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# Preliminary Trial of Lower Leg Thermal Therapy for Patients with Terminal Heart Failure Fitted with Left Ventricular Assist Device

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Additional information is available at the end of the chapter

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## 1. Introduction

In 1989 Tei et al. developed Waon therapy for heart failure that uses a dry sauna (Tei et al., 1994; Tei et al., 1995; Tei 2007). Waon therapy means a thermal therapy using specially designed sauna bath for heart failure. In the therapy, patients were placed in a sitting-position in a 60 °C far infrared-ray dry sauna system for 15 min, and then after leaving the sauna, they underwent bed rest with a blanket to keep them warm for an additional 30 min. And fluids corresponding to perspiration are supplied to protect against dehydration at the end of therapy. In this specially designed sauna system, the body core temperature has increased by 1.0–1.2°C, various beneficial effects for symptoms of heart failure were found (Tei, 2007).

Tei et al. have reported that Waon therapy significantly improved clinical symptoms, increased ejection fraction, and decreased cardiac size on echocardiography and chest radiography in congestive heart failure (CHF) patients (Tei & Tanaka, 1996). Recently, Miyata M et al. confirmed the beneficial effects and safety of Waon therapy applied for 2 weeks in CHF patients in a prospective multicenter case—control study (Miyata et al., 2008). Kihara et al. previously demonstrated that Waon therapy improved not only cardiac function, but also endothelial function in patients with CHF. They have also reported that 2 weeks of Waon therapy significantly reduced brain natriuretic peptide blood levels and improved flow-mediated vasodilation in CHF patients (Kihara et al., 2002). Furthermore, they have reported that Waon therapy for 2 weeks decreased ventricular premature

contractions and increased heart rate variability in CHF patients (Kihara et al., 2004), suggesting that Waon therapy decreased sympathetic nervous activity and improved ventricular arrhythmias.

A large number of end-stage CHF patients in Japan have been implanted with a left ventricular assist device (LVAD) because of prolonged waiting period for heart transplants (Osada et al., 2005). Although we wished to apply sauna thermal therapy to patients with LVAD, we do not have an appropriate sauna facility. Thus, we attempted to apply lower leg thermal therapy to the patients with LVAD awaiting a heart transplant. We describe here a case series of lower leg thermal therapy for the first time to elucidate the safety and effectiveness of this preliminary trial for the patients fitted with left ventricular assist device for end-stage heart failure.

## 2. Methods

### 2.1. Patients and study design

The study subjects included consecutive 6 end-stage CHF patients who were listed on waiting list for heart transplant in National Cerebral and Cardiovascular Center, Suita, Japan. All patients had dilated cardiomyopathy refractory to maximal medical therapy including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, diuretics, and digitalis. Regardless of intensive care with intravenous inotropic agents, heart failure rapidly progressed to cardiogenic shock in the patients. And they were fitted with extracorporeal LVAD (VCT-50, Toyobo Ltd., Osaka, Japan) to stabilize the hemodynamics. None of the patients was implanted with a defibrillator device.

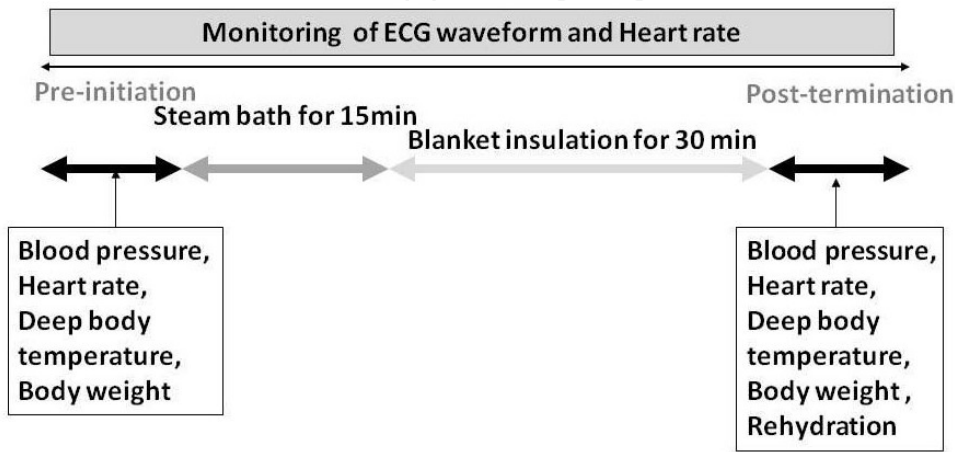
Patients' general condition stabilized thereafter and the status of heart failure at the time of study was New York Heart Association (NYHA) class II<sub>m</sub> with hemodynamic support. Although this status remained stable for at least 6 months, patients' cardiac function did not sufficiently recover to discontinue LVAD support. The patient provided written informed consent to enter into a clinical trial of lower leg thermal therapy for patients with LVAD awaiting a heart transplant. The Ethics Committee at the National Cerebral and Cardiovascular Center approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. Lower leg thermal therapy was conducted with a steam bath at 42 °C. Typical example of lower leg thermal therapy was illustrated in Fig.1.

After 15 min of therapy at 42 °C, the patient remained seated in the steam bath with the lower legs and feet wrapped with a blanket for 30 min. The study consisted of clinical examinations before and after daily thermal therapy for 2 weeks (Fig. 2).

Study protocol for 2 weeks treatment was illustrated in Fig. 3. The procedure of lower leg thermal therapy was accompanied by electrocardiographic monitoring. The patient remained on the same medications with same dose throughout the study period.



**Figure 1.** Typical settings for lower leg thermal therapy for a patient with left ventricular assist device.



**Figure 2.** Illustrative presentation of the lower leg thermal therapy.



Venous blood samples were drawn through an indwelling catheter in the forearm of each patient after they had lain quietly and undisturbed for at least 30 min. Plasma was immediately separated and stored at  $-70^{\circ}\text{C}$  before the norepinephrine (NE) concentrations were determined by high performance liquid chromatography electrochemical detection. Plasma brain natriuretic peptide (BNP) was determined by the chemiluminescent enzyme immunoassay. For nitric oxide (NO) measurement, the blood specimen was placed immediately in an ice bath and centrifuged within 30 seconds for 5 minutes at 2000g. The serum fraction was diluted 1:1 with nitrite- and nitrate-free distilled water, and 400 mL of the diluted sample was centrifuged at 2000g in an ultra-free MC microcentrifuge device (Millipore) to remove substances larger than 10 kD. The filtrate was passed through a copper-plated cadmium column to reduce nitrate to nitrite and then reacted with Griess reagents consisting of 0.1% naphthylethylenediamine dihydrochloride in distilled water and 1% sulfanilamide in 5%  $\text{H}_3\text{PO}_4$ , after which absorbance was measured at 540 nm to provide the total amount of plasma NO end products (nitrate plus nitrite). The efficiency of the cadmium column in the conversion of nitrate to nitrite was confirmed to be 100% by measuring both nitrate and nitrite standards before and after sample measurement (Node et al., 1997). Plasma hydroperoxides, which was determined by Diacron reactive oxygen metabolites test, comprise a marker of oxidative stress (Cesarone et al., 1999) and OXY absorbent test indicates buffering potential against oxidant action of hypochlorous acid (HClO), which is quantified by HClO expense, and comprise a marker of anti-oxidative potency (Trotti et al., 2001).

Endothelial function was quantified by the reactive hyperemic (RH) change in digital blood flow after arm occlusion using a peripheral fingertip arterial tonometry (PAT) device (Endo-PAT 2000 system; Itamar-Medical, Caesarea, Israel) (Bonetti et al., 2004; Hamburg & Benjamin, 2009). After 5 min of baseline recording, a BP cuff was inflated to supra-systolic pressure in the test arm. After 5 min of occlusion, the cuff was rapidly deflated, with PAT tracings recorded. The reactive hyperemic PAT (RH-PAT) response was determined as the ratio of PAT amplitude in the test arm to control arm, averaged in 30-s intervals after cuff deflation, divided by the average PAT ratio measured for the 140-s interval before cuff inflation. RH-PAT ratio was assessed between 60 s and 120 s after occlusion and was log-transformed of the post-deflation to baseline pulse amplitude in the hyperemic finger normalized to the contralateral finger.

### 2.3. Statistical analysis

All data are expressed as the mean value  $\pm$  S.D. Differences between the baseline and 2 weeks after treatment were estimated by paired t test or Mann-Whitney U test, as appropriate for continuous variables, and by Fisher's exact test or chi square test, as appropriate for categorical variables. Value of BNP was log-transformed to remove skewness of data distribution. A  $p$ -value of  $<0.05$  was considered statistically significant.

## 3. Results

### 3.1. Clinical findings and physical examinations

Table 1 summarized the results of clinical findings and physical examinations. During the study, none of the patients treated with lower leg thermal therapy had worsened clinical



symptoms. The changes in the clinical findings and variables after 2 weeks are summarized in Table. Although NYHA functional class remained similar at class II<sub>m</sub>, activity of daily life estimated by SAS system significantly increased from 2.55 Mets to 3.10 Mets ( $p = 0.044$ ).

Systolic and diastolic blood pressure did not differ between the baseline and 2 weeks after the therapy. Heart rate might tend to decrease a little bit from 74 bpm to 72 bpm ( $p = 0.088$ ). Numbers of ventricular premature beats were dispersed among the patients at the baseline as well as 2 weeks after treatment. Thus, the average number of ventricular premature beats was not different between the baseline and 2 weeks after the therapy.

There was no significant change in body weight. Body surface temperature (axillary temperature) in the morning round was not different between the baseline and 2 weeks after the therapy. However, the deep body temperature (sublingual temperature) significantly increased from 36.0 degree Celsius to 36.9 degree Celsius ( $p = 0.004$ ), just after the steam bath for lower legs. The average difference between the baseline and immediately after the therapy was 0.85 degree Celsius.

|                                       | Before      | After       | p value |
|---------------------------------------|-------------|-------------|---------|
| Sample size                           |             | 6           | 6       |
| Age (years)                           | 34.8±8.0    |             |         |
| Activity of Daily Life (Mets)         | 2.55±0.81   | 3.10±0.99   | 0.044   |
| Systolic BP (mmHg)                    | 91.2±10.0   | 92.3±14.4   | 0.682   |
| Diastolic BP (mmHg)                   | 54.8±9.0    | 56.8±9.2    | 0.310   |
| Heart Rate (bpm)                      | 74.0±8.3    | 71.9±8.3    | 0.088   |
| Ventricular Premature Beats (per day) | 92.8±48.1   | 55.3±15.9   | 0.100   |
| Body Weight (kg)                      | 53.2±8.9    | 53.0±9.2    | 0.383   |
| Morning Body Temperature (C)          | 35.8±0.33   | 36.0±0.41   | 0.476   |
| Deep Body Temperature (C)             | 36.0±0.26   | 36.9±0.36   | 0.004   |
| Cardiothoracic Ratio (%)              | 56.6±13.2   | 55.3±13.7   | 0.065   |
| NE (pg/mL)                            | 971.2±403.6 | 848.6±313.5 | 0.077   |
| log BNP (pg/mL)                       | 2.128±0.516 | 2.080±0.505 | 0.030   |
| Nitrogen oxide (μmol/L)               | 30.1±12.1   | 46.5±17.7   | 0.019   |
| Hydroperoxides (carr U)               | 513.0±75.0  | 439.3±78.4  | 0.0001  |
| OXY absorbent test (μmol HCl/mL)      | 400.7±38.2  | 456.7±51.9  | 0.078   |
| LAD (mm)                              | 43.3±9.4    | 41.9±9.5    | 0.063   |
| LVDd (mm)                             | 54.4±10.8   | 53.1±11.9   | 0.130   |
| LVDs (mm)                             | 43.2±13.6   | 40.3±13.8   | 0.025   |
| LV Fractional Shortening (%)          | 21.9±8.7    | 25.3±8.9    | 0.028   |
| Mitral Regurgitation (grade)          | 2.2±1.0     | 1.3±0.8     | 0.061   |
| RH-PAT ratio                          | 1.36±0.22   | 2.09±0.28   | 0.006   |

BNP brain natriuretic peptide, BP blood pressure, LAD left atrial dimension, LV left ventricular, LVDd left ventricular diastolic diameter, LVDs left ventricular systolic diameter, NE norepinephrine, OXY oxidant, RH-PAT reactive hyperemic peripheral arterial tonometry

**Table 1.** Summary of changes in parameters before and after the thermal therapy

### 3.2. Chest radiography and echocardiography

Table 1. described the results of chest radiography and echocardiography. Chest radiography showed a slight decrease of the mean CTR from 57% to 55% after 2 weeks of treatment compared to the baseline ( $p = 0.065$ ).

Echocardiography demonstrated a slight decrease in the mean LAD from 43 mm to 42 mm ( $p = 0.063$ ). While, LVDd showed no changes after treatment (54 mm to 53mm,  $p = 0.130$ ), LVDs significantly decreased after treatment from 43 mm to 40 mm ( $p = 0.025$ ). Therefore, LV fractional shortening also significantly increased after treatment from 22% to 25% ( $p = 0.028$ ).

Doppler echocardiography demonstrated that the extent of mitral regurgitation tended to decrease after treatment (mean MR grade: 2.2 to 1.3,  $p = 0.061$ ). Taken together, the left ventricular function was improved and the heart size tended to decrease after 2 weeks of the therapy.

### 3.3. plasma levels of norepinephrine, BNP, nitrogen oxide and hydroperoxides, and result of OXY adsorbent test

Table 1. showed the changes in plasma concentration of norepinephrine, BNP, nitrogen oxide (nitrate plus nitrite), hydroperoxides and hypochlorous acid. Plasma mean concentration of norepinephrine slightly decreased after 2 weeks of the therapy (971 pg/mL to 849 pg/mL,  $p = 0.077$ ). The plasma mean concentration of BNP significantly decreased after 2 weeks of the therapy, (log BNP: 2.128 to 2.080 pg/mL,  $p = 0.030$ ).

Plasma mean concentration of nitrogen oxide (nitrate plus nitrite), stable metabolites of nitric oxide, significantly increased after 2 weeks of the therapy (30.1  $\mu\text{mol/L}$  to 46.5  $\mu\text{mol/L}$ ,  $p = 0.019$ ). Plasma mean concentration of hydroperoxides, a biomarker reflects oxidative stress, significantly decreased after 2 weeks of the therapy (513 carr U to 439 carr U,  $p = 0.0001$ ). OXY absorbent test, a marker of anti-oxidative potency, showed non-significant increase after 2 weeks of the therapy (401  $\mu\text{mol HClO/mL}$  to 457  $\mu\text{mol HClO/mL}$ ,  $p = 0.078$ )

### 3.4. Endothelial function

The mean RH-PAT ratio determined with Endo-PAT 2000 system was augmented 2 weeks after the therapy compared to the baseline (1.36 to 2.09,  $p = 0.006$ ).

## 4. Discussion

This is the first report of case series of lower leg thermal therapy being applied to patients implanted with LVAD and awaiting heart transplantation. Waon therapy or whole body sauna therapy for CHF is now widely recognized to improve clinical symptoms, cardiac function, quality of life, and ventricular arrhythmia, and decreased levels of abnormally activated neurohumoral factors (Tei et al., 1995; Tei & Tanaka, 1996; Tei 2007; Kihara et al., 2002; Kihara et al., 2004).



Waon therapy is impractical for patients with CHF in usual general hospitals that lack sauna facilities, whereas lower leg thermal therapy using a steam bath can be applied routinely in a patient's room in common general hospitals. Increases in deep body temperature of 1.0-1.2 °C during Waon therapy dilate systemic arteries and veins, and reduce systemic preload and afterload, resulting in increased cardiac output (Tei et al., 1995; Tei & Tanaka, 1996; Tei 2007; Kihara et al., 2002; Kihara et al., 2004). The sublingual temperature of the patients after our lower leg thermal therapy increased by only 0.85 °C. Nevertheless, the clinical benefits seemed to be similar to those of Waon or whole body sauna therapy.

Ikeda et al. found that repeated Waon therapy increases endothelial nitric oxide synthase expression and nitric oxide production, and improves cardiac function in animal models of heart failure (Ikeda et al., 2001; Ikeda et al., 2005). Serum nitrate plus nitrite levels doubled in our patient compared with the baseline values, as did the index of endothelial function determined by RH-PAT. Thus, lower leg thermal therapy might upregulate nitric oxide production in the endothelium.

Recently, Kuwahata et al. demonstrated that Waon therapy suppressed the elevated autonomic nervous activity levels in chronic heart failure (Kuwahata et al., 2011). Fujita et al. reported that Waon therapy reduced oxidative stresses in chronic heart failure (Fujita et al., 2011). Those findings dovetail with the results of the present study. Lower leg thermal therapy may have a stress-reducing effect.

Bathing in hot water might suppress oxidative stress and enhance endothelial function via upregulation of expression of heat shock protein (Okada M et al., 2004). Immersion not in hot water but in warm water (33-34 °C) still ameliorated cardiac dysfunction of chronic heart failure (Cider A et al., 2006). Thus, heating may have a beneficial effects on symptoms of heart failure.

Patients implanted with an LVAD for a long period often develop serious hemorrhage in the cerebrum or elsewhere, and drive-line infections. We were concerned that lower leg thermal therapy would aggravate hemorrhage or infection of patients through its vasodilatory effects. On the contrary, we found that oozing of blood at the insertion site of the LVAD drive-line tended to resolve during the therapy in several patients (data not shown). Furthermore a previous study reported that topical thermal therapy was not expected to be accompanied by marked alterations in heart rate, mean arterial pressure, or cardiac output and therefore would not likely activate the renin-angiotensin aldosterone system (Weber AA et al., 2007). In our present study, we did not find significant changes in hemodynamics of the patients.

Impacts of lower leg exercise on muscles and vessels of lower extremities ameliorates dyspnea in CHF or chronic obstructive pulmonary disease (Benjaminovitz A et al., 2002; Sillen MJ et al., 2009). And lower leg exercise increased endothelial function even in upper arms and affected clinical symptoms of CHF especially in those who cannot do conventional exercise programme (Deftereos S et al., 2010). Exercise in CHF enhances not only endothelial functions in systemic vasculature but also has anti-inflammatory effects on the endothelium (Duscha BD et al., 2008).

Aside from exercise, heat is a natural vasodilator. Thus, judicious use of heat in the form of thermal baths, saunas, and/or heating pads is slowly gaining recognition as a potential supplement to pharmaceuticals to improve endothelial function and cardiorenal hemodynamics in selected patients with CHF. Yoon et al. reported that warm footbath increased coronary blood flow velocity in the left anterior descending coronary artery by 17% in patients with coronary artery disease (CAD) (Yoon SJ et al., 2011). In our experiment, coronary blood flow velocity in the left anterior descending coronary artery before and after the lower leg thermal therapy was determined in a patient with CHF and the velocity increased by 10% after the therapy (data not shown).

We did not conduct lower leg thermal therapy for CAD patients yet. Previous studies showed the thermal therapy for CAD might cause myocardial ischemia (Giannetti N et al., 1999), or myocardial infarction and sudden cardiac death (Hannuksela ML et al., 2001). Thus, CHF due to non-ischemic diseases like dilated cardiomyopathy in our case might be a good indication for lower leg thermal therapy.

Waon therapy attenuates psychological stress (Kihara et al., 2004). Because of a donor shortage in Japan, patients must remain attached to an LVAD and stay for over 2 years in hospital while waiting for a heart transplant (Takatani et al., 2005). The tendency of decrease in plasma norepinephrine in the present study indicated that lower leg thermal therapy also might attenuate psychological, as well as physical stress.

Compared to pharmacological vasodilator therapy and other non-pharmacological therapy, such as cardiac resynchronization therapy (CRT) or cardiac rehabilitation, there are several advantages of lower leg thermal therapy for CHF. First, it is quite safe and has no adverse effects. Second, it might be less expensive and more cost-effective compared to Waon therapy or CRT. Third, unlike cardiac rehabilitation, patients who have severe congestive heart failure, uncontrolled ventricular arrhythmias, or orthopedic limitations are not exempt from undergoing lower leg thermal therapy. Fourth, this treatment may promote mental and physical relaxation. Above all, the most distinctive feature of lower leg thermal therapy is a potential to be useful in conjunction with other therapeutic modalities of pharmacological and non-pharmacological measures. Lower leg thermal therapy may thus be a valuable adjunct to pharmacological or non-pharmacological intervention in the management of CHF. We have a high expectation for the future of lower leg thermal therapy. All that we need is a randomized clinical trial.

## 5. Study limitation

Although the present study is just preliminary one, sample size is very small, and is not randomized. Recruitment of study subjects is still continuing. In the present protocol, study subjects were implanted with LVAD for end-stage heart failure, who were not common in usual hospitals. Furthermore, the endpoints are surrogate ones. Thus, we have to be very careful to interpret the study results.

## 6. Conclusion

Although in a very small cohort, we confirmed that lower leg thermal therapy was quite safe, and improved clinical symptoms and cardiac function in patients with extracorporeal LVAD awaiting heart transplantation. Lower leg thermal therapy may be a valuable adjunct to pharmacological or non-pharmacological intervention in the management of chronic heart failure. The procedure of lower leg thermal therapy might benefit other kinds of patients, including those with end-stage heart failure.

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