Electrically stimulated ventilation feedback improves the ventilation pattern in patients with COPD

KENICHI ITO, PT, PhD1), TATSUO NOZOE, PT2), MIYUKI OKUDA, MD3), KOJI NONAKA, PT, PhD1), JUN YAMAHARA, PT, MS4), JUN HORIE, PT, PhD5), YUKA HAYAMA, NS, PhD6), HIROSUMI KAWAMURA, PT, PhD7)

1) Graduate School of Comprehensive Rehabilitation, Osaka Prefecture University: 3-7-30 Habikino, Habikino-shi, Osaka 583-8555, Japan
2) Department of Rehabilitation Medicine, Hospital, Anti-Tuberculosis Association, Osaka Branch, Japan
3) Department of Internal Medicine, Hospital, Anti-Tuberculosis Association, Japan
4) Department of Rehabilitation Medicine, National Hospital Organization, Osaka Minami Medical Center, Japan
5) Faculty of Health Sciences, Kyoto Tachibana University, Japan
6) Faculty of Nursing, Baika Women’s University, Japan
7) Faculty of Nursing and Rehabilitation, Konan Women’s University, Japan

Abstract. [Purpose] We aimed to determine the effects of ventilation feedback using electrical stimulation on ventilation pattern during exercise in patients with chronic obstructive pulmonary disease (COPD), and develop new rehabilitation methods. [Subjects] This randomized double-blind placebo-controlled trial included 24 patients with COPD. [Methods] Phasic electrical stimulation during expiration (PESE) or a placebo was given to all the cases. Minute ventilation (VE), tidal volume (TV), respiratory rate (RR), expiratory time (Te), total respiratory time (Ttot), dead-space gas volume to tidal gas volume (VD/VT), oxygen uptake (VO2), carbon dioxide output (VCO2), Borg scale (Borg), and percutaneous oxygen saturation (SpO2) during rest and exercise were assessed. [Results] The placebo group showed no obvious change in ventilation measurements at rest or during exercise. However, in the PESE group, TV, Te, and Ttot significantly increased, while RR and VD/VT significantly decreased during exercise compared with the baseline measurements. Borg scores, SpO2, VO2, or VCO2 did not differ significantly. [Conclusion] PESE improves the ventilation pattern during rest and exercise. Furthermore, PESE does not increase VO2, which may indicate an increased workload. Biofeedback may contribute to PESE effects. Stimulation applied during expiration may evoke sensations increasing prolonged expiration awareness, facilitating prolongation.

Key words: Chronic obstructive pulmonary disease, Electrical stimulation, Ventilation

INTRODUCTION

Exercise therapy is at the core of rehabilitation for chronic obstructive pulmonary disease (COPD)1–3), the incidence of which continues to increase worldwide4–6). Both endurance and strength training focusing on the lower limbs can decrease the lactic acid concentration in the blood, carbon dioxide production, and minute ventilation. The effects of exercise therapy can subsequently decrease respiratory muscle work and improve exercise tolerance in patients with COPD7).

In contrast, rapid shallow breathing is a cause of breathlessness during activities of daily living (ADLs) and walking in patients with COPD. Therefore, decreasing the respiratory rate and increasing the tidal volume during movement may help to decrease breathlessness in patients with COPD. Pursed-lip breathing, which involves measuring the increase in duration of the expiratory phase by pursing the lips and applying positive pressure during expiration, is a breathing technique that improves ventilation efficiency in patients with COPD8–9). Most hospital-based programs for patients with mild-to-moderate COPD are developed with exercise therapy and breathing techniques. Therapists instruct patients to perform PLB both at rest and during exercise, although few patients with COPD can maintain this breathing technique throughout exercise therapy sessions. In addition, it is difficult for therapists to both monitor patients during exercise therapy and give feedback on their respiratory sta-
feedback from the device10, 11). However, their method used a large monitor and could be used only at specific locations; therefore, it was unsuitable for use during ADLs or walking. We sought a similar feedback method that is portable and easily used in various rehabilitation programs, and subsequently came across the technique of electrical stimulation. A large number of small, portable, electrical stimulation devices ideal for our purpose are commercially available. Moreover, Kita et al. reported that feedback through electrical stimulation was effective in stroke rehabilitation programs12; electrical stimulation has been used recently in patients with COPD for lower limb strength training13–19. If electrical stimulation can be used for ventilation feedback, then such a method may help overcome the limitation of the study by Collins et al. Therefore, we created an electrical stimulation device that provides feedback on expiration. This feedback method could improve ventilation in COPD patients during exercise and serve as a useful exercise therapy tool. The present study involved basic research investigating whether ventilation feedback delivered through electrical stimulation could improve the ventilation pattern in patients with COPD during exercise in order to develop a new method of rehabilitation.

SUBJECTS AND METHODS

The subjects included 24 patients with COPD who volunteered for the study, and whose participation was approved by their attending physician. Subjects were found through volunteer recruitment posters displayed within hospitals; those with musculoskeletal disease, central nervous system injury or disease, communication disorders, or severe cardiovascular disease were excluded.

The Ethical Review Board of the Osaka Prefecture University Faculty of Comprehensive Rehabilitation approved this study (2010P10). The content of this study was explained to participants both orally and in writing, and their written informed consent was obtained according to the Declaration of Helsinki.

This study was a randomized double-blind trial in which the subjects and a measurer were randomly assigned to either the phasic electrical stimulation during expiration (PESE) group or the placebo group using a random number table.

The protocol included 5 min of rest followed by 5 min of exercise. A bicycle ergometer (STB-1400, Nihon Kohden, Tokyo, Japan) was used to measure exercise load. For both safety and ethical considerations, the exercise intensity was set to a level that was equivalent to the subject’s daily walking routine, which was between 20% and 30% of the predicted maximal heart rate (Karvonen Formula). A respiratory metabolism measuring apparatus (Aeromonitor AE-300S, Minato Medical Science, Osaka, Japan) was used to measure respiratory metabolism at rest and during exercise. Minute ventilation (VE), tidal volume (TV), respiratory rate (RR), respiratory time (Te), total respiratory time (Ttot), dead-space gas volume to tidal gas volume (Vd/VT), end-tidal CO₂ (ETCO₂), oxygen uptake (VO₂), and carbon dioxide output (VCO₂) were measured. Perceived exertion was measured using the Borg scale, and percutaneous oxygen saturation (SpO₂) was measured using a pulse oximeter (PULSOX-300i, Konica Minolta, Tokyo, Japan). The protocol was performed twice for both groups, before and during exercise, followed by data sampling.

We used a portable, commercially available low-frequency electrical stimulation device (remodeled Trio 300; Ito Co., Ltd., Tokyo, Japan) in this study. The device has a pressure transducer system attached to a nasal cannula, which senses the exhalation of air by the patient. The device applies electrical stimulation during expiration, and is fitted with an external input terminal. The nasal cannula/pressure transducer was connected to a control unit that converted the pressure transducer signal into an electrical signal. This signal was subsequently fed into the stimulator’s external input terminal, triggering electrical stimulation. Stimulation was delivered bilaterally near the abdominal muscles (expiratory muscles) of the subjects. Electrodes were placed approximately 2 cm from the umbilical region, with the cathodes attached bilaterally and symmetrically around the midline, and the anodes placed 1 cm above each cathode. Taking into account ethical aspects regarding the possibility of pain resulting from electrical stimulation, electrical stimulation was delivered with a pulse width of 200 μs and at 70% of the current intensity (Ah) at which pain was felt and no muscle contractions occurred.

In the PESE group, stimulation was delivered at a frequency of 20 Hz and the duration of stimulation was equal to that of expiration, whereas the duration of rest was equal to that of inspiration. In addition, the subjects were given the following oral instructions once prior to the test: “Electrical stimulation will continue as long as you exhale, so make a conscious effort to exhale such that the electrical stimulation is maintained as long as possible and consciously perform PLB”.

As the control for the PESE, we included a placebo group to address bias related to electrical stimulation. In the placebo group, weak electrical stimulation was given and measured. In addition, the subjects were asked to perform PLB during the test. The same protocol was used in the placebo group, except that the stimulation was delivered at a frequency of 25 Hz in 10-s phases with 10 s of rest between phases. The frequency for the placebo group was different from that for the PESE group, as the same frequency as used for PESE was not available in the program used for regular interval stimulation. Thus, we used 25 Hz as approximately the same frequency in this study. In addition, subjects were given oral instructions to consciously perform PLB prior to the test.

An allocator prepared all subjects for electrical stimulation. The person taking the measurements was unaware of the group allocations, thus ensuring blinding. Both groups practiced PLB at the beginning of the experiment until they were proficient before performing exercise. PLB in this study involved breathing with prolonged expiration and the
On the basis of the data obtained from a pilot study, sample size was determined by the main outcome measure, the difference in respiratory rate between the two groups, and the difference in respiration rate was 5 breaths/min (SD, 4.3; α, 0.05; power, 0.80). Therefore, we selected a sample size that included 26 individuals, with 13 in each group. We aimed to examine 26 subjects in this study.

The SPSS version 11.0 J (SPSS, IBM, Armonk, NY, USA) statistical software was used for the statistical analysis. A Mann-Whitney U test was used to compare baseline measures between the two groups, and a Wilcoxon rank-sum test was used for intergroup comparisons before and during exercise periods. A p value of < 0.05 was considered statistically significant. The allocator and researcher were different people in order to blind the allocation details in the data analysis.

**RESULTS**

Figure 1 shows the overall procedure for this study. The 24 subjects were assigned to either the placebo group (n = 12) or the PESE group (n = 12), and measurements were taken for all subjects prior to the intervention (baseline), at rest, and during exercise. One subject in the placebo group reported knee pain and was excluded from the analysis. Therefore, data were analyzed from 11 subjects in the placebo group and 12 subjects in the PESE group. Meanwhile, we selected a sample size that included 26 individuals based on the calculated results. However, a significant difference was observed for the main outcome measure, the difference in RR, between the two groups in the data for 24 subjects. Due to ethical considerations, we ended data sampling at that time.

Table 1 describes the age, sex, COPD severity (Global Initiative for Chronic Obstructive Lung Disease staging system), extent of breathlessness (Medical Research Council dyspnea scale), lung function, nutritional status, and motor function of the subjects in both groups. No significant differences were observed between the groups for any parameter. Table 2 shows the results of statistical comparisons of the main parameters between the two groups. No significant differences were observed between the groups for ventilation index, respiratory time index, ventilation pattern index, dyspnea, or SpO\textsubscript{2} baseline data.

Table 3 shows comparisons for each measurement parameter before and during exercise. No significant difference was demonstrated for VE in either group. No significant difference was observed for TV in the placebo group, but a significant increase was observed in the PESE group, both at rest and during exercise (rest, p = 0.002; exercise, p = 0.015). No significant difference was observed for RR in the placebo group, but a significant decrease was observed in the PESE group, both at rest and during exercise (rest, p = 0.007; exercise, p = 0.028). No significant difference was observed for Te in the placebo group, but a significant prolongation was observed in the PESE group, both at rest and during exercise (rest, p = 0.009; exercise, p = 0.049). A significant decrease in VD/VT was observed in the placebo group during exercise (p = 0.003) and in the PESE group both at rest and during exercise (rest, p = 0.006; exercise, p = 0.022). No significant differences were observed for VO\textsubscript{2}, VCO\textsubscript{2}, Borg scale, or SpO\textsubscript{2} in either group.

**DISCUSSION**

The purpose of this study was to determine the effect of ventilation feedback provided by electrical stimulation on ventilatory function during exercise in patients with COPD. The results of this study revealed two new findings. The first was that PESE improves the ventilation pattern in patients with COPD both at rest and during exercise. The second finding was that oxygen uptake does not increase with PESE. Consistent with previous studies, we believe the PESE

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**Fig. 1.** Flow diagram of the study population
ventilation pattern improvement resulted from a properly functioning biofeedback (BF) mechanism\textsuperscript{10, 11). Providing feedback through skin receptors with PESE on expiration both at rest and during exercise may have improved the ventilation pattern by enhancing awareness of prolonged expirations.

While it became clear that the ventilation pattern was improved with PESE, no change was observed in breathlessness (Borg scale) or SpO\textsubscript{2}. It is common for SpO\textsubscript{2} to not improve despite a patient’s ventilatory function improving in clinical settings through drug and oxygen therapy. This may be related to the difficulty in finding a permanent cure for the pathogenesis of bronchial and lung parenchyma damage in COPD and the presence of complex structures damaged by desaturation\textsuperscript{20).}

The Borg scale, which increases with the exercise load, may not have improved in the PESE group because dynamic hyperinflation was not reproduced by the short, low-intensity exercise performed in this study. Furthermore, dyspnea during exercise may have been affected by hyperventilation associated with exercise and accompanying fatigue of respiratory muscles, although this kind of reaction could not be reproduced with short, low-intensity exercise. These effects also could result from small variations in VO\textsubscript{2} when exercise is commenced after resting.

Next, we will discuss why PESE had no effect on SpO\textsubscript{2}. SpO\textsubscript{2} is a parameter that shows the state of oxygenation, and its association with PaO\textsubscript{2} is well known. Therefore, we will proceed with this discussion by substituting PaO\textsubscript{2} for SpO\textsubscript{2}. PaO\textsubscript{2} is calculated with the following formula:

\[
\text{PaO}_2 = 713 \times \text{FIO}_2 - K \times \text{VO}_2/\text{VE} (1 - \text{VD/VT}) - \text{A-aDO}_2,
\]

where PaO\textsubscript{2} is the partial pressure of arterial oxygen, FIO\textsubscript{2} is the fraction of inspired oxygen, K is a constant (0.863), VO\textsubscript{2} is the oxygen uptake, VE is the minute ventilation, VD/VT is the dead-space gas volume to tidal gas volume, and A-aDO\textsubscript{2} is the difference in alveolar arterial oxygen partial pressure.

During the present experiment, FIO\textsubscript{2} was kept constant,
and because no pathologies such as retention of sputum, pneumonia, or pleural effusion were observed in A-aDO₂, it is unlikely that changes occurred during the experiment. Therefore, the parameters that should be considered as factors determining PaO₂ in this experiment are VO₂, VE, and VD/VT. Focusing on these individual parameters, it is clear that VE is not affected by PESE, remaining in the same steady state as before the intervention. While VD/VT showed a statistically significant decline, the actual variation was very small and likely did not affect PaO₂. We believe that the observed lack of change in the study parameters after PESE was because PaO₂ was unchanged, and these results were reflected in the SpO₂ values. We will discuss VO₂ in detail in the next section.

Muscle metabolism decreases in patients with COPD. Encouraging unnecessary muscle contractions in patients with COPD promotes anaerobic metabolism, causes acidosis resulting from lactic acid accumulation, and stimulates the respiratory center, thereby enhancing ventilation. This process may increase respiratory muscle work and exacerbate dyspnea. It needs to be confirmed whether PESE itself triggered the above effects or if they were triggered by voluntary muscle contractions from BF. Thus, it is extremely important to consider the effects of PESE on VO₂.

Below is the Fick equation including the VO₂ calculation and its relevant formula:

\[ VO₂ = Q (CaO₂ - CvO₂), \]

where Q is the cardiac output, CaO₂ is the arterial oxygen content, and CvO₂ is the venous oxygen content.

\[ CaO₂ = 1.34 \times Hb [g/dL] \times SaO₂ [%]/100 + 0.003 \times PaO₂ [mmHg], \]

where CaO₂ is the arterial oxygen content, Hb is the venous oxygen content, and SaO₂ is the O₂ saturation.

From these two formulas, we can see that the determinants of VO₂ are Hb, SaO₂, PaO₂, and CvO₂. In the present study, the PESE intervention resulted in no significant increase in VO₂. Although SpO₂, which was measured in place of SaO₂, decreased with exercise, no specific effect of PESE was observed during rest or exercise. The majority of CaO₂ is not dissolved oxygen in the blood; the CaO₂ shown in the Fick equation is considered unchanged because it is hemoglobin-bound oxygen, as demonstrated by SpO₂. Considering the fact that VO₂ does not change during exercise with PESE, it appears unlikely that PESE increases cardiac output (Q). Furthermore, if we assume that CaO₂ does not change for the aforementioned reasons, CvO₂ also will remain unchanged. This implies that PESE did not induce muscle contractions that could increase VO₂. This is clear from the fact that

| Table 3. Placebo group versus PESE group in COPD patients |
|----------------------------------------------------------|
| Placebo group (n = 11) | PESE group (n = 12) |
|-----------------------|---------------------|
| **VE, mL/min**        | **Baseline**        | **Sham**        | **Baseline**        | **PESE**        |
| Rest                  | 10.5 ± 2.8          | 11.1 ± 2.54     | 10.2 ± 1.6          | 10.1 ± 1.57     |
| Exercise              | 20.2 ± 5.1          | 21.3 ± 5.22     | 19.9 ± 4.4          | 21.3 ± 6.1      |
| **TV, mL**            | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 799.0 ± 321.0         | 894.0 ± 392.0       | 730.0 ± 172.0   | 1,100.0 ± 316.0**   |
| Exercise              | 1,085.0 ± 354.0     | 1,237.0 ± 459.0 | 1,104.0 ± 262.0     | 1,403.0 ± 422.0*|
| **RR, n/min**         | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 16.1 ± 4.22           | 14.1 ± 4.62         | 16.0 ± 3.28     | 10.2 ± 3.84**       |
| Exercise              | 21.6 ± 4.6          | 19.3 ± 6.6      | 20.2 ± 4.6          | 16.9 ± 6.95*    |
| **Te, s**             | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 2.75 ± 1.50           | 3.28 ± 2.43         | 2.43 ± 0.66     | 3.94 ± 1.39**       |
| Exercise              | 1.91 ± 0.74         | 2.24 ± 1.01     | 1.92 ± 0.58         | 2.59 ± 1.24*    |
| **Ttot, s**           | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 4.21 ± 1.91           | 4.86 ± 3.16         | 3.99 ± 1.07     | 6.64 ± 1.84**       |
| Exercise              | 3.04 ± 1.04         | 3.69 ± 1.72     | 3.13 ± 0.70         | 4.21 ± 1.67*    |
| **VD/VT**             | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 0.43 ± 0.07           | 0.41 ± 0.08         | 0.42 ± 0.05     | 0.37 ± 0.03**       |
| Exercise              | 0.40 ± 0.05         | 0.38 ± 0.06**   | 0.37 ± 0.04         | 0.35 ± 0.04*    |
| **ETCO₂, %**          | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 4.43 ± 0.75           | 4.44 ± 0.81         | 4.35 ± 0.33     | 4.44 ± 0.59         |
| Exercise              | 5.08 ± 0.87         | 5.01 ± 0.80     | 4.89 ± 0.53         | 4.99 ± 0.69     |
| **Borg dyspnea, points** | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 0.04 ± 0.15           | 0.13 ± 0.32         | 0.16 ± 0.57     | 0.60 ± 1.06         |
| Exercise              | 1.45 ± 0.16         | 1.36 ± 1.7      | 1.54 ± 1.52         | 1.54 ± 1.40     |
| **SpO₂, %**           | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 95.9 ± 1.8            | 96.1 ± 2.1          | 96.0 ± 1.7      | 95.9 ± 2.0          |
| Exercise              | 92.5 ± 4.0          | 93.4 ± 4.2      | 93.8 ± 2.9          | 93.7 ± 2.8      |
| **VO₂, mL/min/kg**    | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 3.70 ± 0.72           | 3.69 ± 0.30         | 3.90 ± 0.72     | 4.00 ± 0.79         |
| Exercise              | 8.77 ± 1.39         | 8.77 ± 1.68     | 9.10 ± 2.51         | 10.05 ± 2.24    |
| **VCO₂, mL/min/kg**   | **Rest**            | **Exercise**    | **Rest**            | **Exercise**    |
| 3.64 ± 0.52           | 4.04 ± 1.91         | 3.60 ± 0.74     | 3.65 ± 0.82         |
| Exercise              | 8.14 ± 1.86         | 8.48 ± 1.75     | 8.90 ± 2.09         | 8.97 ± 2.49     |

Results are presented as the mean ± SD or %, unless otherwise indicated. ETCO₂: end tidal CO₂; PESE: phasic electrical stimulation during expiration; RR: respiratory rate; SpO₂: percutaneous oxygen saturation; Te: expiratory time; Ti: inspiratory time; Ttot: total respiratory time; TV: tidal volume; VD/VT: dead-space gas volume to tidal gas volume; VE: minute ventilation; VO₂: oxygen uptake; VCO₂: carbon dioxide output. *p<0.05, **p<0.01
VCO₂ did not increase during exercise with PESE.

One limitation of this study was the inability to investigate exercise intensity and duration from the perspective of practicality. Breathlessness in patients with COPD is significant not only during walking, but also during activities such as climbing stairs. The continuation of such activities is often accompanied by muscle fatigue and enhanced ventilation associated with lactate accumulation. Therefore, considering these facts, studies based on exercise intensity and duration are extremely important with regard to practical PESE applications. Another limitation of this study was that dynamic hyperinflation and muscle metabolism assessments could not be performed.

Finally, COPD, which has an increasing incidence in the population, has a high prevalence in the elderly, and the relationship between COPD and decreased cognitive function has been recently reported. The development of new rehabilitation methods is urgently needed to delay the progression of cognitive impairment in patients with COPD.

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