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Original article

Improvement of autonomic nervous activity by Waon therapy in patients with chronic heart failure

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Received 28 July 2010; received in revised form 18 August 2010; accepted 20 August 2010

Available online 29 September 2010

KEYWORDS

Waon therapy;
Heart failure;
Autonomic nervous
system

Summary

Background and purpose: We have reported previously that Waon therapy improves cardiac and vascular function, and prognosis of patients with chronic heart failure (CHF). CHF is characterized by generalized sympathetic activation and parasympathetic withdrawal. The purpose of this study was to evaluate the effect of Waon therapy on autonomic nervous activity in patients with CHF.

Methods and subjects: Fifty-four patients with CHF, who were receiving conventional therapy for CHF, were divided into Waon therapy and control groups. In the Waon therapy group, 27 patients were treated with medication and Waon therapy. In the control group, 27 patients were treated with only conventional CHF therapy. Cardiac function including cardiac output (CO) and left ventricular ejection fraction (LVEF) was evaluated by echocardiography. The heart rate variability, such as the coefficient of variation of RR intervals (CVRR), the low-frequency (LF) component, high-frequency (HF) component, the LF norm [LF/(LF+HF)], and HF norm [HF/(LF+HF)], were measured at admission and 4 weeks after treatment.

Results: Echocardiography demonstrated that CO and LVEF significantly increased after 4 weeks in the Waon therapy group, but did not change in the control group. In the Waon therapy group, CVRR, HF, and HF norm significantly increased 4 weeks after Waon therapy. In addition, the LF/HF ratio and LF norm significantly decreased 4 weeks after Waon therapy. In

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contrast, these parameters remained unchanged in the control group. Moreover, the HF and HF norm were significantly higher, and the LF/HF ratio and LF norm were significantly lower after 4 weeks of Waon therapy group than after 4 weeks of only conventional therapy.

Conclusions: Waon therapy improved cardiac function and autonomic nervous activity by increasing parasympathetic and decreasing sympathetic nervous activity in patients with CHF.

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Introduction

The autonomic nervous system maintains stable hemodynamics by controlling sympathetic and parasympathetic nervous activity. It is well known that the autonomic nervous system may contribute to pathological conditions such as ischemic heart disease, arrhythmia, and congestive heart failure, and influence the prognosis of these diseases [1–3]. In heart failure patients, activation of the sympathetic nervous activity causes myocardial damage [4], and it is one of the important prognostic predictors [5,6].

Heart rate variability (HRV), i.e., the amount of heart rate fluctuations around the mean heart rate, can be used as a marker of the cardiorespiratory control system. It is a valuable tool to investigate the sympathetic and parasympathetic components of autonomic nervous function [7]. Previous studies suggest that a marked reduction of HRV is found in patients with chronic heart failure (CHF) [8]. The high-frequency component of HRV, a marker of parasympathetic modulation, declined markedly from the early asymptomatic stage of pacing-induced heart failure in a dog model. The parasympathetic withdrawal occurred rapidly in a parallel fashion with the decline in left ventricular contractility [9].

We developed a thermal therapy with a 60°C dry sauna, and have been investigating the various effects of thermal therapy such as improvement of hemodynamic parameters, endothelial function, and clinical symptoms in many congestive heart failure patients [10–15]. Furthermore, we have demonstrated that repeated sauna treatment improves the prognosis of CHF in humans [16] and hamsters [17]. Generally, thermal therapy at very high temperature was originally used to treat localized cancer. However, the therapy we developed to treat cardiovascular diseases is quite different, in that it consists of systemic soothing warmth that comfortably refreshes the mind and body. Therefore, we have changed the name from thermal to Waon therapy, since “Waon” in Japanese means soothing warmth [18–20]. To date, we have performed Waon therapy in several hundred CHF patients without any severe adverse effects.

We hypothesize that Waon therapy may improve autonomic nervous function of CHF patients. Thus, the purpose of this study was to evaluate the effect of Waon therapy on autonomic nervous activity in patients with CHF.

Methods

Study population

Fifty-four patients (38 men, 16 women) who had been referred to Kagoshima University Hospital for treatment of CHF were prospectively randomized into Waon therapy and control groups. All patients of both groups had already been

treated with medications for heart failure at admission of this study. In the Waon therapy group, 27 patients were treated with medication and Waon therapy. In the control group, 27 patients continued the conventional medications for CHF.

Inclusion criteria were New York Heart Association (NYHA) functional class II–IV and left ventricular ejection fraction (LVEF) < 50% on echocardiography. Exclusion criteria were the presence of severe aortic valve stenosis, hypertrophic cardiomyopathy with severe obstruction, CHF treated with catecholamines, and renal failure requiring hemodialysis. We also excluded patients with excessive artifacts in the HRV analysis such as atrial fibrillation, frequent atrial or ventricular premature contractions, marked repolarization abnormalities, and implantation of a pacemaker.

Informed consent was obtained from all of the patients prior to participation, and the protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

Study protocol

Patients in the Waon therapy group received medications for heart failure and 20 sessions of Waon therapy (once a day, 5 days a week for 4 weeks). Patients in the control group received conventional treatment for heart failure including rest, oxygen administration, and medication for 4 weeks in the hospital. All examinations were performed at admission and 4 weeks after treatment.

Waon therapy

Waon therapy [18–20], a form of thermal therapy, uses a far infrared-ray dry sauna at 60°C and differs from traditional sauna. Waon therapy has an absence of hydration pressure, and was performed as previously reported [10]. The patients were placed in a 60°C sauna system for 15 min; after leaving the sauna, they underwent bed rest with a blanket to keep them warm for an additional 30 min. All patients were weighed before and after the therapy, and oral hydration with water was used to compensate for weight loss due to perspiration.

Physical examination and cardiac function

Body weight, blood pressure and heart rate were measured at admission and 4 weeks after treatment. The cardiothoracic ratio (CTR) determined by chest radiography, and echocardiography was performed at admission and 4 weeks after treatment. Cardiac output (CO), LVEF, left ventricular end-diastolic volume (LVEDV), and left and right ventricular Tei index (LV-, RV-Tei index) [21–23] were evaluated by

Table 1 Baseline clinical characteristics.

| | Control group (n=27) | Waon therapy group (n=27) | p |
|----------------------------------|----------------------|---------------------------|------|
| Age (years) | 64 ± 16 | 63 ± 15 | 0.76 |
| Gender, M/F | 19/8 | 19/8 | 1.00 |
| NYHA functional class, II/III/IV | 13/10/4 | 12/11/4 | 0.85 |
| Etiology of heart failure, n (%) | | | |
| DCM | 12 (44%) | 8 (30%) | 0.25 |
| ICM | 10 (37%) | 10 (37%) | 1.00 |
| Others | 5 (19%) | 9 (33%) | 0.21 |
| Complication, n (%) | | | |
| Hypertension | 9 (33%) | 11 (41%) | 0.57 |
| Dyslipidemia | 14 (52%) | 16 (59%) | 0.58 |
| Diabetes mellitus | 11 (41%) | 12 (44%) | 0.78 |
| Current or past smoking | 8 (30%) | 12 (44%) | 0.25 |
| Medication, n (%) | | | |
| ACE inhibitor | 17 (63%) | 14 (52%) | 0.40 |
| ARB | 10 (37%) | 13 (48%) | 0.40 |
| Beta-blocker | 25 (93%) | 25 (93%) | 1.00 |
| Statin | 9 (33%) | 11 (41%) | 0.57 |
| Diuretics | 27 (100%) | 27 (100%) | 1.00 |

Values are means ± SD or n (%); ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; NYHA, New York Heart Association.

echocardiography. All Doppler and echocardiographic measurements were performed according to the guidelines of the American Society of Echocardiography specified in 2005 [24]. The LVEF and LVEDV were obtained by the modified biplane Simpson's method from the apical 2- and 4-chamber views. CO was calculated by the product of stroke volume and heart rate. Stroke volume was obtained by the LV outflow Doppler method as the product of area and the time-velocity integral of LV outflow track. The Tei index, the sum of isovolumic contraction and relaxation times divided by the ejection time, is a well-established good indicator of global cardiac function [21,22]. It was obtained from Doppler recordings of LV and RV inflow and outflow.

Laboratory examinations

A fasting plasma blood sample was taken in the morning to measure plasma concentrations of neurohormones, such as catecholamines and brain natriuretic peptide (BNP). Plasma noradrenaline concentration was measured with high-performance liquid chromatography (BML Co., Ltd., Tokyo, Japan), and plasma BNP concentration was measured with a chemiluminescent enzyme immunoassay using a commercially available kit (Pathfast, Mitsubishi Chemical Medience Co., Ltd., Tokyo, Japan), at admission and 4 weeks after treatment.

Measurement and evaluation of the autonomic nervous system

The indices of HRV can be divided into two major categories: time and frequency domain indices. We calculated the time domain index using the coefficient of variation of RR intervals (CVRR), which was determined by dividing the standard deviation of RR intervals (SD) by the mean RR interval (M)

for a 5-min recording of the electrocardiogram at rest. Thus, CVRR, an index of parasympathetic nervous activity, was calculated as follows: CVRR (%) = (SD/M) × 100 [25]. In addition, we analyzed the frequency domain index to assess the magnitude of the individual components of the heart rate power spectrum. Three main spectral components are distinguished in a spectrum calculated from short-term recording of 2 to 5 min: very-low-frequency (VLF; 0.003–0.04 Hz), low-frequency (LF; 0.04–0.15 Hz), and high-frequency components (HF; 0.15–0.40 Hz) [7,26]. We analyzed consecutive RR intervals in order to assess both LF and HF of the heart rate power spectrum using the MemCalc/Tonam® system (Suwa Trust, Tokyo, Japan) [27–29]. Normalized units (nu) were calculated from the following equations: LF norm = LF/(LF + HF), and HF norm = HF/(LF + HF) [7]. The HF element and HF norm reflect only parasympathetic nervous activity, because the HF element is not reduced by sympathetic blockade with propranolol, but rather is abolished by vagal blockade with atropine [30–32]. In contrast, the LF/HF ratio and LF norm are generally used as indices of sympathetic nervous activity, because the LF element reflects both sympathetic and parasympathetic nervous activity [29,32]. Time domain analysis and spectral analysis of HRV were performed for a consecutive 5-min period in this study. HRV has been shown to be influenced by various conditions such as circadian rhythm, room temperature, physical and mental stress, body position, eating, smoking, and sleeping. Therefore, we prohibited the subjects from intense exercise, smoking, and alcohol drinking during hospitalization, and prohibited them from eating for 3 h before the measurement. HRV was measured in a quiet and air-conditioned room. We also measured HRV after at least 15 min of rest in the supine position and at the same time each day to avoid the influence of circadian rhythm. In the Waon therapy group, HRV was measured at 6 h after Waon therapy.

Table 2 Parameters at admission and after 4 weeks in the Waon therapy and control groups.

| Variable | Control group (n = 27) | | Waon therapy group (n = 27) | | Comparison between groups | |
|-----------------------|------------------------|---------------------------|-----------------------------|--------------------------|---------------------------|---------------|
| | Admission | After 4 weeks | Admission | After 4 weeks | Admission | After 4 weeks |
| Body weight (kg) | 58 ± 15 | 57 ± 14 ^{***} | 57 ± 10 | 56 ± 11 ^{***} | 0.63 | 0.69 |
| SBP (mm Hg) | 106 ± 18 | 103 ± 16 [*] | 106 ± 20 | 100 ± 17 ^{***} | 0.95 | 0.62 |
| DBP (mm Hg) | 65 ± 9 | 62 ± 10 [*] | 65 ± 10 | 62 ± 10 | 0.89 | 0.88 |
| HR (beat/min) | 71 ± 11 | 68 ± 10 | 72 ± 14 | 67 ± 10 [*] | 0.91 | 0.82 |
| CTR (%) | 58 ± 5 | 56 ± 5 ^{***} | 57 ± 4 | 54 ± 5 ^{***} | 0.17 | 0.11 |
| CO (l/min) | 3.12 ± 0.71 | 3.06 ± 0.73 | 2.88 ± 0.71 | 3.18 ± 0.72 [*] | 0.34 | 0.44 |
| LVEF (%) | 31 ± 9 | 32 ± 11 | 33 ± 13 | 35 ± 12 [*] | 0.47 | 0.31 |
| LVEDV (ml) | 194 ± 47 | 191 ± 59 | 179 ± 63 | 164 ± 59 [*] | 0.35 | 0.10 |
| LV-Tei index | 0.75 ± 0.21 | 0.80 ± 0.23 | 0.81 ± 0.32 | 0.79 ± 0.28 | 0.41 | 0.84 |
| RV-Tei index | 0.69 ± 0.23 | 0.56 ± 0.22 ^{**} | 0.67 ± 0.40 | 0.54 ± 0.28 [*] | 0.87 | 0.71 |
| BNP (pg/ml) | 522 ± 234 | 387 ± 314 ^{**} | 521 ± 439 | 278 ± 213 ^{***} | 0.99 | 0.14 |
| Noradrenaline (pg/ml) | 626 ± 443 | 472 ± 220 | 673 ± 396 | 436 ± 177 ^{**} | 0.76 | 0.54 |

Values are means ± SD; BNP, brain natriuretic peptide; CO, cardiac output; CTR, cardiothoracic ratio; DBP, diastolic blood pressure; HR, heart rate; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; RV, right ventricle; SBP, systolic blood pressure.

^{*} $p < 0.05$ vs. admission.

^{**} $p < 0.01$ vs. admission.

^{***} $p < 0.001$ vs. admission.

Statistics

Statistical analysis was performed using Stat View Version 5.0 software. Values are expressed as the mean ± SD. Comparisons of data between the two groups were performed using Pearson's χ^2 -test or Student's unpaired t -test. Within-group changes between admission and 4 weeks after treatment were evaluated by paired t -test. Statistical significance was accepted when the p -value was < 0.05 .

Results

Clinical characteristics at admission

The clinical characteristics of patients at admission are shown in Table 1. There were no significant differences in age, gender, NYHA functional class, etiology of heart failure, complications, or the use of medications between the two groups at admission. We used three beta-blockers such as carvedilol, atenolol, and metoprolol. The dosage of atenolol and metoprolol were converted into that of carvedilol, and there was no significant difference in dosage of beta-blockers at admission between the two groups (Waon therapy group: 4.5 ± 3.5 mg/day vs. control group: 3.4 ± 3.5 mg/day).

In addition, as shown in Table 2, there were no significant differences in body weight, systolic blood pressure, diastolic blood pressure, mean heart rate, plasma BNP, and noradrenaline levels, CTR, or echo-derived measures such as CO, LVEF, LVEDV, LV-Tei index, and RV-Tei index between the two groups at admission.

Clinical findings and physical examinations

The changes in the clinical findings and variables after 4 weeks are summarized in Table 2. Body weight and systolic blood pressure significantly decreased at 4 weeks after

treatment compared with admission in both groups. Diastolic blood pressure significantly decreased in the control group after 4 weeks compared with admission, but did not change in the Waon therapy group. Mean heart rate significantly decreased in the Waon therapy group after 4 weeks compared with admission, but did not change in the control group. There were no significant differences in these parameters between the two groups after 4 weeks.

Chest radiography and echocardiography

Changes in chest radiography and echocardiography are also shown in Table 2. Chest radiography showed a significant decrease of the CTR at 4 weeks after treatment compared with admission in both groups. In addition, echocardiography demonstrated that CO, LVEF, LVEDV, and RV-Tei index significantly improved after 4 weeks in the Waon therapy group, but LV-Tei index did not change after Waon therapy. In the control group, only RV-Tei index significantly decreased after 4 weeks, but CO, LVEF, LVEDV, and LV-Tei index did not change after treatment. There were no significant differences in any of these indices between the two groups after 4 weeks.

Plasma levels of BNP and noradrenaline

As shown in Table 2, the plasma levels of BNP significantly decreased 4 weeks after treatment compared with admission in both groups. There was no significant difference in BNP levels between the two groups after 4 weeks. In the Waon therapy group, plasma noradrenaline levels significantly decreased 4 weeks after Waon therapy. In the control group, plasma noradrenaline levels tended to decrease after 4 weeks, but did not reach statistical significance. There was no significant difference in noradrenaline levels between the two groups after 4 weeks.

Analysis of the autonomic nervous system

Changes in the indices of parasympathetic nervous activity such as HF, HF norm, and CVRR are shown in Figs. 1–3. In the Waon therapy group, HF, HF norm, and

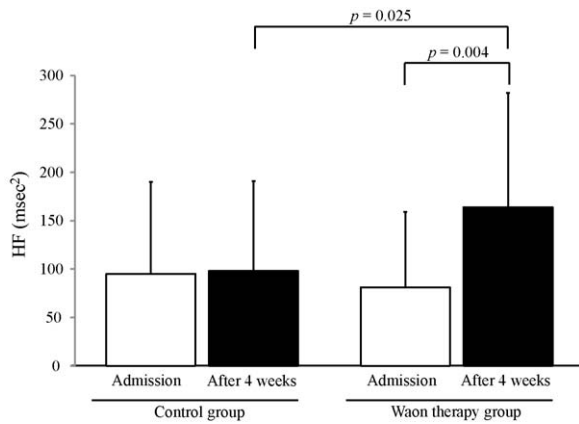


Figure 1 Changes in parasympathetic nervous function demonstrated by HF after 4 weeks of treatment. HF, high-frequency component.

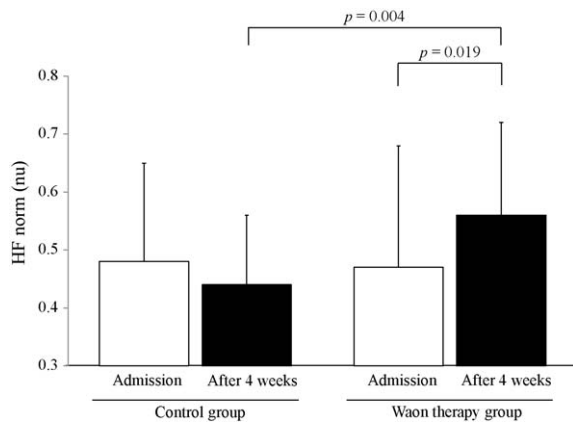


Figure 2 Changes in parasympathetic nervous function demonstrated by HF norm after 4 weeks of treatment. HF norm = normalized HF = HF/(LF + HF); HF, high-frequency component; LF, low-frequency component.

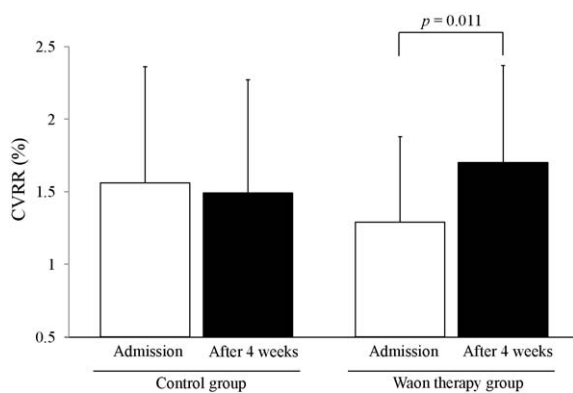


Figure 3 Changes in parasympathetic nervous function demonstrated by CVRR after 4 weeks of treatment. CVRR, coefficient of variation of RR intervals.

CVRR significantly increased 4 weeks after Waon therapy (HF: 81 ± 78 to 164 ± 118 ms², $p=0.004$; HF norm: 0.47 ± 0.21 to 0.56 ± 0.16 nu, $p=0.019$; CVRR: 1.29 ± 0.59 to $1.70 \pm 0.67\%$, $p=0.011$). In contrast, these parameters remained unchanged in the control group (HF: 95 ± 95 to 98 ± 93 ms², $p=0.86$; HF norm: 0.48 ± 0.17 to 0.44 ± 0.12 nu, $p=0.31$; CVRR: 1.56 ± 0.80 to $1.49 \pm 0.78\%$, $p=0.72$). Moreover, the HF and HF norm after 4 weeks in the Waon therapy group were significantly higher than those in the control group (HF: $p=0.025$; HF norm: $p=0.004$).

Changes in the indices of sympathetic nervous activity such as the LF/HF ratio and LF norm are shown in Figs. 4 and 5. In the Waon therapy group, the LF/HF ratio and LF norm significantly decreased 4 weeks after Waon therapy (LF/HF: 2.31 ± 2.03 to 1.20 ± 0.93 , $p=0.001$; LF norm: 0.53 ± 0.21 to 0.44 ± 0.16 nu, $p=0.019$). In contrast, these parameters remained unchanged in the control group (LF/HF: 2.06 ± 1.90 to 1.85 ± 1.15 , $p=0.56$; LF norm: 0.52 ± 0.17 to 0.56 ± 0.12 nu, $p=0.31$). Moreover, the LF/HF ratio and LF norm after 4 weeks in the Waon therapy group were significantly lower than those in the control group (LF/HF ratio: $p=0.013$, LF norm: $p=0.004$).

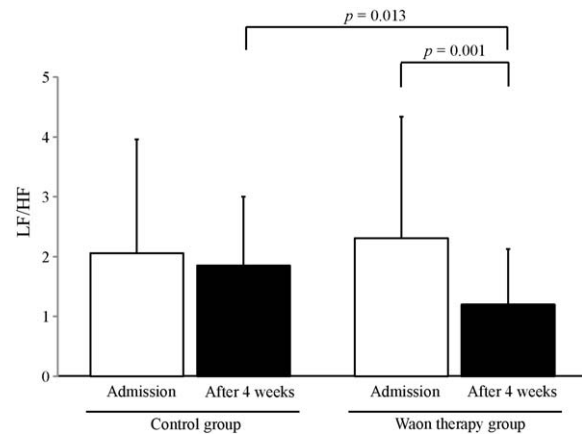


Figure 4 Changes in sympathetic nervous function demonstrated by the LF/HF ratio after 4 weeks of treatment. HF, high-frequency component; LF, low-frequency component.

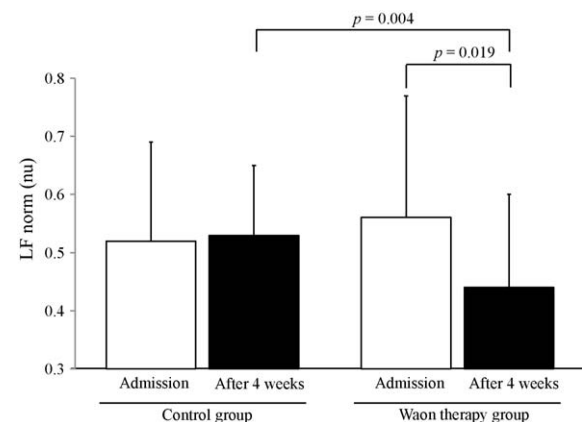


Figure 5 Changes in sympathetic nervous function demonstrated by LF norm after 4 weeks of treatment. LF norm = normalized LF = LF/(LF + HF); HF, high-frequency component; LF, low-frequency component.

Discussion

The major novel finding of the current study is that repeated Waon therapy improved cardiac autonomic nervous activity in CHF patients. Several mechanisms may contribute to the improvement of autonomic nervous activity by Waon therapy. In acute heart failure, heart rate will rise through arterial baroreflex-mediated vagal withdrawal and sympathetic activation to maintain CO. In addition, there is an inverse relationship between muscle sympathetic nerve burst frequency and hemodynamic variables, such as LV stroke-work index and stroke-volume index, and a direct correlation with atrial, pulmonary artery, and LV filling pressures [33]. Indeed, Waon therapy significantly improved CO, LVEF, and LVEDV in this study. Moreover, we previously reported that cardiac and stroke volume index increased and systemic vascular resistance decreased significantly during and after Waon therapy [10]. Furthermore, we also reported significant decreases in mean pulmonary artery, mean pulmonary capillary wedge, and mean right atrial pressures during Waon therapy [10]. These reductions in cardiac preload and afterload, and an increase in CO are attributable to the improvement of autonomic nervous activity.

Interestingly, mean heart rate significantly decreased in only the Waon therapy group. As heart failure progresses inhibitory input from arterial and cardiopulmonary receptors decreases and excitatory input increases. The net response to this altered balance includes a generalized increase in sympathetic nerve traffic, and blunted parasympathetic and sympathetic control of heart rate [4].

It is widely recognized that nitric oxide (NO), which largely accounts for the biological effects of endothelium-derived relaxing factor, is an important regulator of vascular function. The nitric oxide synthase (NOS) system plays salutary roles in a variety of cardiovascular diseases in mice [34]. Young et al. [35] reported that pharmacological inhibition of NOS causes sympathetic activation, and NO is involved in the regulation of sympathetic nervous activity in humans. In this regard, we previously demonstrated that Waon therapy improves endothelial function [11,36] and increases mRNA expression and protein levels of endothelial nitric oxide synthase (eNOS) in the aorta of Syrian golden hamsters [37] and TO-2 cardiomyopathic hamsters [38]. Thus, the improvement in endothelial function and increased eNOS expression by Waon therapy may lead to the normalization of autonomic nervous activity.

Study limitations

Some limitations of this study should be considered when interpreting the results. First, because the number of participating patients was small, the statistical power of the study to discern significant differences between the two treatment groups was reduced. Second, diabetic patients were included in both groups. Although diabetic neuropathy causes autonomic nervous dysfunction [39], the percentage of diabetic patients did not differ between the two groups in the current study.

Conclusions

Repeated Waon therapy improved cardiac function and normalized cardiac autonomic nervous activity by increasing parasympathetic and decreasing sympathetic nervous activity in CHF patients. Waon therapy is an innovative and promising nonpharmacological treatment for CHF.

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