,¹⁹ but whether repeated Waon therapy may improve hard endpoints such as mortality, especially in a prospective study, needs to be explored in future studies.

We could not perform a double blind study, as the Waon therapy procedure cannot be blinded. However, we attempted to overcome this limitation by having the clinical data corrected by each attending physician, but the statistical analyses performed by blinded statisticians.

Among the patients there were statistically significant differences in body mass index and the frequency of diabetes between the 2 groups. The influence of this on the results is unknown, but the numerical values of body mass index were within normal limits in both groups.

We could not measure several echocardiographic parameters, including the diameter of the inferior vena cava and the degree of mitral regurgitation. Although we could not show the diameter of the inferior vena cava after Waon therapy, systemic blood pressure may represent the preserved systemic volume even after Waon therapy. The size of the left atrium remained unchanged after Waon therapy. Although we previously reported improvement of mitral regurgitation by Waon therapy, such benefit may not have been seen in this study, because of the severity of HF and the short period of therapy.

All patients received medical therapy for at least >1 week before the randomization. A longer observation period may be needed to optimize medical therapy. However, all patients had a history of hospitalization for HF, and had already received anti-HF treatment before admission. Among such patients, "at least 1 week" may be sufficient to optimize medical therapy.

Conclusions

Waon therapy, a holistic soothing warmth therapy, was demonstrated to have advantages over optimal medical therapy alone in terms of safety and efficacy even in patients with advanced HF.

Acknowledgments

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Disclosures

None.

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Appendix

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