ORIGINAL RESEARCH

Short running header: Waon therapy effects on exercise tolerance in COPD patients
Hiroshi Kikuchi et al

Effect of repeated Waon therapy on exercise tolerance and pulmonary function in patients
with chronic obstructive pulmonary disease: A pilot controlled clinical trial

Hiroshi Kikuchi\(^{a,b}\), Nobuyoshi Shiozawa\(^{a}\), Shingo Takata\(^{a}\), Kozo Ashida\(^{a}\) and Fumihiro Mitsunobu\(^{a}\)

\(^{a}\)Division of Medicine, Misasa Medical Center, Okayama University Hospital, Misasa, Tottori,
Japan

\(^{b}\)Division of Internal Medicine, Takamatsu Hospital KKR, Takamatsu, Japan

Corresponding author: Fumihiro Mitsunobu
Okayama University Hospital Misasa Medical Center
827 Yamada, Misasa, Tohaku, Tottori 682-0122, Japan
Tel: +81 858431211; Fax: +81 85843130
E-mail: fumin@cc.okayama-u.ac.jp
Abstract:

Purpose: Controlled clinical trials evaluating the efficacy of repeated Waon therapy for patients with chronic obstructive pulmonary disease (COPD) have yet to be conducted. The purpose of the present study is to evaluate whether repeated Waon therapy exhibits an adjuvant effect on conventional therapy for COPD patients. Patients and methods: This prospective trial comprised 20 consecutive COPD patients who satisfied the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, stages 2–4. They were assigned to either Waon or control group. Patients in the Waon group received both repeated Waon therapy and conventional therapy; medications such as long-acting inhaled β2 agonists, long-acting anticholinergics and xanthine derivatives, and pulmonary rehabilitation. They sat in a 60°C sauna room for 15 min, followed by 30 min of being warmed with blankets once a day, five days a week, for a total of 20 times. Patients in the control group received only conventional therapy. Pulmonary function and six-minute walk test (6MWT) were assessed before and at four weeks after the program. Results: The amount of changes in vital capacity (VC) (0.30 ± 0.4 L) and peak expiratory flow (PEF) (0.48 ± 0.79 L/s) in the Waon group showed a tendency to be larger than those in VC (0.02 ± 0.21 L) (p = 0.077) and PEF (−0.11 ± 0.72 L/s) (p = 0.095) in the control group. The amount of changes in forced expiratory flow after 50% of expired FVC (FEF50) in the Waon group, 0.08 (0.01–0.212 L/s), was larger than that in FEF50 in the control group, −0.01 (−0.075–0.04 L/s) (p = 0.019). Significant differences were not observed in the amount of change in any parameters in the 6MWT. Conclusion: The addition of repeated Waon therapy to conventional therapy for COPD patients can possibly improve airway obstruction.

Keywords: Waon therapy, exercise tolerance, modified Borg scale, airway obstruction, COPD

Introduction

The number of patients diagnosed with chronic obstructive pulmonary disease (COPD) has been gradually increasing in Japan as the population ages. As various kinds of drugs, such as long-acting β2 agonists and long-acting anticholinergics, have come into wide use in recent years, the number of COPD patients who can live in a stable condition for many years has increased.
However, pulmonary rehabilitation plays an irreplaceable role, and is one of the most effective interventions in improving quality of life (QOL), exercise tolerance, and fatigue for all COPD patients.3

Especially in clinical practice, the purpose of treatment for COPD patients is to improve certain respiratory symptoms such as dyspnea on exertion and coughing up of sputum. Improvement of symptoms can expand patients' functional participation in activities of daily living, and improve their QOL.

Some studies indicating that pulmonary rehabilitation improves QOL for COPD patients have been reported. Godoy et al4 reported that the benefits provided by a pulmonary rehabilitation program in terms of the indices of QOL, as well as improved six-minute walk test performance, persisted throughout the 24-month study period in patients with COPD. Pulmonary rehabilitation does not always need to be conventional. Sindhwani et al5 reported that a domiciliary pulmonary rehabilitation program improved the QOL and exercise endurance of patients with severe COPD, and acted as a substitute for conventional pulmonary rehabilitation programs in resource-limited situations. Effective pulmonary rehabilitation for COPD patients is not necessarily formulaic. For example, the study by Rae et al6 suggested that the swimming pool was a feasible and positive alternative venue for pulmonary rehabilitation for COPD patients in primary care. These reports demonstrated that not only medication but also nondrug therapy, such as lung physical therapy or exercise therapy, is important for COPD patients and improves their QOL.

Tei et al7 were the first to report on hemodynamic changes in patients with congestive heart failure (CHF) during a sauna bath using an experiment using far infrared-ray dry sauna. Cardiovascular hemodynamics improved after a water bath or sauna in patients with chronic heart failure due to ischemic or idiopathic dilated cardiomyopathy. Twenty-eight patients showed improvement in left and right ventricular functions associated with reduction in afterload (total peripheral vascular resistance for the left ventricle and pulmonary vascular resistance for the right ventricle) on thermal vasodilatation after Waon therapy. Warming is also expected to dilate the venous system, which decreases pulmonary congestion. Results in this paper indicate that
cardiac index, stroke index, peripheral vascular resistance and pulmonary artery pressure significantly decreased during and for 30 min after Waon therapy. The duration of the effectiveness of Waon therapy has not been verified yet. Tei et al believed the endothelial nitric oxide synthase (eNOS) upregulation induced by the sauna was caused by increases in the cardiac output and blood flow, which in turn increased the shear stress.

In recent years in Japan, repeated Waon therapy has been put into practical use for patients with heart failure as nondrug therapy. Umehara et al reported that repeated Waon therapy improved pulmonary hypertension (PH) during exercise in 13 patients with severe COPD. The lowest SpO₂ during exercise, as assessed by ergometer, was significantly elevated and the exercise time also significantly increased after Waon therapy. We supposed that the improvement of exercise tolerance with COPD after repeated Waon therapy might be associated with improvement of airway obstruction in addition to improved PH.

There have been no controlled clinical trials to evaluate the effectiveness of repeated Waon therapy as nondrug therapy for COPD patients. The purpose of the present study is to evaluate whether repeated Waon therapy can exhibit an added effect to conventional therapies for COPD patients.

Patients and methods

Patients

This study comprised 20 consecutive inpatients and outpatients with COPD (age range, 50–80 years) who satisfied the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, stages 2–4. Subjects who had suffered from acute exacerbation, left-side heart failure and who were unable to walk because of arteriosclerosis obliterans and knee osteoarthritis within the month prior to the study were excluded. Subjects that went into respiratory distress and needed to receive additional therapy, or had difficulty walking because of leg pain during the study were also excluded.

Waon therapy
As previously reported, a far infrared-ray dry sauna (NOMS, Aichi, Japan) was used for Waon therapy. Patients were seated in a 60°C sauna room for 15 min, and, after leaving the sauna, they rested on a bed while covered with a blanket to keep warm for an additional 30 min. Patients were weighed before and after sauna bathing, and oral hydration with water was used to compensate for lost weight. Repeated Waon therapy was performed once a day, five days a week from Monday through Friday for four weeks, for a total of 20 times.\textsuperscript{6,14}

\textit{Conventional therapy}

For conventional therapy, subjects were approved to receive medical treatment for COPD, such as long-acting $\beta_2$ agonists (LABA), long-acting anticholinergics, xanthine derivatives (oral theophyllines), inhaled glucocorticoids (alone or in combination with LABA), systemic glucocorticoids and pulmonary rehabilitation, such as walking, swimming training, ergometer exercise and respiratory training. However, the medications and pulmonary rehabilitation programs are assumed not to have changed for at least two weeks before and during this study.

\textit{Pulmonary function test}

Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV\textsubscript{1}), forced expiratory flow after 50\% of expired FVC (FEF\textsubscript{50}), forced expiratory flow after 75\% of expired FVC (FEF\textsubscript{25}) and peak expiratory flow (PEF) were measured in all subjects using a spirometer (CHESTAC 33, Chest Co., Tokyo, Japan) linked to a computer.

\textit{Exercise tolerance}

The functional status as exercise tolerance was assessed using the six-minute walk test (6MWT). The 6MWT followed the pulmonary function test according to a standardized protocol.\textsuperscript{9} It is now the most commonly used timed walking test\textsuperscript{10,11} that can predict the risk of death in COPD patients.\textsuperscript{12,13} The distance walked in six minutes has been accepted as a good outcome measure after interventions such as pulmonary rehabilitation.\textsuperscript{15} In our study, the 6MWT was carried out in a hospital corridor with a length of 100 m. The subjects were allowed to slow down
or stop if necessary, but were required to resume walking as soon as they felt able. They were given feedback on the elapsed time each minute, and were encouraged to continue walking. All subjects were informed of the details of the 6MWT and how it worked. Dyspnea, as measured with the modified Borg dyspnea scale, oxygen saturation, and pulse rate were assessed at the start and end of the 6MWT. Oxygen saturation was measured using Wrist OxTM (Model 3100), Star Product, Tokyo, Japan.

**Study protocol**

COPD patients were alternately assigned in the enrolled sequence to either the Waon or control group; the former received repeated Waon therapy plus conventional therapy, while the latter received only conventional therapy. The physician explained the study protocol and obtained written informed consent from all participants prior to alternately assigning the patients to the regimen.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Okayama University. This clinical trial is registered with the University Hospital Medical Information Network (UMIN) clinical trials registry, number UMIN000004391.

To rule out any acute effects of Waon therapy, the pulmonary test and 6MWT were performed before the first treatment and on the next day after the last treatment.\(^8\) The outcome measured first was pulmonary function, and then 6MWT.

**Statistical analysis**

All data were expressed as absolute value, means ± SD, or median (25th–75th percentile). Unpaired t-test or Mann-Whitney test was used for comparison between groups. Statistical analysis was performed using SPSS version 16.0 J for Windows (SPSS Inc., Chicago, IL, USA), and p values < 0.05 were considered statistically significant.

**Results**

**Patients**
Table 1 shows the demographic characteristics, smoking history, respiratory function degree of severity, and typical therapeutic regimen for COPD patients. No important differences were seen between the two groups in these characteristics and therapeutic regimen. A total of 20 patients were alternately assigned to each group. Our study program lasts at least four weeks, so only two outpatients could participate in each group. The study was performed from April 2010 to May 2011 at Misasa Medical Center, Okayama University Hospital.

**Exercise tolerance**

All the parameters for the 6MWT are shown in Table 2. A significant between-group difference was not observed in the amount of change in any parameters in the 6MWT.

**Pulmonary function**

Table 3 shows the change in ventilator parameters at baseline and after 4 weeks. Figure 1, Figure 2 and Figure 3 show the amount of change in VC, PEF and FEF\(_{50}\), respectively. The amount of change in VC (0.30 ± 0.4 L) in the Waon group showed a tendency to be larger than that in the control group (0.02 ± 0.21 L), as shown in Figure 1 (p = 0.077). The amount of change in PEF (0.48 ± 0.79 L/s) in the Waon group showed a tendency to be larger than that in the control group (−0.11 ± 0.72 L/s), as shown in Figure 2 (p = 0.095). A significant between-group difference was observed in the amount of change in FEF\(_{50}\), which was larger in the Waon group, 0.08 (0.01−0.212 L/s), than in the control group, −0.01 (−0.075−0.04 L/s), as shown in Figure 3 (p = 0.019). By comparison, there was no significant difference in the amount of change in FEV1.0 between the Waon group (0.12 ± 0.23 L) and the control group (−0.14 ± 0.12 L) (p = 0.120). There was also no significant difference in the amount of change in FVC between the Waon group (0.17 ± 0.44 L) and the control group (−0.06 ± 0.37 L) (p = 0.233). Furthermore, there was no significant difference in the amount of change in FEF\(_{25}\) between the Waon group, 0.03 L/s (−0.03−0.057 L/s), and the control group, 0.01L/s (−0.075−0.032 L/s) (p = 0.208).
Discussion

The goal of this study was to evaluate the effect of repeated Waon therapy for COPD patients. The amounts of change in VC, PEF and FEF₅₀ in the Waon group were statistically larger than those in the control group. Notably, a significant between-group difference was observed in the amount of change in FEF₅₀. These results indicate that the combination of repeated Waon therapy and conventional therapies may be beneficial for comprehensive COPD treatment from the aspect of improving airway obstruction, which in turn improves exercise tolerance in patients with COPD.

COPD is characterized by progressive worsening of airflow limitation associated with abnormally inflamed airways in older smokers. Leukocytes recruited to the lung contribute to COPD pathology by releasing reactive oxygen metabolites and proteolytic enzymes.¹⁶ Thus, the larger improvement of VC, PEF and FEF₅₀ after repeated Waon therapy in our results was speculated to result from suppression of airway inflammation and alleviation of airway obstruction after repeated Waon therapy; the expansibility of lung parenchyma might also be heightened. In 2001, Ikeda et al demonstrated that after repeated Waon therapy, eNOS protein expression and NO production increases significantly in the peripheral arteries of the healthy golden hamster,¹⁷ and also increases in cardiomyopathic hamsters with heart failure.¹⁸ In a pilot study of 13 consecutive patients with severe COPD, Umehara et al⁸ found that repeated Waon therapy significantly improved pulmonary hypertension during exercise. They surmised that Waon therapy increases the expression of eNOS in the pulmonary artery (PA), and improves PA vascular function. However, it is unclear whether repeated Waon therapy influences the NO level in the airway. It is possible that repeated Waon therapy influences the NO level in the airway for COPD patients.

Many studies on NO and pulmonary function parameters have been reported. Ansarin and colleagues demonstrated that among patients with COPD, exhaled NO was inversely correlated with FEV₁.₀, further suggesting a relationship between NO production and bronchoconstriction.¹⁹ Moreover, Tadié et al reported that nitric oxide synthase 2, one of the
isoforms that produces NO, seems to be involved in a constriction response to airway stretch. Brindicci et al\textsuperscript{21} studied 47 patients with different severities of COPD according to the GOLD guidelines. They found that COPD severity was correlated with an increased steady-state alveolar concentration or peripheral NO regardless of the patient's smoking habit or current treatment. Moreover, McCurdy et al showed that in patients with GOLD stages 3 and 4 COPD, peripheral NO correlated with functional status, and large airway NO parameters correlated with health status. In this study, worsening global health status and increasing subjective symptoms were associated with increasing airway NO flux.\textsuperscript{22} Our study did not evaluate the airway inflammation using NO flux in the airway before and after the program, but from the results of various studies, we speculated that NO level in the airway was decreased after repeated Waon therapy, and decreased NO flux influenced relaxation of airway smooth muscles and alleviated airway obstruction.

The improvement of subjective symptoms is of particular importance in the evaluation of COPD treatment. This study was the first controlled clinical trial to evaluate repeated Waon therapy by 6MWT and pulmonary function test.

Six-minute walk distance (6MWD) is often intercorrelated with QOL for COPD patients. Mangueira et al found that health-related quality of life (HRQOL) presented a negative correlation with the 6MWD and a positive correlation with the sensation of dyspnea and fatigue, as measured by the Borg scale in a cross-sectional study involving 30 women with COPD.\textsuperscript{23} Umehara et al\textsuperscript{9} reported in a pilot study that repeated Waon therapy significantly improved St. George's Respiratory Questionnaire (SGRQ) scores, and prolonged the mean exercise time of the constant load of a cycle ergometer exercise test in patients with severe COPD. In contrast, grades on the Medical Research Council (MRC) dyspnea scale, which measures dyspnea severity, did not change.\textsuperscript{24} In our controlled clinical trial as well, dyspnea did not show a significant difference in the amount of change in the maximum Borg scale ($p = 0.147$).

This study did have several limitations. The sample size was small, and an obvious selection bias was present due to the study being non-randomized and unblinded. Thus, the results from
this study for evaluating the effect of repeated Waon therapy should only be viewed as preliminary. Further studies are needed to investigate not only exercise tolerance and pulmonary function, but also the changes in biological markers, such as the NO flux for understanding the mechanism of improvement of airway obstruction. Changes of NO flux before and after Waon therapy may provide insight into the association between repeated Waon therapy and the airflow limitation.

Over the 4-week study period, none of the patients assigned to the study experienced arrhythmias, angina or respiratory distress during Waon therapy and the conventional therapy. There were no incidences of non-tolerance to the therapies.

In conclusion, this study provides new information on the effect of repeated Waon therapy for patients with COPD. The results obtained in this study show that the addition of repeated Waon therapy to conventional therapy for COPD patients could be useful for improving airway obstruction and might reduce dyspnea on exertion.

Acknowledgments

We would like to thank the staff (clinical technologists, physical therapists and clinical nurses) at Okayama University Hospital, Misasa Medical Center for their assistance.

Disclosure

No company or organization had any financial involvement or direct financial interest in this study. The authors report no conflicts of interest in this work.
References


Figure legends

**Figure 1** Amount of change in VC for each patient for the pulmonary function test.

*p = 0.077* compared to control, analyzed by unpaired t-test. Data are represented as means ± SD.

**Figure 2** Amount of change in PEF for each patient for the pulmonary function test.

*p = 0.095* compared to control, analyzed by unpaired t-test. Data are represented as means ± SD.

**Figure 3** Amount of change in FEF_{50} for each patient for the pulmonary function test.

*p = 0.019* compared to control, analyzed by Mann-Whitney test. Data are represented as median (with ranges in parentheses, 25th–75th percentile).
<table>
<thead>
<tr>
<th></th>
<th>Waon (n=10)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>9/1</td>
<td>9/1</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.3±5.8</td>
<td>73.6±6.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>former</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>current</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pack years</td>
<td>56 (27–94)</td>
<td>57 (34–103)</td>
</tr>
<tr>
<td>FEV₁, %pred</td>
<td>54.1±14.7</td>
<td>63.2±26.6</td>
</tr>
<tr>
<td>Resting SpO₂, %</td>
<td>95.6±1.8</td>
<td>95.9±0.7</td>
</tr>
<tr>
<td>Height</td>
<td>162.4±5.0</td>
<td>160.4±4.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.3±2.4</td>
<td>23.0±2.4</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long-acting anticholinergics</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>long-acting β₂ agonist</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>xanthine derivatives</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Lung physical therapy</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Notes: Data are absolute numbers, presented as means±SD or median (25th–75th percentile).
Abbreviations: FEV₁=forced expiratory volume in one second; %pred=percentage of predicted value; SpO₂=oxygen saturation; BMI=body mass index.
<table>
<thead>
<tr>
<th></th>
<th>Waon (n=10)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Borg scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>3.0 (1.9–7.0)</td>
<td>3.5 (1.8–5.5)</td>
</tr>
<tr>
<td>after 4 weeks</td>
<td>2.0 (0.37–5.0)</td>
<td>2.5 (0.9–7.0)</td>
</tr>
<tr>
<td><strong>Walk distance (m)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>287±131</td>
<td>291±114</td>
</tr>
<tr>
<td>after 4 weeks</td>
<td>333±106</td>
<td>310±110</td>
</tr>
<tr>
<td><strong>Minimum SpO₂ (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>88±5</td>
<td>85±4</td>
</tr>
<tr>
<td>after 4 weeks</td>
<td>89±5</td>
<td>87±5</td>
</tr>
<tr>
<td><strong>Maximum heart rate (beats/min)</strong> at baseline</td>
<td>112±20</td>
<td>101±15</td>
</tr>
<tr>
<td>after 4 weeks</td>
<td>109±26</td>
<td>107±15</td>
</tr>
</tbody>
</table>

Notes: Data are presented as means ±SD or median (25th–75th percentile).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Waon (n=10)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF (L/s)</td>
<td>3.08±0.999</td>
<td>3.85±1.543</td>
</tr>
<tr>
<td></td>
<td>3.58±1.478</td>
<td>3.73±1.64</td>
</tr>
<tr>
<td>FEF_{50} (L/s)</td>
<td>0.37 (0.31–0.71)</td>
<td>0.50 (0.26–0.82)</td>
</tr>
<tr>
<td></td>
<td>0.52 (0.28–0.82)</td>
<td>0.52 (0.24–0.77)</td>
</tr>
<tr>
<td>FEF_{25} (L/s)</td>
<td>0.17 (0.15–0.27)</td>
<td>0.22 (0.16–0.31)</td>
</tr>
<tr>
<td></td>
<td>0.21 (0.12–0.33)</td>
<td>0.22 (0.17–0.28)</td>
</tr>
<tr>
<td>VC (L)</td>
<td>2.87±0.88</td>
<td>2.90±0.65</td>
</tr>
<tr>
<td></td>
<td>3.16±0.69</td>
<td>2.92±0.63</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.6±0.784</td>
<td>2.71±0.938</td>
</tr>
<tr>
<td></td>
<td>2.77±0.969</td>
<td>2.65±0.869</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.22±0.43</td>
<td>1.34±0.66</td>
</tr>
<tr>
<td></td>
<td>1.35±0.56</td>
<td>1.32±0.644</td>
</tr>
</tbody>
</table>

Notes: Data are presented as means ± SD or median (25th–75th percentile).
Abbreviations: VC=vital capacity; FVC=forced vital capacity; FEV1=forced expiratory volume in one second.
PEF=peak expiratory flow; FEF_{50}=forced expiratory flow after 50% of expired FVC; FEF_{25}=forced expiratory flow after 75% expired FVC.