



Repeated Waon therapy improves pulmonary hypertension during exercise in patients with severe chronic obstructive pulmonary disease

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KEYWORDS

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Abstract

Objectives: Repeated Waon therapy, which uses a far infrared-ray dry sauna system, improved the vascular endothelial function and the cardiac function in patients with chronic heart failure. In patients with chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH) is associated with a poor prognosis. We investigated whether repeated Waon therapy improves PH, cardiac function, exercise tolerance, and the quality of life (QOL) in patients with COPD.

Methods: Consecutive 13 patients with COPD, who met the Global Initiative for Chronic Obstructive Lung Disease criteria and had breathlessness despite receiving conventional treatments, were recruited for this study. They underwent Waon therapy at 60 °C in sauna for 15 min following 30 min warmth with blankets outside of the sauna room. This therapy was performed once a day, for 4 weeks. Cardiac function, exercise tolerance, and St. George's Respiratory Questionnaire (SGRQ) were assessed before and 4 weeks after Waon therapy.

Results: Right ventricular positive dP/dt at rest elevated significantly from 397 ± 266 to 512 ± 320 mmHg/s ($p=0.024$) after the therapy. While the PH at rest did not significantly decrease, the PH during exercise decreased significantly from 64 ± 18 to 51 ± 13 mmHg ($p=0.028$) after Waon therapy. Furthermore, the therapy prolonged the mean exercise time of the constant load of cycle ergometer exercise test from 360 ± 107 to 392 ± 97 s ($p=0.032$). The total scores of SGRQ improved from 59.7 ± 16.9 to 55.3 ± 17.2 ($p=0.002$). In addition, no adverse effects were observed related to Waon therapy.

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Conclusions: Repeated Waon therapy improved right ventricular positive dP/dt , PH during exercise, exercise tolerance and the QOL in patients with severe COPD.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, debilitating and fatal lung disease. Many patients with COPD suffering from breathing-related problems in spite of receiving conventional therapies such as medication, physical therapy and oxygen inhalation [1]. Therefore, there is a great demand for the development of new therapies for COPD.

In patients with COPD, pulmonary hypertension (PH) is associated with a poor prognosis. Remodeling of the pulmonary vessels is the principal causative factor of PH in COPD. PH is a common complication of COPD, and its presence is associated with shorter survival and worse clinical course [2]. However, severe PH at rest is uncommon in patients with COPD [3]. Kessler et al. assessed the evolution of pulmonary hemodynamics in a group of 131 patients with moderate COPD who did not have PH at rest, although 76 patients (58%) developed PH during exercise [4].

We developed a form of thermal therapy, namely Waon therapy (soothing warm therapy) that differs from the traditional sauna [5]. We previously reported that repeated Waon therapy improved the vascular endothelial function in persons with risk factors for atherosclerosis [6]. Furthermore, this therapy improved the cardiac function and exercise tolerance in patients with congestive heart failure, who suffered from chronic symptoms despite the administration of full medications, and it was also performed safely in patients with high risk [7,8]. These effects are attributable to the reduction in the cardiac preload and afterload [7]. We also have reported that the mechanism of improvement of vascular function due to an overexpression of endothelial nitric oxide synthase (eNOS) in Syrian golden hamsters [9]. We consider that the eNOS upregulation induced by sauna is caused by increases in the cardiac output and blood flow, which in turn results in an increased shear stress. Therefore, we expect that repeated Waon therapy may relieve the symptoms in COPD patients by improving PH.

The present study investigated whether repeated Waon therapy improves PH, cardiac function, exercise tolerance, and the quality of life (QOL) in patients with severe COPD.

Subjects and methods

Study group

We studied consecutive 13 patients with COPD who satisfied the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (i.e. $FEV_1/FVC < 70\%$ after bronchodilator agent administration). They had symptoms such as cough and dyspnea with grade 4 or 5 of Medical Research Council (MRC) dyspnea scale in spite of conventional treatments, no acute exacerbation of COPD in the past 3 months and no signs of any respiratory tract infection. All patients have already received medications for COPD, such as inhaled β_2 -agonists, anticholinergics and oral theophyllines. The medications and pulmonary rehabilitation programs had not been changed for at least 4 weeks before and during this study. Written informed consent was obtained from all of the patients before participation. This protocol was approved by the Ethics Committee of the Faculty of Medicine, Kagoshima University.

Waon therapy

Waon therapy used a far infrared-ray dry sauna which is evenly maintained at 60°C and differs from traditional sauna. Waon therapy has an absence of hydration pressure, and was performed as previously reported [7]. Briefly, the patients were placed in a supine position on a bed in a 60°C sauna for 15 min, and then after leaving the sauna, they were then underwent bed rest with a blanket to keep them warm for an additional 30 min. All patients were weighed before and after the therapy, thereafter oral hydration with water was used to compensate for the lost weight.

Waon therapy was performed once a day, 5 days a week for 4 weeks, a total of 20 times. To rule out acute effects of Waon therapy, all examinations were performed before the first treatment and on the next day after the last treatment.

Measurements

Physical examinations

The blood pressure (BP), pulse rate, body weight and body temperature were measured before and after Waon therapy.

Cardiac function tests

Echocardiography was performed to evaluate the cardiac function and to determine the tricuspid regurgitation speeds by the continuous wave Doppler echocardiography, in which the pulmonary systolic pressure was estimated by the use of Bernoulli's equation. The LV and RV functions were analyzed by the Tei index, the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time [10]. Right ventricular (RV) positive dP/dt at rest was assessed by using tricuspid regurgitation (TR) estimated with Doppler echocardiography before and after Waon therapy. Two points at 1.0 and 2.0 m/s were selected on the rising segment of the TR velocity curve and the time interval (Δt) between them was measured. The increase in instantaneous velocity between the two points was converted to RV-right atrial pressure gradient (ΔP) using the simplified Bernoulli equation. The rate of RV pressure rise was obtained as $\Delta P/\Delta t$ [11].

In addition, we performed echocardiograms during ergometer exercise to monitor the changes in the pulmonary arterial pressure. Studied patients pedaled a bicycle (Aerobic Exercise Ergometer, STB-1200; Nihon Kohden; Tokyo, Japan) with a 10 W load for 3 min and after that, the load of the bicycle increased by 10 W for additional every 3 min. And they kept pedaling at the speed of 60 rpm and were encouraged to continue exercising for as long as possible. We recorded TR velocity by the continuous wave Doppler echocardiogram every 3 min.

We evaluated exercise tolerance by ergometer. At first, the patients pedaled a bicycle without a

load for 3 min and after that, the load of a bicycle increased by 10 W every minute. They pedaled a bicycle at the speed of 60 rpm. The patients were encouraged to continue exercising for as long as possible. The test was terminated at symptom limitation or if there were any safety concerns. We monitored oxygen saturation by pulse oximeter (SpO_2), BP, heart rate (HR) and ECG during exercise.

St. George's Respiratory Questionnaire (SGRQ) scores

The health-related quality of life was evaluated with the Japanese versions of St. George's Respiratory Questionnaire (SGRQ) which is a measure of impaired health in disease of chronic airflow limitation. SGRQ contains 50 items that can be divided into three dimensions (symptoms, activity and impacts), and their scores ranged from 0 to 100 (worst status) [12].

Laboratory measurements

A blood sample was obtained to measure the plasma levels of the brain natriuretic peptide (BNP) with a radioimmunoassay, hematocrit and albumin before and after repeated Waon therapy.

Statistical analysis

All data are expressed as the mean value $\pm$ S.D. The data before and after Waon therapy were compared using the paired Student's *t*-test. A *p*-value of <0.05 was considered to be significant.

Table 1 Patient's profile

Case	Age	Gender	Height (cm)	BW (kg)	BMI (kg/m ²)	%FEV1	GOLD stage	MRC scale	SI (pak-year)
1	67	M	161.5	56.0	20.5	18.9	IV	5	88
2	73	M	155.0	37.4	15.6	34.3	IV	5	68
3	80	M	160.9	70.3	27.1	34.2	IV	5	50
4	69	M	156.0	47.0	19.3	34.4	III	4	34
5	67	M	166.3	61.5	22.2	11.9	IV	5	60
6	76	M	166.1	43.4	15.7	40.2	IV	5	92
7	76	M	163.7	43.4	16.1	37.5	IV	5	46
8	86	M	161.8	54.5	20.8	48.5	III	5	45
9	77	M	159.8	46.0	18.0	37.5	III	5	61
10	79	M	150.6	51.1	22.7	51.5	II	4	60
11	71	M	163.0	49.0	18.4	39.7	IV	4	45
12	75	M	164.0	56.2	20.9	61.2	IV	4	80
13	78	M	155.4	57.2	23.7	57.5	II	4	114

M, male; BW, body weight; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council; SI, smoking index.

Table 2 Physical findings and laboratory examinations

	Before therapy	After therapy	p-Value
BW (kg)	50.8 ± 7.8	50.9 ± 7.8	0.926
HR (bpm)	86 ± 9	85 ± 13	0.820
SBP (mmHg)	130 ± 17	120 ± 15	0.002
DBP (mmHg)	74 ± 9	69 ± 8	0.0002
Hematocrit (%)	40.3 ± 9.2	40.0 ± 8.5	0.617
Alb (g/dl)	4.1 ± 0.3	4.1 ± 0.3	1.0
BNP (pg/ml)	25.7 ± 19.6	21.3 ± 13.4	0.294

Value given as mean ± S.D.; BW, body weight; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; BNP, brain natriuretic peptide.

Results

Clinical characteristics

The clinical characteristics of 13 patients are summarized in [Table 1](#). All patients were male with a mean age of 74.9 ± 5.5 years (range, 67–86 years). The mean BMI was 20.1 ± 3.4 , and the mean %FEV₁ was $39.0 \pm 13.8\%$. They were all past smokers. According to the GOLD classification, eight patients were in stage IV (very severe), while 3 patients were in stage III (severe), and the other 2 patients were in stage II (moderate). Eight patients were MRC dyspnea scale grade 5 and 5 patients were grade 4.

Effects of Waon therapy on body weight, heart rate, blood pressure and laboratory variables

We performed repeated Waon therapy without any problems for all enrolled patients. None of the patients experienced dyspnea in the sauna room. Physical findings and laboratory examinations before and after repeated Waon therapy are demonstrated in [Table 2](#). All patients did not have any cardiac disorders either during or after Waon therapy. The mean body weight and the mean HR did not substantially change before and after Waon therapy. On the other hand, systolic

and diastolic blood pressure decreased significantly (systolic blood pressure: 130 ± 17 to 120 ± 15 , $p = 0.002$; diastolic blood pressure: 74 ± 9 to 69 ± 8 , $p = 0.0002$) after Waon therapy. The hematocrit, albumin and plasma BNP concentrations did not change. The MRC dyspnea scale grades did not change. In addition, the liver function, renal function and electrolytes did not change after Waon therapy (data not shown).

Cardiac function

Cardiac function was evaluated by the use of echocardiography before and after repeated Waon therapy. The ejection fraction and systolic pulmonary artery (PA) pressure at rest did not change after the therapy in comparison to baseline. The RV Tei index tended to decrease after the therapy (0.51 ± 0.15 to 0.46 ± 0.11 , [Table 3](#)). RV positive dP/dt elevated significantly from 397 ± 266 to 512 ± 320 mmHg/s ($p = 0.024$) after the therapy ([Table 3](#)). No patients had any symptoms or signs of heart failure during this therapy.

Exercise tolerance

The PA pressure at rest did not improved after repeated Waon therapy. However, the PA pressure during exercise decreased significantly after

Table 3 Echocardiographic parameters

	Before therapy	After therapy	p-Value
LVDd (mm)	41.0 ± 5.7	39.2 ± 5.6	0.184
LAD (mm)	30.3 ± 7.2	28.8 ± 8.7	0.923
EF (%)	68.8 ± 8.8	67.8 ± 8.8	0.602
LV Tei index	0.41 ± 0.08	0.43 ± 0.13	0.534
RV Tei index	0.51 ± 0.15	0.46 ± 0.11	0.169
Systolic PAP (mmHg)	41.0 ± 8.3	37.4 ± 6.4	0.168
IVC (mm)	9.2 ± 1.5	9.3 ± 1.6	0.675
RV dP/dt (mmHg/s)	397 ± 266	512 ± 320	0.024

Value given as mean ± S.D.; EF, ejection fraction; PAP, pulmonary artery pressure.

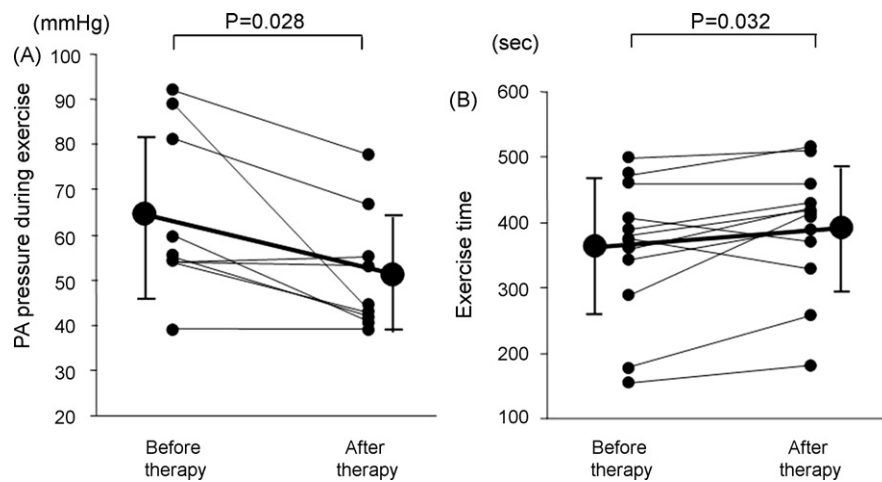


Figure 1 PA pressure during exercise (A) and exercise time (B) before and after 4 weeks of Waon Therapy. The mean of pulmonary arterial pressure during exercise decreased significantly after Waon therapy with the same loading dose of exercise. The exercise time significantly prolonged after Waon therapy. PA = pulmonary artery.

repeated Waon therapy in comparison to baseline (64.0 ± 18.0 to 51.3 ± 13.1 mmHg, $p=0.028$), with the same loading dose of exercise (Fig. 1A). The exercise time also significantly increased after repeated Waon therapy (359.6 ± 106.5 to 391.5 ± 97.0 s, $p=0.032$) (Fig. 1B). In addition, the lowest SpO_2 during exercise significantly elevated after the therapy (89.4 ± 4.8 to $91.3 \pm 4.1\%$, $p=0.022$) (Fig. 2).

St. George's Respiratory Questionnaire (SGRQ) scores measurements

SGRQ scores were measured to evaluate the change of QOL, which is consisted of 50 questionnaires

about symptoms, activity and impacts, before and after the repeated Waon therapy. The symptoms scores significantly decreased after repeated Waon therapy in comparison to baseline (67.7 ± 20.6 to 56.5 ± 23.5 , $p=0.007$). In addition, the total scores and the impacts scores in SGRQ significantly decreased (59.7 ± 16.9 to 55.3 ± 17.2 , $p=0.002$, 43.7 ± 21.8 to 40.1 ± 21.2 , $p=0.024$). The activity scores tend to decrease (83.3 ± 16.4 to 81.2 ± 15.0) (Fig. 3).

In contrast, the MRC did not change because it is a questionnaire only about dyspnea.

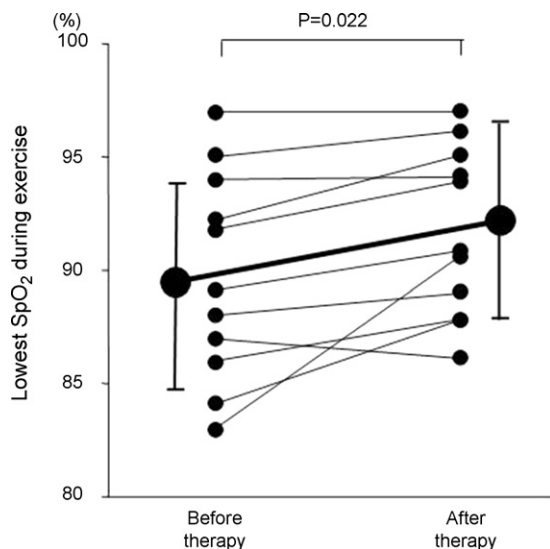


Figure 2 Changes of SpO_2 during exercise before and 4 weeks after Waon Therapy. SpO_2 during exercise is increased significantly.

Discussion

This is the first report to demonstrate that Waon therapy regimen improves PH during exercise, exercise time, in addition, the symptoms, impacts and total scores of SGRQ in the patients with severe COPD.

We suppose that the prolongation of exercise time by Waon therapy is related to the pulmonary arterial pressure during exercise, not at rest. An improvement of ventilation competence may be related to the prevention of desaturation during exercise. Previous studies have identified a number of mechanisms for exercise-induced PH in COPD, including hypoxic vasoconstriction, reduction of the capillary bed by emphysema, extramural compression by increased alveolar pressure or impaired release of endothelium-derived relaxing factors. These factors may together contribute to the development of PH during exercise, and dynamic hyperinflation due to the expiratory flow limitation that results in increased alveolar pressure [13–16].

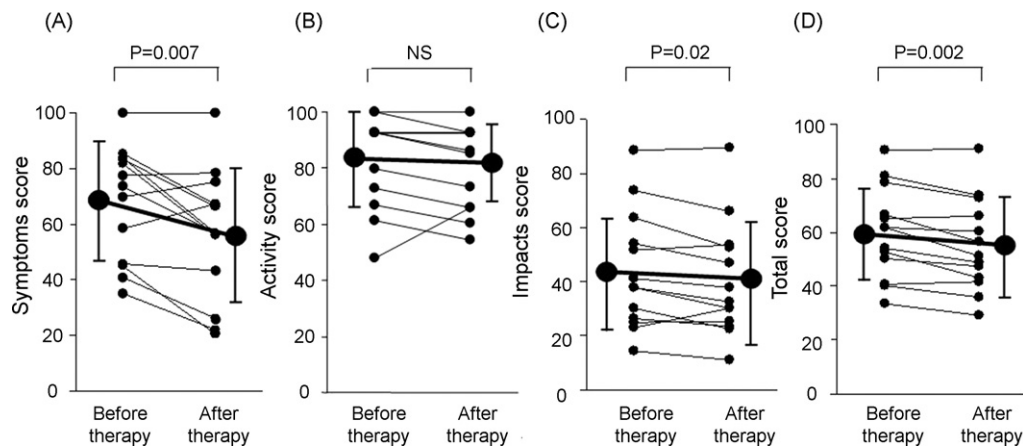


Figure 3 Changes of SGRQ symptoms score (A), activity score (B), impacts score (C), total score (D) before and 4 weeks after Waon Therapy. The symptoms, the impacts and the total scores significantly decreased after repeated Waon therapy. SGRQ= St. George's Respiratory Questionnaire.

Kubo et al. examined the relationship between vessel remodeling and the physiology of pulmonary circulation in severe COPD patients who underwent lung-volume-reduction surgery [17]. They analyzed the pulmonary hemodynamics at rest and during exercise, and the morphology of the pulmonary arteries in these patients. As a result, they have described that pulmonary artery remodeling leads to a reduced recruitability and distensibility of the pulmonary vessels and it is therefore closely related to exercise PH. Therefore, they suggested that the degree of the remodeling cannot be estimated by the resting pulmonary artery pressure. The expression of eNOS in pulmonary arteries is reduced in COPD patients with PH [18] and also in smokers [19]. The diminished synthesis of nitric oxide may contribute to the alterations in the structure and endothelial function of pulmonary vessels in cigarette-smoke-induced respiratory disease. In addition, the structural and functional changes of pulmonary circulation are apparent at the initial stages of COPD [19]. Recent investigations have shown endothelial dysfunction and the changes in the expression of endothelium-derived mediators that regulate vascular tone and cell growth in the pulmonary arteries of patients with mild COPD. The expression of eNOS decreases in the pulmonary arteries of COPD patients with pulmonary hypertension [20].

We previously demonstrated that the gene expression and protein level of eNOS increase significantly in the peripheral arteries from the golden hamster after 4-week repeated Waon therapy [9]. Moreover, we also reported this therapy improves the impaired vascular endothelial function in a setting of coronary risk factors [6]. We suggest that this therapy improves endothelial function in

COPD patients in the same way. The significant decrease in BP after this therapy is probably due to an improved endothelium-dependent vasodilation. Anconina et al. described RV dP/dt provides a reliable noninvasive index to approach RV contractility [11]. According to our data, RV dP/dt elevated significantly after the therapy, suggesting the improvement of RV contractility. We expect that Waon therapy increase the expression of eNOS in PA, and improve PA vascular function. Thereafter, RV contractility improved by reducing the afterload of RV. As a result, we therefore assume that the PH during exercise and the exercise tolerance also improved.

The present study indicates that 4-week Waon therapy regimen was found to improve symptoms and QOL in patients with COPD. Oga et al. reported the SGRQ total score to be a predictive factor of mortality, independent of FEV_1 and age [21]. In addition, Domingo-Salvany et al. reported the SGRQ total score to be independently associated with the total and respiratory mortality in Cox models, including age, FEV_1 , and BMI [22]. It was also notable that the SGRQ total score improved by Waon therapy in 4 weeks. Improvements in the symptoms score contributed to most of the improvements in the total score. We previously reported that a self-assessment QOL of the patients with chronic heart failure improved after this therapy [8]. In the items of a concrete questionnaire regarding symptoms, the frequency of a cough, respiratory symptomatic frequency and the period of being well conditioned were improved in this study. Ernst et al. suggested that regular sauna bathing may reduce the incidence of acute respiratory infections [23]. No patient demonstrated any respiratory tract infection during this study.

Masuda et al. reported that repeated Waon therapy may be useful for mildly depressed patients with appetite loss and other subjective complaints [24]. Patients with severe COPD are at an increased risk of developing depression [25]. We therefore suppose that this therapy may diminish the psychological distress in patients with COPD. Further studies are needed to investigate the change in the SGRQ scores and the frequency of acute exacerbations by continuing Waon therapy for a longer time period.

Study limitations

This study is not a case–control study and the study group was also very small. As a result, it remains necessary to investigate more COPD patients, including those with mild COPD. We also need to evaluate the airway inflammation in COPD after this therapy.

In addition, we need a further evaluation of the vascular endothelial function and changes in the pulmonary arterial pressure in COPD by continuing such Waon therapy for a longer period of time.

Conclusion

The repeated Waon therapy was thus found to improve the RV positive dP/dt , PH during exercise, exercise tolerance and SGRQ scores in the patients with severe COPD. This therapy may therefore be a novel, safe, and promising therapy for patients with severe COPD.

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