Effect of Repeated Sauna Treatment on Exercise Tolerance and Endothelial Function in Patients With Chronic Heart Failure

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Repeated sauna treatment, known as Waon therapy, has been shown to improve cardiac function as well as exercise tolerance in patients with chronic heart failure. However, the underlying mechanisms of this therapy regarding these improvements remain to be elucidated. Forty-one patients with chronic heart failure (mean age 68.3 ± 13.5 years old) underwent Waon therapy 5 times a week for 3 weeks. Before and after treatment, a number of assessments were performed in all subjects: 6-minute walk test, echocardiography, determination of neurohumoral factors and number of circulating $CD34^+$ cells, and a flow-mediated dilation (FMD) test of endothelial function. Cardiopulmonary exercise testing was also performed in 20 patients. Waon therapy increased the left ventricular ejection fraction (from 30.4 ± 12.6% to 32.5% ± 12.8%, $p = 0.023$) and reduced plasma levels of norepinephrine (from 400 ± 258 to 300 ± 187 pg/ml, $p = 0.015$) and brain natriuretic peptide (from 550 ± 510 to 416 ± 431 pg/ml, $p = 0.035$). Waon therapy increased the 6-minute walk distance (from 337 ± 120 to 379 ± 126 m, $p < 0.001$) in association with an improvement in FMD (from 3.5 ± 2.3% to 5.5% ± 2.7%, $p < 0.001$) and an increase in the number of circulating $CD34^+$ cells ($p = 0.025$). Changes in 6-minute walk distance were correlated positively with those in the left ventricular ejection fraction and FMD and negatively with those in plasma levels of norepinephrine and brain natriuretic peptide levels. A multivariate analysis revealed that an increase in FMD was the only independent determinant of 6-minute walk distance improvement. Finally, Waon therapy significantly increased peak Vo_2, and this increase was also correlated with changes in FMD. In conclusion, repeated sauna therapy in patients with chronic heart failure improves exercise tolerance in association with improvement in endothelial function. **(Am J Cardiol 2012; 109:100–104)**

Repeated sauna treatment, known as Waon therapy,[1] has favorable effects in patients with chronic heart failure (CHF)[2–5] and also those with peripheral artery disease,[6] including improvements in cardiac and autonomic nerve function and inhibition of neurohumoral activation. These effects might be mediated by an increase in endothelial nitric oxide synthase activity and subsequent improvement of endothelial dysfunction.[7] Endothelial dysfunction has been documented in patients with CHF[8,9] and might play an important role in exercise capacity in these patients.[10] The purpose of the present study was to investigate whether Waon therapy could improve exercise tolerance in patients with CHF and, if so, to elucidate the underlying mechanisms involved.

Methods

All patients included in the present study had to satisfy ≥1 of the following criteria: CHF-associated symptoms of New York Heart Association functional class ≥II and/or previous hospitalization for worsening of heart failure. All patients were in compensated, stable conditions at the time of enrollment. The protocol of the present study was approved by the ethics committee of University of Toyama. Written informed consent was obtained from all study patients before the enrollment.

According to methods described previously,[11] the study patients underwent Waon therapy with a far-infrared dry sauna, which was uniformly maintained at 60°C. Patients were placed in the sitting position in the dry sauna for 15 minutes and then kept on bed rest with a blanket to keep warm for an additional 30 minutes, resulting in an increase in the core temperature by 1.0°C to 1.2°C. Patients were weighed before and after the therapy and drank water to compensate for the weight loss. All patients underwent daily Waon therapy Monday through Friday for 3 weeks. Regular treatment for heart failure was continued during the study period.

The number of $CD34^+$ cells in the peripheral blood, a putative precursor of endothelial progenitor cells (EPCs), was quantified using flow cytometry (EPICS-MCL; Beckman Coulter, Brea, California). White blood cells were dually stained with fluorescein isothiocyanate–conjugated CD45 and phycoerythrin-conjugated CD34 (StemONE System; Beckman Coulter). Cells expressing CD34 were deter-

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0002-9149/12/$ – see front matter
doi:10.1016/j.amjcard.2011.08.014

Table 1
Baseline characteristics of the study patients (n = 41)

Variable	Value
Age (years)	68.3 ± 13.5
Men	21 (51%)
Body mass index (kg/m^2)	21.5 ± 4.2
New York Heart Association functional class	
I	4
II	15
III	22
IV	0
Cause of heart failure	
Dilated cardiomyopathy	20 (49%)
Ischemic heart disease	14 (34%)
Hypertrophic cardiomyopathy	3 (7%)
Valvular heart disease	2 (5%)
Hypertensive heart disease	2 (5%)
Co-morbidities	
Diabetes mellitus*	10 (24%)
Hypertension†	10 (24%)
Dyslipidemia‡	13 (32%)
Atrial fibrillation or flutter	12 (29%)
Medications	
Digoxin	13 (32%)
β blockers	28 (68%)
Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers	34 (83%)
Diuretics	38 (93%)
Nonpharmacologic therapy	
Pacemaker	4 (10%)
Implantable cardioverter-defibrillator/cardiac resynchronization therapy	5 (12%)
Oxygen/noninvasive positive-pressure ventilation	6 (15%)

Data are expressed as mean ± SD or as number (percentage).

* Fasting plasma glucose ≥126 mg/dl or plasma glucose ≥200 mg/dl under 75-g oral glucose tolerance test or long-term treatment with oral hypoglycemic agents or insulin.

† Blood pressure >140/90 mm Hg on repeated observations or long-term antihypertensive therapy.

‡ Plasma low-density lipoprotein cholesterol ≥140 mg/dl or plasma triglyceride ≥150 mg/dl or long-term lipid-lowering therapy.

Table 2
Comparisons between data at baseline and after 3-week Waon therapy

Variable	Baseline	After 3-Week Waon Therapy	p Value
Heart rate (beats/min)	70 ± 11	66 ± 11	0.021
Systolic blood pressure (mm Hg)	101 ± 13	99 ± 14	0.099
Diastolic blood pressure (mm Hg)	64 ± 11	61 ± 9	0.109
Body weight (kg)	55 ± 16	54 ± 16	0.021
New York Heart Association functional class			0.535
I	4	7	
II	15	16	
III	22	18	
IV	0	0	
Specific activity scale (METs)	4.2 ± 1.6	4.7 ± 1.5	<0.001
Left ventricular end-diastolic dimension (mm)	66 ± 11	64 ± 11	<0.001
Left ventricular ejection fraction (%)	30 ± 13	33 ± 13	0.023
Left atrial dimension (mm)	47 ± 8	45 ± 9	0.010
6MWD (m)	337 ± 120	379 ± 126	<0.001
Peak V_{O_2} (ml/min)	804 ± 385	871 ± 362	<0.001
VE/V_{CO_2} slope	38 ± 10	33 ± 7	0.018
Hematocrit (%)	37 ± 6	36 ± 6	0.011
Brain natriuretic peptide (pg/ml)	550 ± 510	416 ± 431	0.035
Plasma norepinephrine (pg/ml)	400 ± 258	300 ± 187	0.015
Circulating CD34$^+$ cells (per mm^3)	1.1 ± 1.0	1.3 ± 1.3	0.025
FMD (%)	3.5 ± 2.3	5.5 ± 2.7	<0.001

Data are expressed as mean ± SD or as numbers.

mined by gating the progenitor population and expressed as the number of cells per microliter.

Exercise tolerance was evaluated by 6-minute walk distance (6MWD) in all study patients and by cardiopulmonary exercise testing in patients who were able to pump the pedals of an ergometer (n = 20). In the upright position, symptom-limited cardiopulmonary exercise testing was performed using expired gas analysis (Aeromonitor AE-300S; Minato Medical Science Co. Ltd., Osaka, Japan) and an ergometer (75XL III; Combiwelness, Tokyo, Japan). Peak oxygen uptake (peak V_{O_2}) and ventilatory efficiency as assessed by the relation of minute ventilation (VE) to carbon dioxide production (V_{CO_2}; VE/V_{CO_2} slope) were determined.

Vascular endothelial function was evaluated by flow-mediated dilation (FMD) of the brachial artery. Patients were instructed to fast overnight and to abstain from smoking and taking caffeine, vitamins, and medications for ≥12 hours before FMD testing. Vasodilatation responses of the brachial artery were determined via ultrasound technique using a semiautomatic device (EF18G; Unex, Nagoya, Japan). Briefly, the diameter of the brachial artery was measured from B-mode ultrasound images using a 10-MHz linear-array transducer. A blood pressure cuff placed over the proximal portion of the right forearm was inflated to 50 mm Hg above the systolic blood pressure for a period of 5 minutes. FMD was determined as the maximum change in diameter after cuff release normalized to the baseline diameter (percentage of baseline diameter).

All data are presented as mean ± SD. Paired Student's *t* tests were performed for comparisons of pre– and post–Waon therapy data. Categorical variables were compared using chi-square tests. The relation between Waon therapy–induced changes in 6MWD and other variables was determined using Pearson's product-moment correlation coefficients. A multiple regression analysis was performed to identify the independent determinants of Waon therapy–induced changes in 6MWD. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study patients are listed in Table 1, and the effects of 3-week Waon therapy are summarized in Table 2. In response to therapy, 6MWD increased, and peak V_{O_2} and VE/V_{CO_2} slope by cardiopulmonary exercise testing improved. The left ventricular ejection

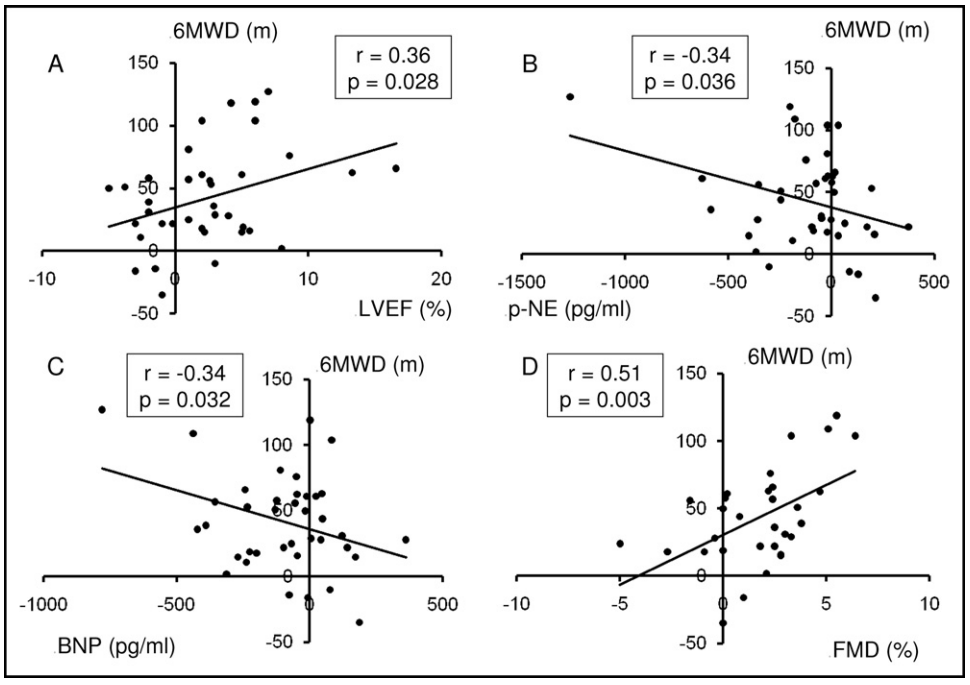

Figure 1. Relations between change in 6MWD (Δ6MWD) induced by Waon therapy and changes in the left ventricular ejection fraction (ΔLVEF) *(A)*, plasma norepinephrine (Δp-NE) *(B)*, brain natriuretic peptide (ΔBNP) *(C)*, and FMD (ΔFMD) *(D)*. Change in 6MWD was correlated positively with ΔLVEF and ΔFMD and negatively with ΔBNP and Δp-NE.

Table 3
Determinants of Waon therapy–induced improvement of 6-minute walk distance

Variable	Univariate Analysis		Multivariate Analysis	
	r	p Value	β	p Value
Change in $CD34^+$ cells	0.11	0.49	—	—
Change in the left ventricular ejection fraction	0.36	0.028	0.164	0.419
Change in plasma norepinephrine	−0.34	0.036	0.032	0.871
Change in brain natriuretic peptide	−0.34	0.032	−0.308	0.126
Change in FMD	0.51	0.003	0.405	0.049

fraction increased modestly but significantly, while neurohumoral activations were inhibited. The number of circulating $CD34^+$ cells and FMD increased, a finding indicative of improvement of endothelial function. There were no differences in improvements in exercise tolerance and FMD according to age or the severity or cause of heart failure (i.e., ischemic vs nonischemic; data not shown).

Waon therapy–induced change in 6MWD was not correlated with age. However, significant correlations were found between change in 6MWD and changes in the left ventricular ejection fraction, plasma levels of norepinephrine and brain natriuretic peptide, and FMD (Figure 1). A multivariate analysis revealed that change in FMD was the only independent determinant of change in 6MWD (Table 3). Waon therapy–induced change in peak Vo_2 was significantly correlated with change in FMD (Figure 2).

Discussion

The major findings of the present study were as follows. First, 3-week Waon therapy improved exercise tolerance, cardiac function, and endothelial function and inhibited neurohumoral activation in patients with CHF. Second, change in 6MWD because of Waon therapy was significantly correlated with those in the left ventricular ejection fraction, plasma levels of norepinephrine and brain natriuretic peptide, and FMD. Additionally, Waon therapy–induced improvement of FMD was correlated with an increase in peak Vo_2 and was the only independent determinant of increased 6MWD. Thus, Waon therapy improves exercise tolerance in patients with CHF, at least in part, through the improvement in endothelial function.

In the present study, clinical variables including exercise tolerance, cardiac function, neurohumoral factors, and endothelial function were all improved by Waon therapy, in a manner consistent with previous studies.[3,12] These clinical variables are important markers of prognosis in patients with CHF. Indeed, a retrospective study by Kihara et al[5] revealed that Waon therapy reduced mortality as well as hospitalization due to worsening of heart failure in patients with CHF.

Endothelial dysfunction plays an important role in the pathophysiology and progression of CHF and is an independent predictor of poor prognosis in patients with CHF.[13] Kihara et al[3] reported an improvement in endothelial function by Waon therapy and a significant correlation between Waon therapy–induced changes in FMD and plasma brain natriuretic peptide level. Nitric oxide plays an important role in the regulation of endothelial function, and endothelial dysfunction is associated with impaired exercise toler-

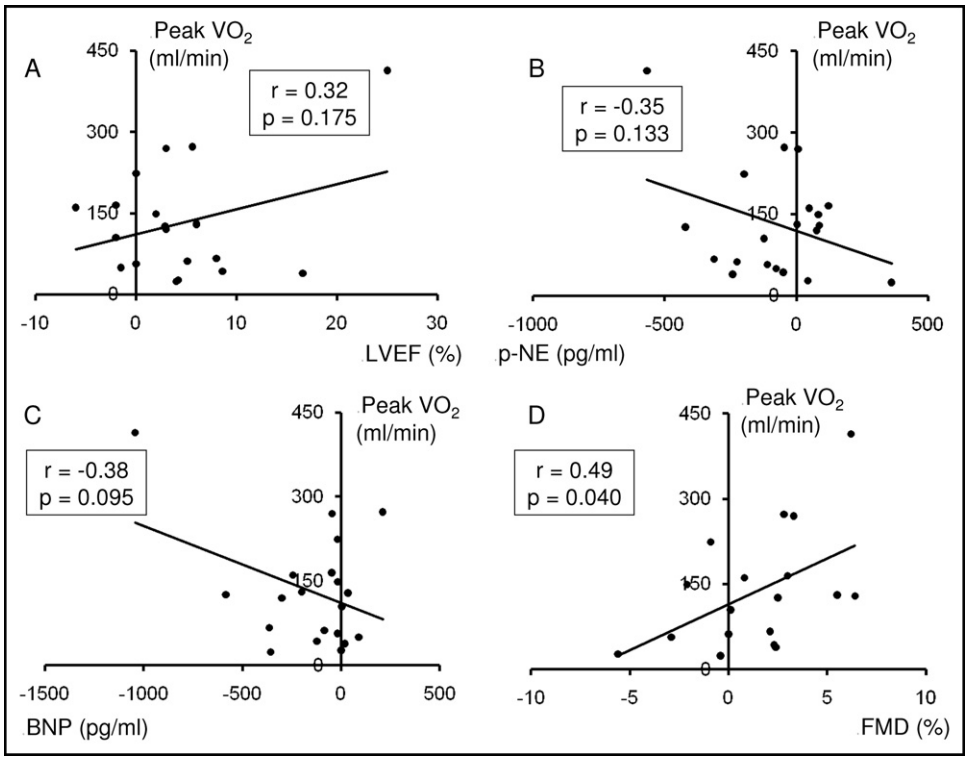

Figure 2. Relations between change in peak Vo_2 (ΔPeak Vo_2) induced by Waon therapy and changes in the left ventricular ejection fraction (ΔLVEF) *(A)*, plasma norepinephrine (Δp-NE) *(B)*, brain natriuretic peptide level (ΔBNP) *(C)*, and FMD (ΔFMD) *(D)*. Change in peak Vo_2 was positively correlated with ΔFMD but not with other variables.

ance.[13] Exercise training improves endothelial function, thereby leading to improvement of exercise tolerance.[14] Similarly, enhanced external counterpulsation increased FMD, and the mechanism of enhanced external counterpulsation–induced increases in FMD might be involved in increasing nitric oxide bioavailability.[15] A recent experimental study demonstrated that impaired endothelium-dependent vasodilation as induced via nitric oxide synthesis inhibition was associated with reduced exercise capacity.[10] In patients with CHF, the release of endothelial nitric oxide and the responsiveness of vascular smooth muscle to nitric oxide are impaired, resulting in reduced exercise tolerance.[8,9,16] In fact, the average value of FMD in the present patients before Waon therapy was 3.5%, considerably lower compared to that in healthy subjects.[17] Given that previous studies have reported that Waon therapy increases endothelial nitric oxide synthase activity and improves FMD,[3,18] the augmentation of nitric oxide bioavailability is a plausible mechanism underlying the beneficial effects of Waon therapy. In the present study, Waon therapy–induced improvement of endothelial function was associated with increased exercise tolerance assessed not only by 6MWD but also by peak Vo_2. Furthermore, this improvement in endothelial function was found to be the only independent determinant of increased 6MWD. Taken together, the improvement in exercise tolerance induced by Waon therapy might be accomplished, at least in part, through an improvement of endothelial but not cardiac function. The relations between changes in 6MWD and other variables, including the left ventricular ejection fraction, plasma levels of norepinephrine and brain natriuretic peptide, and FMD, were fairly weak (Figure 1), and Waon therapy–induced improvement in 6MWD was relatively small compared to that of FMD (Table 2). A previous study reported in patients with CHF that exercise training resulted in a greater improvement in acetylcholine-induced increase of peripheral blood flow by 203%, compared to a 26% increase of peak Vo_2,[14] a finding consistent with the present results.

Circulating EPCs were positively correlated with endothelial function as assessed by FMD in healthy men.[19] In another study, circulating EPCs were shown to be an independent predictor of mortality in patients with CHF.[20] Treatment with statins increased the number of circulating EPCs and enhanced functional capacity, an effect likely mediated by statin-induced stimulation of the Akt/endothelial nitric oxide synthase pathway.[21] Waon therapy increased myocardial endothelial nitric oxide synthase and vascular endothelial growth factor messenger ribonucleic acid levels in rats after myocardial infarction.[22] The angiogenic cytokine of vascular endothelial growth factor is a mobilizing factor of EPCs from bone marrow.[23] Therefore, as shown in the present study, Waon therapy could increase the number of circulating $CD34^+$ cells, a putative precursor of EPCs. However, in general agreement with a previous study,[24] increases in circulating $CD34^+$ cells in the present study did not correlate with improvement in exercise tolerance.

The present study had several limitations. First, this study included a modest number of patients and lacked a control group. Therefore, we are unable to draw definitive conclusions. Although patients tend to improve exercise performance on several exercise tests without effective ther-

apy, previous studies have demonstrated that Waon therapy–induced improvement in FMD and 6MWD was prominent, but control patients did not show significant improvement after their follow-up studies.[3,25] In a review based on randomized trials,[26] the mean change in 6MWD was 20 m in placebo groups, considerably lower compared to Waon therapy–induced changes in 6MWD (45 m) in the present study. Second, the follow-up period was relatively short, and thus the long-term effect of Waon therapy on exercise tolerance remains to be further elucidated, although in some of the present patients, twice-a-week Waon therapy for 4 months maintained the improvement in exercise tolerance induced by 3-week Waon therapy. Prospective, multicenter, long-term studies are required to clarify these issues.

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