Clinical Effects Of Acupuncture On The Pathophysiological Mechanism Of Chronic Obstructive Pulmonary Disease During Exercise

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Purpose: Pharmacological therapy and pulmonary rehabilitation are useful for exertional dyspnoea in patients with chronic obstructive pulmonary disease (COPD); however, several patients have no meaningful improvements. Although acupuncture significantly improves exercise intolerance and dyspnoea, the pathophysiological mechanism of these effects is unknown; therefore, we evaluated this mechanism using cardiopulmonary exercise testing in a single-arm, open experimental study.

Patients and methods: Sixteen patients with COPD underwent acupuncture once a week for 12 weeks. Primary outcomes were exercise performance parameters, including peak oxygen uptake in the incremental exercise tests (IETs) and the time to the limit of tolerance measured in constant work rate exercise tests (CWRETs) at 70% peak work-rate of the IET. IETs and CWRETs were performed at baseline and at weeks 12, 16, and 24.

Results: During the time course, there were significant increases in peak oxygen uptake (p = 0.018) and minute ventilation (VE, p = 0.04) in the IETs. At 12 weeks, the endurance time significantly increased (810 ± 470 vs 1125 ± 657 s, p < 0.001) and oxygen uptakes at terminated exercise were significantly lower (771 ± 149 mL/min, p < 0.05) than those at baseline (822 ± 176 mL/min) in CWRETs. The significant decreases in oxygen uptake and minute ventilation and improvements in Borg scale scores were also observed during CWRETs after acupuncture. The decreases at isotime in the Borg scale (r = −0.789, p = 0.0007) and VE (r = −0.6736, p = 0.0042) were significantly correlated with the improvement of endurance time.

Conclusion: The positive effects of acupuncture on exertional dyspnoea were associated with increased endurance time influenced by improved oxygen utilisation and reduced ventilation during exercise. Acupuncture may be a new intervention for COPD in addition to conventional maintenance therapies.

Keywords: chronic obstructive pulmonary disease, COPD, acupuncture, exercise intolerance and dyspnoea, cardiopulmonary exercise test, CPET

Plain Language Summary

Although acupuncture significantly improves exercise intolerance and dyspnoea, the pathophysiological mechanism of these effects is unknown; we evaluated this mechanism using cardiopulmonary exercise testing. We found that peak oxygen uptake and ventilation capacity significantly improved in the IETs and the endurance time significantly increased in the CWRETs. The Borg scale scores, oxygen uptake, and minute ventilation were significantly lower during CWRET after acupuncture than those at baseline. These results indicated that COPD patients treated with acupuncture have been able to exercise with less oxygen consumption and ventilation. The positive
effects of acupuncture on exertional dyspnoea were mainly associated with increased endurance time influenced by improved oxygen utilisation and reduced ventilation during exercise.

**Introduction**

Chronic obstructive pulmonary disease (COPD) is characterised by irreversible airflow limitation and is currently the third leading cause of death worldwide in 2018. Exertional dyspnoea, the most debilitating symptom of COPD, affects many aspects of daily living. Dyspnoea can progressively increase in severity and predicts the survival of patients with COPD. Therefore, dyspnoea management is an important target in COPD. Pharmacological therapy for COPD, such as bronchodilators, can reduce symptoms and the frequency and severity of exacerbations and improve exercise intolerance and health status. Pulmonary rehabilitation also alleviates symptoms and has socioeconomic benefits. We previously reported that personalised pulmonary rehabilitation, including occupational therapy (PPR-OT), improves the survival of patients with advanced COPD. We had experienced that 34 cases (18.4%) had no improvements in exercise intolerance and dyspnoea in 185 patients with PPR-OT. Several patients also showed no meaningful clinical improvements in response to well-established treatments. For these patients, it is necessary to develop new options in addition to conventional therapies.

Acupuncture significantly improves exercise intolerance, dyspnoea on submaximal exercise, and quality of life in patients with COPD. Acupuncture is an oriental medicine, and some of its physiological benefits include relaxation of muscle tension, improvement of muscle/anti-muscle fatigue, improvement of muscle blood flow, and sympathetic control. Considering these benefits, acupuncture may be effective in treating COPD-associated skeletal muscle disorders. However, the pathophysiological mechanism for how exercise capacity is improved by acupuncture is currently unknown. In the present study, the effect of acupuncture on the pathophysiological mechanism of COPD during exercise was evaluated using cardiopulmonary exercise tests (CPETs) for the first time.

**Subjects And Methods**

**Patient Recruitment**

This single-arm, open experimental study was conducted from May 25, 2015, to May 30, 2017, at the National Hospital Organization Osaka Toneyama Medical Center. All participants met the following criteria: 1) COPD diagnosed and classified as stage II or more according to the
Table 1 Patients’ Baseline Characteristics (N=16)

|                          | Mean | SD  | Min | Max |
|--------------------------|------|-----|-----|-----|
| Age, years               | 72.7 | 6.3 | 61  | 83  |
| Sex, male/female         | 16/0 |     |     |     |
| BMI, kg · m⁻²            | 21.9 | 3.0 | 15.0| 25.7|
| Cigarette smoking, pack years | 56.1 | 21.1| 25  | 96  |
| GOLD, I/II/III/IV, number| 0/7/8/1 |     |     |     |

Pulmonary function tests
- FEV₁, L: 1.40 ± 0.51
- %FEV₁, %predicted: 50.6 ± 17.2
- FEV₁/FVC, %: 43.0 ± 13.9
- VC, L: 3.32 ± 0.52
- %VC, %: 93.2 ± 11.9

Incremental work rate exercise testing At peak exercise
- Dyspnoea, Borg scale: 6.1 ± 1.7
- V₁O₂, mL · min⁻¹ · kg⁻¹: 14.3 ± 3.2

Constant work rate exercise testing
- Time to the limit of tolerance (tLIM), s: 810 ± 470
- SGRQ scores
  - Total: 40.4 ± 16.3
  - Symptoms: 49.9 ± 22.7
  - Activity: 56.9 ± 17.9
  - Impacts: 28.1 ± 17.0

Medications, number
- LAMA: 16
- LABA: 7
- SABA: 2
- ICS: 7
- Methylxanthines: 2

Notes: Data are presented as the mean, standard deviation (SD) and the minimum–maximum values. Medications are presented separately. Evaluations for eligibility, including pulmonary function testing, were performed before pre-treatment measurements.

Abbreviations: BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease category; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; LABA, long-acting β₂-agonist; SABA, short-acting β₂-agonist; SGRQ, St George’s Respiratory Questionnaire; tLIM, time to the limit of tolerance; VC, vital capacity; V₁O₂, oxygen uptake.

Acupuncture Intervention
The patients underwent acupuncture once a week for 12 weeks, in addition to their daily medications. The following 11 standardised acupuncture points were selected according to previous research: lung meridian, LU1 (Zhongfu) and LU9 (Taiyuan); large intestine meridian, LI18 (Futu); conception vessel, CV4 (Guanyuan) and CV12 (Zhongwan); stomach meridian, ST36 (Zusanli); kidney meridian, KI3 (Taixi); gall-bladder meridian, GB12 (Wangu); and bladder meridian, BL13 (Feshu), BL20 (Pishu), and BL23 (Shenshu). No other acupuncture points were used. Therapeutic acupuncture needles (stainless steel; disposable; length, 40 mm; thickness, 0.16 mm; SEIRIN, Shizuoka, Japan) were inserted to a depth of 5 to 25 mm and manually rotated counter-clockwise for 10 s to 1 min during the 50-min treatment period. Perception of de qi (ie, tingling, numbness, heaviness, and other feelings) was confirmed after needle insertion and manipulation. The acupuncturist had been treating respiratory patients for >5 years at the study institution.

Pulmonary Function Tests
Spirometry measurements (Autospirometer System 9; Minato Medical Science, Osaka, Japan) were obtained in accordance with the recommendations of the American Thoracic Society before the CPET at baseline and at 12 and 24 weeks.

Cardiopulmonary Exercise Tests
CPETs were performed at baseline and at 12, 16, and 24 weeks.

a) Incremental exercise test (IET)

Symptom-limited incremental exercise tests were performed using an electrically braked cycle ergometer (CV-1000SS; Lode, Groningen, Netherlands) and a CPET system (Marquette CASE series T 2001, GE Healthcare, Tokyo, Japan; Aero monitor AE310S, Minato Medical Science Co., Ltd, Osaka, Japan; and pulse oximeter Pulsox-M24, Teijin Co Ltd, Tokyo, Japan) with the following protocol: starting with zero workload, the power was progressively increased by increments of 10 W every 2 mins, as previously described. The following parameters were obtained: heart rate, respiratory frequency, tidal volume, minute ventilation (Vₑ), oxygen uptake (V₁O₂), carbon dioxide output (V₁CO₂), ventilatory equivalent for oxygen (Vₑ/O₂), ventilatory equivalent for carbon dioxide (Vₑ/V₁CO₂), saturation pulse oxygenation (SpO₂), SpO₂-slope [(SpO₂ at peak exercise - SpO₂ at rest)/ (V₁O₂ at peak exercise - V₁O₂ at rest)], difference (D-F₁O₂%)
between fractional content of inspired (FiO₂) and expired (FeO₂) oxygen, difference between inspiratory and expiratory tidal volume (VTi - VTe), which indicates the remains of expiration, and oxygen pulse measured on a breath-by-breath basis and presented as 30-s averages at rest, during exercise at 2-min intervals, and at the end of exercise. Dyspnea was measured using the modified Borg scale. The anaerobic threshold (AT) was identified using the V-slope method, and the nadir of the parameter VET/VO₂ was measured during exercise. The dyspnea break points during exercise were determined using the intersection of two lines on individual plots of the Borg scale curve. The patient was unable to regain the target frequency despite encouragement was defined as the time to the limit of tolerance (tLIM). Submaximal isotime was defined as the end of 30-s averages prior to the time of shorter peak exercise either during baseline or the period after acupuncture.

### Respiratory Muscle Strength

The maximum inspiratory (MIP) and expiratory (MEP) pressures were measured using a standard mouthpiece and a respiratory muscle strength testing device (Vitalpower KH101; Chest M.I., Inc., Tokyo, Japan) according to the American Thoracic Society/European Respiratory Society. Respiratory system resistances were measured at 5 Hz (R5) and 20 Hz (R20) using a commercial forced oscillation technique device (MostGraph1; Chest M.I., Inc.). Daily physical activities, such as total energy expenditure, were measured using a triaxial accelerometer (Actimarker; Panasonic, Osaka, Japan).

### Table 2: Peak Parameters Of The Incremental Exercise Test After 12 Weeks Of Acupuncture Treatment And Follow-Up Data

|                     | Week 0 (n=16) | Week 12 (n=16) | Week 16 (n=14) | Week 24 (n=13) | p-Value (F-Value)* |
|---------------------|---------------|----------------|---------------|---------------|-------------------|
| Work rate, W        | 47.5 (17.9)   | 50.0 (18.0)    | 50.7 (18.7)   | 52.3 (20.1)   | 0.142 (1.918)     |
| VO₂, mL - kg⁻¹ - min⁻¹ | 14.3 (3.2)   | 14.7 (3.9)     | 15.0 (3.8)    | 15.0 (4.0)    | 0.018 (3.763)     |
| VO₂, mL · min⁻¹   | 854 (201)     | 874 (229)      | 879 (239)     | 885 (221)     | 0.039 (3.066)     |
| CO₂, mL · min⁻¹    | 883 (232)     | 921 (269)      | 921 (257)     | 931 (266)     | 0.063 (2.630)     |
| Dyspnea, Borg scale | 6.1 (1.7)     | 6.3 (1.8)      | 6.1 (2.1)     | 6.5 (1.9)     | 0.809 (0.322)     |
| Leg fatigue, Borg scale | 4.7 (2.7)   | 4.8 (3.1)      | 4.6 (3.0)     | 4.9 (3.1)     | 0.797 (0.340)     |
| VTi, L             | 1.29 (0.33)   | 1.32 (0.40)    | 1.31 (0.36)   | 1.34 (0.32)   | 0.805 (0.328)     |
| VTi - VTe, mL      | 13.9 (14.3)   | 6.4 (16.5)     | 1.2 (25.7)    | 17.5 (20.7)   | 0.112 (2.125)     |
| fE, breaths · min⁻¹ | 29.1 (5.2)    | 30.4 (5.9)     | 29.6 (5.1)    | 29.7 (4.6)    | 0.334 (1.167)     |
| VE, L · min⁻¹      | 37.0 (9.9)    | 39.3 (12.0)*   | 38.0 (9.7)    | 39.6 (11.8)   | 0.040 (3.048)     |
| VO₂/VTi            | 0.37 (0.04)   | 0.37 (0.05)    | 0.36 (0.05)   | 0.36 (0.04)   | 0.383 (1.046)     |
| VO₂/VO₂            | 43.7 (7.5)    | 45.2 (8.0)*    | 44.5 (9.4)    | 45.1 (9.2)    | 0.306 (1.246)     |
| VO₂/CO₂            | 42.2 (5.4)    | 42.9 (5.8)     | 42.2 (8.1)    | 43.1 (7.9)    | 0.631 (0.582)     |
| HR, beats · min⁻¹  | 121 (10)      | 123 (13)       | 125 (14)      | 125 (14)      | 0.264 (1.377)     |
| SpO₂, %            | 91.4 (4.5)    | 90.3 (4.7)     | 90.1 (4.6)    | 89.5 (5.2)    | 0.132 (1.985)     |
| SpO₂-slope, % (L · min⁻¹)⁻¹ | –10 (0.2)   | –11 (0.2)      | –12 (0.2)     | –12 (0.2)     | 0.898 (0.197)     |
| DF₅₀₂₂, %          | 2.87 (0.50)   | 2.79 (0.50)*   | 2.81 (0.55)   | 2.82 (0.62)   | 0.341 (1.149)     |
| PETCO₂, mmHg       | 35.8 (5.9)    | 35.4 (5.8)     | 35.8 (6.8)    | 35.7 (7.7)    | 0.740 (0.419)     |
| FeCO₂, %           | 3.17 (0.45)   | 3.13 (0.41)    | 3.21 (0.58)   | 3.14 (0.61)   | 0.341 (1.150)     |
| AT, mL · min⁻¹     | 650 (168)     | 647 (156)      | 637 (125)     | 640 (150)     | 0.464 (0.875)     |
| AT, %              | 76.9 (10.2)   | 74.1 (10.4)    | 75.8 (10.1)   | 72.7 (7.3)    | 0.490 (0.824)     |
| Dyspnea break point, % | 75.6 (2.7)   | 75.2 (2.6)     | 79 (3.8)      | 78.4 (2.9)    | 0.722 (0.449)     |

Notes: Data are presented as the mean (standard deviation). Treatment effect: mean difference from pre-treatment value. *P < 0.05, pre-treatment vs 12 weeks, paired t-test. Dyspnea break points and ATs at pre-treatment, 12, 16, and 24 weeks were detectable in 15, 15, 14, and 13 patients and in 14, 14, 12, and 11 patients, respectively. Time course effect of 12-week acupuncture treatment by one-way repeated measures analysis of variance.

Abbreviations: AT, anaerobic threshold; DF₅₀₂₂, difference between fractional content of inspired oxygen and fractional content of expired oxygen; FeCO₂, fractional content of expired carbon dioxide; fE, breathing frequency; HR, heart rate; PETCO₂, end-tidal partial pressure of CO₂; VO₂/VTi, dead space/tidal volume ratio; SpO₂-slope, saturation pulse oxygenation; SpO₂-slope, (SpO₂ at peak exercise - SpO₂ at rest)/(VO₂ at peak exercise - VO₂ at rest); Vp, minute ventilation; VCO₂, CO₂ output; VO₂, oxygen uptake; VTi - VTe, inspiratory tidal volume - expiratory tidal volume.
Dual-Energy X-Ray Absorptiometry
To assess body composition, including lean body mass, dual-energy X-ray absorptiometry was performed with patients lying in a supine position.

Primary Outcomes
Primary outcomes were exercise performance parameters, including peak oxygen uptake ($V_{O2peak}$), representing the highest oxygen uptake achieved in the IET at the subject’s limit of tolerance and tLIM measured in CWRET, and the quality of life measured with the St George’s Respiratory Questionnaire (SGRQ).

Secondary Outcomes
Secondary outcomes were forced expiratory volume in one second (FEV₁), MIP, MEP, total lean body mass, and total energy expenditure.

Sample Size
The effects of acupuncture have not been previously evaluated using CPET. Therefore, the sample size calculation was using the estimated effect of acupuncture for improving SGRQ. The sample size of 16 was used to provide the power (90%) to detect a mean difference of 4 in SGRQ with a standard deviation SD of 3.32 using a two-sided $\alpha$ of 0.05.

Figure 2 Responses and follow-up data after 12 weeks of acupuncture treatment at maximum exercise in (A) incremental exercise testing (IET): 1) peak oxygen uptake and 2) peak minute ventilation. (B) Constant work rate exercise testing (CWRET): 1) endurance time, 2) oxygen uptake at terminated exercise, 3) $DF_{O2}$ at terminated exercise, 4) Borg scale at isotime. Data are expressed as the mean ± standard error: $V_{O2}$: oxygen uptake; $V_{E}$: minute ventilation; $DF_{O2}$: inspired oxygen concentration ($F_{I_{O2}}$) - expired oxygen concentration ($F_{E_{O2}}$); p-values: time course effect of 12-week acupuncture treatment by one-way repeated measures analysis of variance; *p < 0.05, ***p < 0.001: pre-treatment vs 12 weeks, paired t-test.
Statistical Analysis

The data are expressed as means ± SD unless otherwise indicated and as means ± SE in a part of Table and Figures. Changes in parameters at week 12 were assessed by the paired t-test. The time course (baseline, 12-week, 16-week, and 24-week) changes in parameters treated by 12-week acupuncture were verified using one-way repeated-measures analysis of variance. The relationships between parameters were assessed using Pearson’s correlation coefficients and linear regression analyses. A p-value < 0.05 was considered statistically significant (JMP software, version 11; SAS Institute Inc., NC, United States).

Results

Recruitment And Follow-Up

Of the 20 patients meeting the defined criteria, 18 agreed to participate and underwent acupuncture (Figure 1). Of those, two female patients were unable to complete the study protocol because one patient was prescribed a steroid for rheumatoid arthritis, and the other patient was affected by depression. The follow-up assessments were not performed in two patients due to acute respiratory infections and severe arrhythmia in one patient. The baseline characteristics of the remaining 16 patients are shown in Table 1. Medications for all patients did not change throughout the study. All patients had previously undergone a CPET in the clinical practise.

Primary Outcomes

During the time course of 12 weeks of acupuncture, the $\Delta V_{O_2}$peak and $V_{E}$peak were significantly improved in IET (Table 2, Figure 2). The peak aerobic capacity improved by >50 mL/min from baseline in 5 of the 16 (31%) patients. The D-Fo2% significantly decreased at peak exercise after 12 weeks of acupuncture, although there were no effects on the Spo2-slope and Spo2.

The tLIM significantly increased after 12 weeks of acupuncture and in the follow-up in CWRET (Table 3, Figure 3). The tLIM improved by >100 s after 12 weeks of acupuncture compared to baseline in 14 of the 16 (88%) patients. After 12 weeks of acupuncture in CWRET, the $\Delta V_{O_2}$ and the D-Fo2% significantly decreased at terminated exercise, but minute ventilation did not change. The best improvement in tLIM, defined as the greatest percentage increase among three CWRETs in each patient, was
observed at week 12 (8 patients) and 16 (remaining 8 patients). The SGRQ score, especially the symptom score, was significantly improved at 12 and 24 weeks (Table 4).

Secondary Outcomes
After completing 12 weeks of acupuncture, there were improvements in respiratory muscle strength (i.e., MIP and MEP), but there were no changes in FEV₁, total lean body mass, and total energy expenditure (Table 4).

Parameters Contributing To Best tLIM Improvement After Acupuncture
After acupuncture, dyspnoea significantly improved at 2, 4, 6 mins and isotime, the $\dot{V}_{O_2}$ was significantly decreased at 2, 4, 6 mins and isotime, and $\dot{V}_{E}$ significantly decreased at 4, 6 mins and isotime during CWRET (Figure 3). In the stages showing significant changes from the pre-acupuncture, 1) the decreases in the Borg scale at 6 mins ($r = -0.608, p = 0.0211$) and isotime ($r = -0.789, p = 0.0007$), and $\dot{V}_{E}$ at 6 mins ($r = -0.5809, p = 0.0294$) and isotime ($r = -0.6736, p = 0.0042$) were significantly correlated with the improvement (sec) of tLIM improvement (Figure 4). 2) The decrease in $\dot{V}_{O_2}$ at isotime was not significantly correlated to tLIM improvements ($r = -0.4587, p = 0.0739$). 3) The increases in D-F $O_2$% at isotime ($r = 0.6884, p = 0.0032$) were positively correlated with the improvement (sec) of tLIM (Table 5; Figure 4). 4) The decreases in the modified Borg scale ($r = -0.6795, p = 0.0038$) and $\dot{V}_{E}$ ($r = -0.6880, p = 0.0032$) were significantly correlated with the D-F $O_2$% changes at isotime.

The ($V_{Ti} - V_{Te}$) was significantly decreased at isotime (16.7 ± 4.1 to 3.3 ± 4.2, $p = 0.0327$) after acupuncture, and
this decrease was correlated with the decrease in $V_E$ ($r = 0.606$, $p = 0.0129$). In addition, the improvement (sec) of tLIM was significantly correlated with the respiratory gas exchange ratio ($r = -0.5587, p = 0.0244$) at isotime in CWRET, but not with the improvement of $V_{O2peak}$ and peak $V_E$ in IET after acupuncture. Consequently, improvements in dyspnoea, reduction in $V_E$, and the increase of D-F$O_2\%$ between post- and pre-acupuncture values at isotime have greatly contributed to the improvement (sec) of tLIM (Figure 4).

**Adverse Reactions**

Some patients reported 1 fatigue, 3 subcutaneous bleedings, and 2 pains at the needle insertion site as adverse reactions. All events were minor responses and patients recovered within a short time. Significant events caused by the acupuncture procedure have not been reported.

**Discussion**

The effects of acupuncture, applied once a week for 12 weeks in stable COPD patients, were evaluated at baseline and at 12, 16, and 24 weeks, and the underlying pathophysiological mechanisms were analysed using CPET. We observed improvements in $V_{O2peak}$, $V_E$peak, tLIM, and dyspnoea including SGRQ score after acupuncture. Thus, this study confirmed the effectiveness of acupuncture using CPET in the previous study. The improvement of exercise intolerance largely contributed to the increase in tLIM rather than in $V_{O2peak}$ based on the minimal clinically important differences, which were considered as a $V_{O2peak}$ change of 50 mL/min and tLIM change of 100 s. Following acupuncture, the $V_{O2peak}$ values, calculated using the product of $V_E \times D-F_{O2\%}$, were low throughout the CWRET. From the pre-acupuncture, the decrease in $V_E$ and Borg scale and increase in D-F$O_2\%$ at isotime significantly contributed to tLIM improvement.

In the two cases without tLIM improvement of 100 s (cases 17 and 18 in Table 5), the Sp$O_2$-slope, indicative of pulmonary gas exchange, was clearly deteriorated. Furthermore, case 17 had a very severe obstructive disorder (FEV$_1\%$ predicted: 26.6%) and lost 3.1 kg of body-weight during the study period. The respiratory muscle strength was also decreased (MEP, 56.9 to 45.8 cmH$_2$O; MIP, 51.5 to 39.5 cmH$_2$O); moreover, the parameter $V_{Epeak}$-$V_{Tc}$, representing the remaining volume of expiration, was increased to +32 mL. In case 18, the C-reactive protein

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### Table 4  St. George's Respiratory Questionnaire Scores, Pulmonary Functions, and Other Parameters After 12 Weeks Of Acupuncture Treatment And Follow-Up Data

|                      | Week 0 (n=16) | Week 12 (n=16) | Week 24 (n=14) | p-Value (F-Value)* |
|----------------------|--------------|---------------|---------------|-------------------|
| **SGRQ scores**      |              |               |               |                   |
| Total                | 40.4 (16.3)  | 35.0 (15.4)*  | 35.2 (16.0)   | 0.009 (5.577)     |
| Symptoms             | 49.9 (22.7)  | 40.7 (17.7)*  | 42.3 (17.4)   | 0.029 (4.019)     |
| Activity             | 56.9 (17.9)  | 52.2 (18.8)   | 51.7 (21.6)   | 0.020 (4.542)     |
| Impacts              | 28.1 (17.0)  | 23.4 (15.2)   | 24.3 (17.5)   | 0.110 (2.392)     |
| **Pulmonary function tests** |           |               |               |                   |
| FEV$_1$, L           | 1.42 (0.54)  | 1.39 (0.51)   | 1.46 (0.55)   | 0.358 (1.067)     |
| FEV$_1$/FVC, %       | 51.6 (18.9)  | 50.8 (18.6)   | 52.4 (20.2)   | 0.532 (0.646)     |
| VC, L                | 43.0 (13.8)  | 43.6 (16.1)   | 44.4 (14.2)   | 0.915 (0.089)     |
| %VC, %               | 3.32 (0.52)  | 3.28 (0.55)   | 3.42 (0.49)   | 0.273 (1.359)     |
| %VC, %               | 93.7 (12.2)  | 92.5 (12.9)   | 95.5 (13.8)   | 0.247 (1.473)     |
| **Others**           |              |               |               |                   |
| MIP, cmH$_2$O        | –50.7 (17.4) | –58.3 (17.2)* | –53.8 (16.9)  | 0.029 (4.006)     |
| MEP, cmH$_2$O        | 53.4 (16.9)  | 60.6 (18.8)** | 56.0 (21.2)   | 0.111 (2.378)     |
| Total lean body mass, kg | 43.4 (4.5)  | 43.7 (4.2)    | 43.1 (3.6)    | 0.992 (0.303)     |
| Total energy expenditure, kcal · day$^{-1}$ | 1812 (189)   | 1789 (218)    | 1851 (184)    | 0.201 (1.705)     |
| R5, cmH$_2$O·L$^{-1}·s^{-1}$ | 3.9 (1.7)   | 3.9 (1.2)     | 3.9 (1.6)     | 0.999 (0.001)     |
| R20, cmH$_2$O·L$^{-1}·s^{-1}$ | 2.9 (1.1)   | 2.9 (1.1)     | 2.9 (1.1)     | 0.999 (0.001)     |

**Notes:** Data are presented as the mean (standard deviation). *P < 0.05, **P < 0.01: pre-treatment vs 12 weeks, paired t-test. *Time course effect of 12-week acupuncture treatment by one-way repeated measures analysis of variance.

**Abbreviations:** FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; SGRQ, St George's Respiratory Questionnaire; VC, vital capacity.
level was slightly increased to 1.03 mg dL⁻¹, and the respiratory system resistance values were also increased at week 12 (R5, 2.7 to 5.4 cmH₂O L⁻¹ s⁻¹; R20, 2.4 to 3.9 cmH₂O L⁻¹ s⁻¹). And then, this patient withdrew from the study due to pneumonia. Given these results, it is understandable that their endurance times were not improved by acupuncture.

The effects of acupuncture on \( \Delta V_{O2}^{peak}, \Delta tLIM, \) and quality of life continued to be observable at 24 weeks. By contrast, the effects on respiratory muscle strength, \( \Delta V_{O2} \) and D-FO₂ (%) at terminated exercise in CWRET tended to decline. It is generally unlikely that acupuncture effects will sustain over 12 weeks after terminating the treatment. Of the 16 participants, 11 had previously undergone the PPR-OT program at our institute,¹⁰ and the remaining 5 participants had been riding bicycles in everyday life. The PPR-OT program included practical guidance regarding inhalation therapy, exercise training in a home setting, nutrition and diet therapy, and self-management. We speculated that these daily exercises sustained the effects of acupuncture. Further studies are necessary to determine the synergistic effect between exercise training and acupuncture.

The improvements in pulmonary functions and nutritional status observed in previous papers were not replicated in our study,¹³,²⁵ although the same acupuncture points were used. However, we used a thinner needle (0.16 mm vs 0.35 mm) in this study because of the weak pain stimulus. An improvement of FEV₁ has also been observed in patients with COPD who are treated with transcutaneous electrical nerve stimulation, which was associated with a concurrent increase in \( \beta \)-endorphin levels.²⁶ The increase in \( \beta \)-endorphin levels also correlated with a reduction in breathing frequency.²⁷ A significant decrease in breathing frequency was not observed in the current study, which may be due to a weaker pain stimulus and/or differences in acupuncture procedures. Although the detailed reasons for the observed differences in our study findings compared to previous findings are unknown, our data might have been influenced by baseline managements, including appropriate medications (i.e., inhalation therapy) and pulmonary rehabilitation.

Patients with COPD experience tension and fatigue of both main and accessory respiratory muscles; therefore, many of the acupuncture points used in the present study

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### Table 5 Improvement In Time To The Limit Of Tolerance In Constant Workload Exercise Testing And Related Parameters In Each Patient

| Case No. | tLIM Improvement | Parameters At Isotime | Incremental Exercise Testing |
|----------|------------------|-----------------------|-----------------------------|
|          | s                | %                     | **R ratio** | **ΔBS** | **ΔV_{O2}^{peak}** | **ΔV_{E}** | **ΔD-FO₂** | **ΔV_{T,Ti}^{V_{O2}}** | **V_{O2}^{peak}** | **peak V_{E}** | **ΔSpO₂:Slope** |
| 1        | 1510             | 385                   | 0.92       | -4      | -80               | -6.5      | 0.49      | -14               | -2.2          | 2.3           | -2            |
| 2        | 1089             | 58                    | 0.98       | -3      | -112              | -7.1      | 0.24      | -77               | 16.0          | 13.3          | 0.5           |
| 4        | 656              | 120                   | 0.98       | -2      | -33               | 0         | -0.10     | 11                | 17.5          | 26.7          | 4.6           |
| 5        | 602              | 45                    | 0.94       | -2      | -4                | -3.6      | 0.20      | -21               | -12.9         | 1.7           | -4            |
| 6        | 558              | 85                    | 1.00       | -2      | -61               | 0         | -0.20     | 17                | 4.9           | 4.7           | -2.4          |
| 7        | 554              | 52                    | 0.94       | -2      | 32                | 1.2       | 0.27      | -7                | 23.1          | 27.7          | 29.9          |
| 8        | 447              | 52                    | 0.97       | -1      | 8                 | -3.4      | 0.15      | -48               | 3.2           | -4.7          | 0.2           |
| 10       | 334              | 19                    | 0.97       | 0       | -96               | 2.2       | -0.50     | 21                | -5.2          | 9.1           | -1.2          |
| 11       | 333              | 95                    | 0.89       | -2      | 32                | 0.8       | 0.03      | -2                | 4.0           | 9.0           | -0.8          |
| 12       | 266              | 51                    | 1.00       | -2      | -33               | 0         | -0.10     | -8                | 4.5           | 5.2           | -2.9          |
| 13       | 263              | 34                    | 0.99       | 1       | -65               | -3.0      | 0.01      | -31               | 6.3           | 1.0           | 2.5           |
| 14       | 212              | 39                    | 1.02       | -1      | -36               | -0.2      | -0.10     | -15               | 6.3           | 4.5           | 0.2           |
| 15       | 123              | 20                    | 1.08       | 1       | -162              | 0.4       | -0.30     | -19               | 4.7           | 7.1           | -3.9          |
| 16       | 118              | 16                    | 1.05       | -1      | -21               | -1.7      | 0.03      | -35               | 16.1          | 24.7          | -8.5          |
| 17       | 20               | 4                     | 0.99       | 1       | -64               | -2.2      | -0.20     | 32                | -5.7          | -3.8          | -13.2         |
| 18       | 16               | 5                     | 1.14       | -1      | -15               | 2.1       | -0.10     | -12               | 7.1           | 5.5           | -14.4         |

**Notes:** Differences (Δ) between post- and pre-acupuncture measurement are shown for the following: BS, Borg scale; D-FO₂: % difference between fractional content of inspired oxygen and fractional content of expired oxygen; SpO₂:Slope: (SpO₂ at peak exercise - SpO₂ at rest)/(V_{O2}^{peak} at peak exercise - V_{O2} at rest) in %/L/min; V_{E}: minute ventilation in L/min; V_{O2}^{peak}: oxygen uptake in mL/mm; V_{T,Ti}^{V_{O2}}: inspiratory tidal volume - expiratory tidal volume in mL.

**Abbreviations:** R ratio, gas exchange ratio (V_{CO2}/V_{O2}); SE, standard error; tLIM, time to the limit of tolerance.
corresponded to those accessory muscles. We believe that acupuncture decreases the tone of accessory muscles and alleviates muscle fatigue, leading to a significant improvement in respiratory muscle strength (MEP/MIP) and peak $V_E$. Respiratory muscle unloading may also improve the oxygen supply to lower-limb muscles. This effect may be due to the ability of acupuncture to reduce myostatin gene expression, leading to muscle satellite cell proliferation and activation of muscle protein synthesis. Consequently, muscle atrophy is reduced and muscle strength is restored. Improvements in muscle blood flow were indicated by an increase in muscle oxygenation and blood volume, which may be caused by calcitonin gene and peptide-related antidromic local vasodilation and the axon reflex in the muscle stimulated by acupuncture. Furthermore, electrical acupuncture stimulation showed increased blood fluidity in an animal study. This effect might involve an endogenous adrenergic mechanism because it was inhibited by a $\beta$-antagonist.

We hypothesised that improvements in muscle strength and circulation after acupuncture may have contributed to the lower $\dot{V}_{O_2}$ and $V_E$ values throughout the CWRET. No effects on pulmonary gas exchange were observed; therefore, the responses of D-F$O_2\%$ at isotime may be caused by an improved oxygen utilisation in the muscle. Although the IET did not detect a significant AT increase, the acupuncture-induced tLIM increase likely reflects a delayed onset of metabolic and/or respiratory acidosis due to the lowered oxygen consumption per workload because decreases in respiratory gas exchange ratio at isotime after acupuncture were significantly correlated with tLIM improvements. Furthermore, this effect on oxygen utilisation may improve the prognosis of COPD as well as outcomes of occupational therapy.

The limitations of this study were as follows: 1) blood samples (to determine arterial blood gases, lactate, catecholamine, or $\beta$-endorphin) were not collected for the elucidation of pathophysiological mechanism because of financial constraints; 2) for the more accurate measurement of exercise tolerance, the tLIM at baseline in the CWRET (at 70% peak WR of the IET) was longer than the recommended value and the optimal time point for acupuncture-induced improvements should be determined in advance.

**Conclusion**

The effectiveness of acupuncture was due to the improvements in ventilation capacity in IETs and the increase of endurance time in CWRETs at 12 weeks. In the CWRET, the values of oxygen uptake during exercise and at terminated exercise were significantly lower after acupuncture than those at baseline. These results indicate that COPD patients treated with acupuncture have been able to exercise with less oxygen consumption. Our findings indicate...
that acupuncture may be a new intervention for COPD in addition to conventional maintenance therapies.

Ethics Approval And Informed Consent And Consent For Publication
This study was performed in accordance with the Declaration of Helsinki and its amendments, the Guidelines for Good Clinical Practice for Epidemiological Studies, the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA), and the Guidelines for Clinical Research issued by the Japanese Ministry of Health. The institutional review board of the National Hospital Organization Osaka Toneyama Medical Center approved this study (number: 1580), and each patient provided written informed consent. The study protocol is registered at the University Hospital Medical Information Network in Japan (UMIN000017609).

Data Availability
The authors confirm that the data supporting the findings of this study are available within the article.

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Author Contributions
All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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