ORIGINAL INVESTIGATION

# A Randomized, Placebo-Controlled Trial of Acupuncture in Patients With Chronic Obstructive Pulmonary Disease (COPD)

## *The COPD-Acupuncture Trial (CAT)*

*Masao Suzuki, LAc, PhD; Shigeo Muro, MD, PhD; Yuki Ando, MSc; Takashi Omori, PhD; Tetsuhiro Shiota, MD, PhD; Kazuo Endo, MD; Susumu Sato, MD, PhD; Kensaku Aihara, MD; Masataka Matsumoto, MD; Shinko Suzuki, MD; Ryo Itotani, MD; Manabu Ishitoko, MD; Yoshikazu Hara, MD; Masaya Takemura, MD, PhD; Tetsuya Ueda, MD, PhD; Hitoshi Kagioka, MD, PhD; Masataka Hirabayashi, MD; Motonari Fukui, MD, PhD; Michiaki Mishima, MD, PhD*

**Background:** Dyspnea on exertion (DOE) is a major symptom of chronic obstructive pulmonary disease (COPD) and is difficult to control. This study was performed to determine whether acupuncture is superior to placebo needling in improving DOE in patients with COPD who are receiving standard medication.

**Methods:** Sixty-eight of 111 patients from the Kansai region of Japan who were diagnosed as having COPD and were receiving standard medication participated in a randomized, parallel-group, placebo-controlled trial (July 1, 2006, through March 31, 2009) in which the patients, evaluators, and statistician were unaware of the random allocation. Participants were randomly assigned to traditional acupuncture (real acupuncture group, n=34) or placebo needling (placebo acupuncture group, n=34). Both groups received real or placebo needling at the same acupoints once a week for 12 weeks. The primary end point was the modified Borg scale score evaluated immediately after the 6-minute walk test. Measurements were obtained at baseline and after 12 weeks of treatment.

**Result:** After 12 weeks, the Borg scale score after the 6-minute walk test was significantly better in the real acupuncture group compared with the placebo acupuncture group (mean [SD] difference from baseline by analysis of covariance, −3.6 [1.9] vs 0.4 [1.2]; mean difference between groups by analysis of covariance, −3.58; 95% CI, −4.27 to −2.90). Patients with COPD who received real acupuncture also experienced improvement in the 6-minute walk distance during exercise, indicating better exercise tolerance and reduced DOE.

**Conclusion:** This study clearly demonstrates that acupuncture is a useful adjunctive therapy in reducing DOE in patients with COPD.

**Trial Registration:** umin.ac.jp/ctr Identifier: UMIN000001277

*Arch Intern Med. 2012;172(11):878-886.*
*Published online May 14, 2012.*
*doi:10.1001/archinternmed.2012.1233*

CHRONIC OBSTRUCTIVE PULMONARY disease (COPD), a common disease characterized by irreversible airflow limitation, is predicted to be the third leading cause of death worldwide by 2020.[1] Dyspnea, the most fundamental and debilitating symptom of COPD, is associated with considerable disease burden, affecting many aspects of everyday life. The severity of dyspnea generally progresses over time in patients with COPD,[2] and dyspnea has been found to be predictive of survival in COPD. Therefore, the management of dyspnea is one of the most important targets in the treatment of COPD.

Acupuncture has been shown to reduce breathlessness in patients with cancer.[3] A review[4] of 16 randomized controlled trials, involving 2937 participants, concluded that acupuncture is a safe and potentially effective intervention for patients with asthma and COPD.

*See Invited Commentary at end of article*

We previously demonstrated that dyspnea and exercise capacity evaluated by Borg scale scores and the 6-minute walk distance (6MWD) test could be markedly improved with acupuncture in a prospective, matched-pair trial in COPD patients who were receiving standard medication.[5] However, the interpretation of our results is somewhat limited be-

**Author Affiliations** are listed at the end of this article.

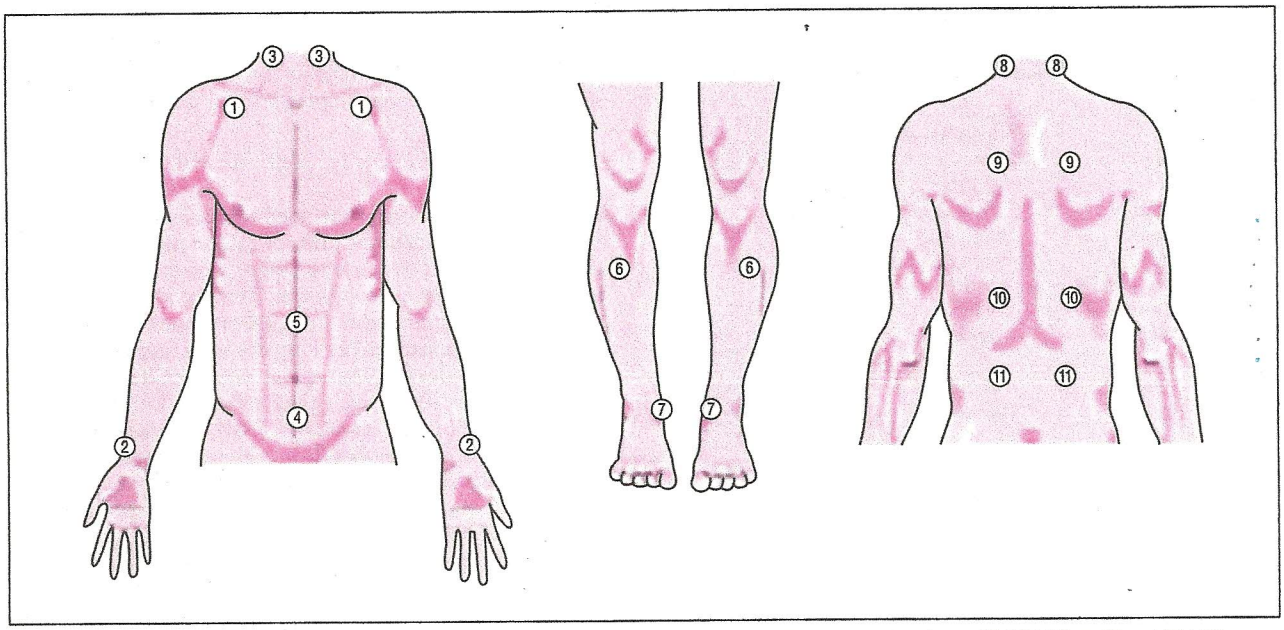

**Figure 1.** Acupuncture points used. The acupuncture points were selected according to traditional Chinese medicine theory: (1) LU1 (*Zhongfu*) and (2) LU9 (*Taiyuan*) in the lung meridian; (3) LI18 (*Futu*) in the large intestine meridian; (4) CV4 (*Guanyuan*) and (5) CV12 (*Zhongwan*) in the conception vessel; (6) ST36 (*Zusanli*) in the stomach meridian; (7) KI3 (*Taixi*) in the kidney meridian; (8) GB12 (*Wangu*) in the gallbladder meridian; and (9) BL13 (*Feishu*), (10) BL20 (*Pishu*), and (11) BL23 (*Shenshu*) in the bladder meridian.

cause the study was neither randomized nor masked in terms of patient allocation. In the present study, our objective was to evaluate the efficacy of acupuncture in patients with COPD, especially focusing on changes in dyspnea on exertion (DOE) evaluated with the 6-minute walk test (6MWT) and fully assessed respiratory functions, including respiratory muscular strength, in a randomized, single-blind trial.

## METHODS

### STUDY DESIGN

The present study was conducted as a prospective, single-blind randomized controlled trial. The study blinding procedure was achieved by using a device specially designed for placebo needle. The physician and the evaluators, including hospital staff and statisticians, were not involved in the treatment program. All outcome measures in the present study were assessed at baseline and after completion of 12 weeks of intervention.

### PATIENTS AND RECRUITMENT

The study was conducted from July 1, 2006, through March 31, 2009, at the Graduate School of Medicine Kyoto University Hospital, Ako City Hospital, Division of Respiratory Medicine, Respiratory Disease Center, Kitano Hospital, and Hyogo Prefectural Amagasaki Hospital, all of which are located in the Kansai region of Japan. Physicians in the Department of Respiratory Medicine recruited the participants at their outpatient sites. All participants met the following criteria: (1) diagnosed as having stage II, III, or IV COPD, in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[1]; (2) clinically stable with no history of infections or exacerbation of respiratory symptoms, no changes in medication within the 3 months preceding the study outset, and no signs of edema; (3) stage II or higher dyspnea according to the Medical Research Council (MRC) criteria[6]; (4) able to walk unassisted; (5) no pulmonary rehabilitation in the previous 6 months; and (6) outpatients only. Patients presenting with evidence of cardiovascular disease, collagen disease, renal failure, thyroid dysfunction, hepatic function disorder, cancer, and severe mental disorders were excluded. This study was performed in accordance with the Declaration of Helsinki and its amendments and the Guidelines for Good Clinical Practice for Epidemiological Studies and Clinical Research issued by the Japanese Ministry of Health. The institutional review board of Kyoto University Graduate School and Faculty of Medicine approved the study, and each patient provided written informed consent. The protocol of this study has been registered as a clinical trial at the University Hospital Medical Information Network in Japan (C000001217).

### INTERVENTION

Patients in the real acupuncture group (RAG) received acupuncture treatment once a week for 12 weeks, in addition to daily medication. Selection of standardized acupuncture points was done in accordance with past research on acupuncture for pulmonary dysfunction[4,5] and literature describing traditional prescription of acupuncture points for bronchial asthma and chronic bronchitis, of which the effect on COPD was verified through our clinical experiences during the past 10 years. Also, the importance of acupuncture points close to the respiratory accessory muscles was emphasized in the process of determination of the standardized treatment. The standardized acupuncture points used in the present study were as follows: (1) LU1 (*Zhongfu*) and (2) LU9 (*Taiyuan*) in the lung meridian; (3) LI18 (*Futu*) in the large intestine meridian; (4) CV4 (*Guanyuan*) and (5) CV12 (*Zhongwan*) in the conception vessel; (6) ST36 (*Zusanli*) in the stomach meridian; (7) KI3 (*Taixi*) in the kidney meridian; (8) GB12 (*Wangu*) in the gallbladder meridian; and (9) BL13 (*Feishu*), (10) BL20 (*Pishu*), and (11) BL23 (*Shenshu*) in the bladder meridian (**Figure 1**).

A Park sham device, which comprises a needle (real or placebo), was used with a guide tube mounted on a base adher-

**Table 1. Modified 10-Point Borg Scale[a]**

| Score | Severity |
|---|---|
| 0 | Nothing at all |
| 0.5 | Very, very slight, just noticeable |
| 1 | Very slight |
| 2 | Slight, light |
| 3 | Moderate |
| 4 | Somewhat severe |
| 5 | Severe |
| 6 | |
| 7 | Very severe |
| 8 | |
| 9 | |
| 10 | Very, very severe, maximal |

[a] At the beginning of the 6-minute walk test (6MWT), show the scale to the patient and ask the patient the following: "Please grade your level of shortness of breath using this scale." At the end of the 6MWT, remind the patient of the breathing number that he or she chose before the 6MWT and ask the patient to grade his or her breathing level again.

ent to the skin.[7] The tips of the placebo needles used for the placebo acupuncture group (PAG) were blunt and appeared to be penetrating the skin but actually telescoped back into place. The real and placebo needles appear similar and were the same size (0.35 × 70 mm, stainless steel; Dong Bang Acupuncture, Inc). To achieve proper handling of the Park sham device, the acupuncturists had been trained for at least 2 weeks before the commencement of the study. For the RAG patients, needles were inserted to a depth ranging from 5 to 25 mm and were manually rotated clockwise and counterclockwise for 3 to 4 minutes at each point during a 50-minute treatment period. No electrical stimulation was performed. Perception of *de qi* (tingling, numbness, heaviness, and other feelings that occur after acupuncture needle insertion) during insertion and/or manipulation was confirmed at every point in the RAG.

The PAG underwent treatment at the same acupuncture points as the RAG. Perception of sensation during treatment sessions in PAG included pricking or poking, but no sensation like *de qi* was reported.

## RANDOMIZATION

After obtaining informed consent, participants were registered at a randomization center by a clinical trial coordinator. They were stratified by age (<75 or ≥75 years)[8] and then randomly assigned to the RAG or PAG using a computer-generated random allocation sequence with permutated block design.

## PRIMARY OUTCOME MEASURE

We conducted the 6MWT using the standard method for assessment of severity of DOE.[9] To rate breathlessness before and immediately after the 6MWT, a modified 10-point Borg category ratio scale was used, where 0 signified "breathing very well, barely breathless" and 10 signified "severely breathless"[10] (**Table 1**). The score after the 6MWT was used in the analysis.

## SECONDARY OUTCOME MEASURES

Secondary outcome measures in the present study included the 6MWD[9]; the lowest oxygen saturation during the 6MWT, which was monitored at 1-minute intervals with a saturation pulse oxygen meter; and forced expiratory volume in 1 second ($FEV_1$), which was monitored using a computed spirometer according to the protocol for lung function measurements of the American Thoracic Society.[11] Quality of life of the patients was measured with the St George Respiratory Questionnaire (SGRQ).[12]

## OTHER OUTCOME MEASURES

Other outcome measures included respiratory function, such as diffusing capacity of the lung for carbon monoxide (DLCO), residual volume, and total lung capacity. Arterial blood gas was measured under stable conditions. The maximum inspiratory mouth pressure and maximum expiratory mouth pressure were measured using a standard mouthpiece and a respiratory muscle strength testing device (Vitaropower KH115; Chest MI Co Ltd) according to the American Thoracic Society/European Respiratory Society.[13] Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and serum prealbumin levels were evaluated as indices of nutritional status. Evaluation of thorax mobility was made by measuring the difference of the girth of the chest between the residual volume level and total lung capacity level on the basis of the fourth intercostal using a tape measure. Dyspnea during activities of daily living was scored using the MRC dyspnea scale.[6] Measurements were taken at baseline and after completion of the acupuncture treatment.

At the end of the intervention period, we asked the following question to all patients to ascertain the perception of the placebo needling. "Please select one of the following regarding treatment procedures you think you had been received: 1. Real acupuncture, 2. Placebo acupuncture, 3. Do not know."

## STATISTICAL ANALYSIS

Statistical analysis in the present study was conducted by 2 biostatisticians (Y.A. and T.O.). The sample size of this study was computed based on the primary end point, which was a change in the Borg scale score at the end of the 6MWT. Calverley[14] reported that the minimal clinically important difference in the Borg scale score in COPD patients was 2 units. Thus, the required sample size was estimated to be 60 patients, which was calculated to detect a minimal difference between means in the Borg scale score of 2.0 at a significance level of .05 with a power of 0.8.

All data are presented as mean (SD) or mean (95% CI). The difference between baseline and final volumes was compared using analysis of covariance with baseline values and age as covariates and treatment group as the factor of interest. All main analyses in the present study were performed with SAS statistical software, version 9.1.3 (SAS Institute, Inc).

# RESULTS

## STUDY RECRUTMENT AND FOLLOW-UP

Of the 111 patients who met the inclusion and exclusion criteria, 68 agreed to participate in the study. **Figure 2** shows the trial profile. Of those participants, 6 were unable to complete the study because they believed it was too difficult to continue (2 in the PAG and 1 in the RAG) or they had acute exacerbation of respiratory infections (3 in the RAG). Baseline characteristics of the patients in each group, including medications taken by the patients during the study, are listed in **Table 2**. All medications remained unchanged through the study period.

## MAIN OUTCOME

After 12 weeks of treatment, the Borg scale score after the 6MWT improved from 5.5 (2.8) to 1.9 (1.5) in the RAG. On the other hand, no improvement was seen in the Borg scale score in the PAG before and after acupuncture treatment (4.2 [2.7] and 4.6 [2.8], respectively). The difference in the Borg scale score in the RAG (−3.6 [1.9]) was statistically significant compared with that in the PAG (0.4 [1.2]; mean difference by analysis of covariance, −3.58; 95% CI, −4.27 to −2.90) (**Table 3** and **Figure 3**A).

## SECONDARY OUTCOMES

Significant improvement was found in the 6MWD, oxygen saturation during the 6MWT, and SGRQ results after treatment in the RAG of which the difference from the baseline was significantly greater than that in the PAG, whereas changes in the $FEV_1$ did not reach statistical significance (Table 3, **Table 4**, andFigure 3B).

## OTHER OUTCOME MEASURES

### Dyspnea During Activities of Daily Living

After 12 weeks of acupuncture, significant improvements in the MRC score were found in the RAG, with a significantly greater reduction in scores compared with the PAG (**Table 5**).

### Nutritional Evaluation, Arterial Blood Gas, and Range of Motion in the Rib Cage

Improvement in the nutritional status (BMI and prealbumin level), arterial blood gas ($PaO_2$), and range of motion in the rib cage was found in the RAG of which the difference from the baseline showed a statistically significant difference compared with that in the PAG (Table 5).

### Respiratory Function and Respiratory Muscle Strength

After 12 weeks of acupuncture, significant improvements in respiratory function (forced vital capacity, percentage of $FEV_1$, DLCO, and percentage of DLCO) and respiratory muscle strength (maximum expiratory mouth pressure and maximum inspiratory mouth pressure) were found in the RAG compared with the PAG (**Table 6**).

### Perception of the Placebo Needling by the Patients

Regarding perception of the needling, 4, 2, and 26 patients in the PAG answered "real acupuncture," "placebo acupuncture," and "don't know," respectively. These responses were given in 2, 3, and 25 patients, respectively, in the RAG.

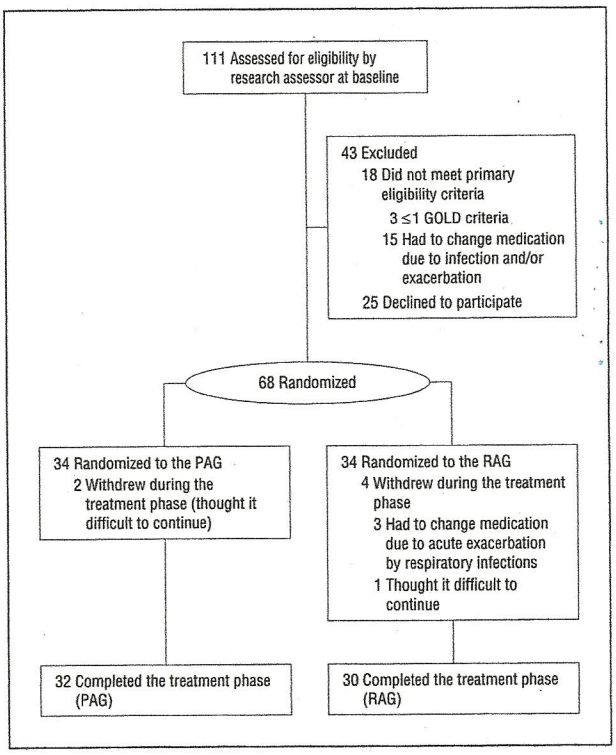


**Figure 2.** Study participant flow diagram. GOLD indicates Global Initiative for Chronic Obstructive Lung Disease; PAG, placebo acupuncture group; and RAG, real acupuncture group.

## ADVERSE REACTIONS

The following minor adverse reactions were reported by some patients during the study: fatigue (4 in the RAG and 5 in the PAG), subcutaneous hemorrhage (5 in the RAG), dizziness (1 in the RAG and 2 in the PAG), and needle site pain (5 in the RAG). All events were minor reactions and patients recovered in a short time. No serious events due to acupuncture treatment were reported.

# COMMENT

## ACUPUNCTURE AND COPD

This is the first placebo-controlled, randomized study, to our knowledge, that demonstrated the efficacy of acupuncture treatment for improvement of DOE and exercise tolerance in patients with COPD. Although previous studies[15,16] have evaluated efficacy of acupuncture on dyspnea of patients with COPD, participants in those studies had various diseases, such as bronchial asthma, interstitial pneumonia, cystic fibrosis, and COPD. It is therefore inconclusive whether acupuncture is capable of improving symptoms of COPD from these studies alone. The standardization of acupuncture points as used in the present study may be a strength because it may increase the reproducibility of the technique by other practitioners.

The mean reduction in the Borg scale score after the 6MWT, the main outcome of this study, and the increase in the 6MWD with the acupuncture procedure were significantly greater in the RAG than in the PAG.

**Table 2. Baseline Patient Characteristics of Full Analysis Set**

| Characteristic | PAG (n = 34) | RAG (n = 34) | Mean Difference |
|---|---|---|---|
| Sex | | | |
| Male | 32 | 31 | |
| Female | 2 | 3 | |
| Age, mean (SD), y | 72.5 (7.4) | 72.7 (6.8) | 0.1 |
| MRC score, mean (SD) | 2.9 (1.1) | 3.3 (1.0) | 0.4 |
| Brinkman index, mean (SD) | 1433.9 (759.8) | 1292.5 (526.4) | −141.4 |
| GOLD criteria | | | |
| I | 0 | 0 | |
| II | 13 | 6 | |
| III | 8 | 16 | |
| IV | 13 | 12 | |
| GOLD stage, mean (SD) | 3.0 (0.9) | 3.2 (0.7) | 0.2 |
| Home oxygen therapy | 11 | 9 | |
| $\beta_2$-Agonist | | | |
| Salbutamol sulfate | 5 | 6 | |
| Salmeterol xinafoate | 7 | 12 | |
| Tulobuterol hydrochloride | 13 | 8 | |
| Anticholinergic | | | |
| Oxitropium bromide | 2 | 2 | |
| Tiotropium bromide hydrate | 29 | 30 | |
| Inhaled corticosteroid | | | |
| Fluticasone propionate | 11 | 16 | |
| Beclomethasone dipropionate | 4 | 1 | |
| Budesonide | 4 | 4 | |
| Ciclesonide | 0 | 1 | |
| Salmeterol xinafoate and fluticasone propionate | 1 | 2 | |
| Oral corticosteroid | | | |
| Prednisolone | 3 | 3 | |
| Exercise capacity | | | |
| 6MWT post-Borg scale score, mean (SD) | 4.1 (2.7) | 5.5 (2.8) | 1.3 |
| 6MWD, mean (SD), m | 404.5 (109.5) | 358.7 (132.5) | −45.9 |
| $Spo_2$, mean (SD), % lowest rate | 88.4 (6.1) | 86.4 (6.7) | −2.1 |
| Pulmonary function, mean (SD) | | | |
| VC, L | 3.1 (0.7) | 2.8 (0.5) | −0.3 |
| IC, L | 1.9 (0.5) | 1.8 (0.4) | −0.1 |
| ERV, L | 1.3 (0.3) | 1.1 (0.4) | −0.2 |
| FVC, L | 3.0 (0.7) | 2.8 (0.6) | −0.2 |
| $FEV_1$, L | 1.2 (0.4) | 1.0 (0.3) | −0.2 |
| $FEV_1$, % predicted | 48.0 (16.5) | 44.5 (16.3) | −3.5 |

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ERV, expiratory reserve volume; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; MRC, Medical Research Council; PAG, placebo acupuncture group; RAG, real acupuncture group; $Spo_2$, oxygen saturation as measured by pulse oximetry; VC, vital capacity.

These improvements in the Borg scale score and the 6MWD during the 6MWT were in line with studies[17] that suggest clinically important differences in COPD. Previous review articles[18,19] indicated that the reduction in the Borg scale score and the increase in the 6MWD with standard care, such as rehabilitation or exercise, was 1.1 to 3.6 U and 54 to 80 m, respectively. Thus, our results are comparable to or better than these interventions. Also, the increase in lowest oxygen saturation during the 6MWT after real acupuncture was found. These results indicate the efficacy of acupuncture for improving exercise capacity.

## POSSIBLE MECHANISM UNDERLYING THE EFFECT OF ACUPUNCTURE ON DYSPNEA

Several factors are thought to relate to DOE in patients with COPD, including dynamic hyperinflation, hypoxemia, hypercapnia, and limitation of rib cage movement. Increased workload causes fatigue and dysfunction of accessory muscles, and at the end of exercise in patients with COPD, when dyspnea intensity reaches intolerable levels, the inspiratory muscles are maximally shortened, and thoracic displacement is greatly constrained.[20] These phenomena lead to accumulation of various algesic or sensitizing substances under ischemic conditions, which consequently cause muscle fatigue and pain. Kawakita et al[21] reported that acupuncture suppressed electromyogram activity of the muscle that was experimentally hyperactivated by repeated eccentric contraction. We therefore speculate that a similar phenomenon is evoked in the accessory respiratory muscles by needling on the acupuncture points on the rib cage. Decreased muscle tone consequently caused the recovery of the muscle strength in the rib cage, resulting in the increased mobility in the rib cage. Relaxation of accessory respiratory muscles may also contribute to rib cage motion. In fact, the present study showed increases in