The effects of acupoint-catgut embedment combined with medical treatment on the BODE index scores of chronic obstructive pulmonary disease (COPD) patients

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Abstract. Chronic Obstructive Pulmonary Disease (COPD) is now the fourth leading cause of death in the world. As COPD medications are associated with high mortality levels, continuous research into the improvement of treatment modalities is being conducted. This study aimed to identify the effects of acupoint-catgut embedment combined with medical treatment on the Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index scores of COPD patients. A single-blind randomized controlled trial was conducted on 48 patients; participants were allocated into either the acupoint-catgut embedment with medication group (case group) or the sham acupuncture with medication group (control group). Acupoint-catgut embedment was conducted at the BL13 Feishu, BL43 Gaohuangshu, BL20 Pishu, BL23 Shenshu, and ST40 Fenglong points two times at an interval of 15 days. The BODE index, a primary outcome indicator, was assessed on Day 1 and Day 30. The results showed statistically and clinically significant differences between the two groups—in fact, BODE index scores were reduced by 1.83 points in the case group (p = 0.000). Ultimately, BODE index scores were lower in the intervention group than in the control group, thus indicating a statistically significant and clinically important improvement of COPD-related symptoms. According to these results, acupoint-catgut embedment combined with medical treatment is concluded to be more effective than medical treatment alone in reducing BODE index scores.

1. Introduction
Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable lung disease that is characterized by the presence of a progressive and not entirely reversible airflow obstruction; COPD is also associated with pulmonary inflammatory responses to toxic or hazardous particles or gases and with extra lung effects that contribute to a degree of illness [1,2]. COPD is currently the fourth leading cause of death across the world and as such causes enormous economic and social losses [2]. According to basic health research conducted in 2013, the prevalence of COPD in Indonesia has reached 3.7% [3].

Research on COPD is continuously conducted around the world in an effort to establish early diagnosis techniques, develop individual management systems, and improve prevention techniques that are considered unsatisfactory [4]. The guidelines for the classification and management of COPD...
have continued to improve since the first GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification was issued in 2001. In the updated GOLD 2014, treatment recommendations were based not only on VEP1 (forced expiratory volume over one second) spirometry, but also on a consideration of the symptoms of dyspnea, activity limitations, exacerbations, and the disruption of health status. Multi-dimensional scoring systems such as the BODE Index (body mass index, degree of airflow obstruction, dyspnea, and exercise capacity) were developed to serve as improved predictors of the severity of COPD [5].

Acupoint-catgut embedment is a stimulating acupuncture method that involves catgut embedment at various acupuncture points. As compared to manual acupuncture techniques that use needle filiforms, this method has the advantage of using fewer acupuncture points; additionally, while the frequency of acupoint-catgut embedment therapy is rarer, the effects of stimulation are longer lasting [6]. This study aims to determine the effectiveness of acupoint-catgut embedment combined with medical treatment on the BODE index scores of COPD patients.

2. Materials and Methods

The research design chosen for this study was a system of double-blind clinical trials with controls. The study was conducted at the Lung Polyclinic of Jakarta's Persahabatan General Hospital. The inclusion criteria called for subjects between the ages of 40 and 75 years, male or female, who had been diagnosed with COPD by a pulmonary specialist and who met the criteria for COPD groups B, C, and D according to GOLD; these participants were stable COPD patients who agreed to follow the study schedule and signed informed consent documents. According to this study's rejection criteria, patients with acute exacerbated COPD were excluded from participation, as were those who required regular supplemental oxygen, mechanical ventilation, or surgery; additionally, patients who required medicamental treatment for COPD that fell outside the GOLD 2014 standards, patients with upper respiratory tract infections, pulmonary complications, heart disease, and uncontrolled diabetes mellitus (whose random blood sugar at the time of the study was >200 mg/dl), and patients who had undergone previous acupoint-catgut embedment therapy were also excluded. Also prohibited from participating in this study were those with contraindications to acupoint-catgut embedment, those with injuries to the acupuncture points to be pricked, medical emergency cases, patients with blood clotting disorders, patients who were taking anticoagulant drugs, pregnant individuals, those with malignancy, and those with a history of allergies to animal protein.

Using a computer program, research subjects were divided into two groups according to a stratified random block method based on their degree of disease. Next, concealment procedures were conducted and selection bias was avoided. The inclusion and exclusion criteria were strictly applied, and attempts were made to minimize the possibility of participant loss by calling the patients according to an established research schedule. The case group received acupoint-catgut embedment and medical treatment, while the control group received sham acupuncture and medical treatment. Acupoint-catgut embedment involves a 1 cm sterile catgut chromic 3.0 embedment action, which is accomplished by inserting a 21 G needle 1.5 G deep into the BL13 Feishu, BL43 Gaohuangshu, BL20 Pishu, BL23 Shenshu, and ST40 Fenglong points. Acupoint-catgut embedment was conducted twice at an interval of 15 days. Sham acupuncture, however, is a shallow suppression action that also uses a 21 G needle; this treatment is performed on the same body segments but at locations that are not acupuncture points. This is accomplished without injuring the patient and without embedding the catgut. Sham acupuncture was also performed twice at an interval of 15 days.

For this study, data was collected in the form of the BODE index scores of the treatment group and control group members. Assessments were performed at the beginning of the study and on Day 30 (the end of study) by independent evaluators. A statistical analysis of the research output data was conducted using the SPSS. This research was conducted after gaining ethical approval from the Ethics Committee. Patients who participated in this study agreed to take part voluntarily and without coercion; to this end, they signed an informed consent document that guaranteed confidentiality.
3. Results and Discussion

3.1 Results
This study assessed 48 patients with COPD who met the inclusion criteria and did not meet the exclusion criteria. The study participants were randomly divided into two groups: the acupoint-catgut embedment and medical treatment group (case group) and the sham acupuncture and medical treatment group (control group). Each group consisted of 24 research subjects who participated in this study for 30 days in accordance with the study protocols. No failed subject was reported until the study was concluded. The mean age of the study subjects was 64 (64.71) years, and most participants were men (89.6%). Additionally, 43.8% of the study subjects were middle-educated; only 4.2% had continued on to higher education. Although 66.7% of the study subjects were currently inactive (retired), all subjects reported to have health insurance. No significant differences were found between the case group and the control group in terms of the profile characteristics of the study subjects.

Table 1. Basic data of research subjects' demographics

| Characteristic             | Case Group (n=24) | Control Group (n=24) | p-value |
|---------------------------|------------------|----------------------|---------|
| Age (years)               |                  |                      |         |
| Mean (SD)                 | 64.71 (7.09)     | 63.88 (6.81)         | 0.340   |
| Gender                    |                  |                      |         |
| Male, n (%)               | 22 (91.7)        | 21 (87.5)            | 0.500   |
| Female, n (%)             | 2 (8.3)          | 3 (12.5)             |         |
| Education                 |                  |                      |         |
| Elementary school, n (%)  | 5 (20.8)         | 4 (16.7)             | 0.496   |
| Junior high school, n (%) | 6 (25)           | 10 (41.7)            |         |
| Senior high school, n (%) | 12 (50)          | 9 (37.5)             |         |
| Diploma, n (%)            | 0 (0)            | 1 (4.2)              |         |
| Bachelor's degree, n (%)  | 1 (4.2)          | 0 (0.0)              |         |
| Occupation                |                  |                      |         |
| Trader, n (%)             | 4 (16.7)         | 4 (16.7)             |         |
| Housewife, n (%)          | 1 (4.2)          | 2 (8.3)              | 0.500   |
| Employee, n (%)           | 3 (12.5)         | 2 (8.3)              |         |
| Retired, n (%)            | 16 (66.7)        | 16 (66.7)            |         |
| Health insurance ownership, n (%) | 24(100) | 24(100) |         |

Table 2. Basic data of research subjects' disease profiles

| Characteristic                        | Case Group (n=24) | Control Group (n=24) | p-value |
|---------------------------------------|------------------|----------------------|---------|
| Brinkman index                        |                  |                      |         |
| Mean (SD)                             | 689.50 (308.61)  | 690.42 (310.78)      | 0.497   |
| Degree of disease                     |                  |                      |         |
| COPD B, n (%)                         | 8(33.3)          | 9(37.5)              | 0.418   |
| COPD C, n (%)                         | 6(25)            | 7(29.2)              |         |
| COPD D, n (%)                         | 10(41.7)         | 8(33.3)              |         |
| Long-term COPD drug use               |                  |                      |         |
| LAMA+SABA and/or SAMA, n (%)          | 4(1.12)          | 2.5(1.13)            | 0.272   |
| LAMA+SABA and/or SAMA+Teofillin, n (%)| 5(20.8)          | 5(20.8)              |         |
| LAACS/ICS+LAMA+SABA and/or SAMA, n (%)| 7(29.2)          | 8(33.3)              |         |
| LABACS/ICS+LAMA+SABA and/or SAMA, n (%)| 8(33.3)          | 7(29.2)              |         |
| SAMA+Teofillin+Karbosistein, n (%)    | 4(16.7)          | 4(16.7)              | 0.500   |

Note: SAMA = Short-acting anti-muscarinic/anti-cholinergic; LAMA = Long-acting anti-muscarinic/anti-cholinergic; SABA = Short-acting β2 agonist; LABACS = Inhaled corticosteroid + long-acting β2 agonist; ICS = Inhaled corticosteroid.
Table 3. Basic data of research subjects’ BODE index variables

| Variable                          | Case Group (n=24) | Control Group (n=24) | p-value |
|----------------------------------|------------------|----------------------|---------|
| Initial BMI Mean (SD)            | 22.82 (3.60)     | 22.38(3.20)          | 0.349   |
| Initial %VEP1 Mean (SD)          | 49.98(15.87)     | 49.99 (15.87)        | 0.258   |
| Initial MMRC Median (min–max)    | 2(0–4)           | 2(0–4)               | 0.374   |
| Initial UJ6M Mean (SD)           | 313.79 (58.78)   | 308.88 (52.98)       | 0.381   |
| Initial BODE index Mean (SD)     | 4.08 (2.08)      | 3.75 (1.85)          | 0.204   |

Note: BMI=Body Mass Index; VEP1=Volume Expiration Force (over one second); MMRC=Modified Medical Research Council for Dyspnea; UJ6M=Six Minute Walking Test

The average subject was classified as a heavy smoker (Brinkman index >600). There were no significant differences between the case and control groups in terms of the degree of COPD disease, the duration of COPD, or the type of COPD drugs used. The four BODE index variables of BMI%, VEP1, MMRC, and UJ6M showed no significant differences between the case and control groups. The mean BODE index score of the case group was 4.08 (2.08), and the mean BODE index score of the control group was 3.75 (1.85); there was no significant difference between these scores. The BODE index was measured twice: once on the first day (at the beginning of the study), prior to the administration of the interventions, and again on Day 30 (after both groups had received their interventions).

Table 4. BODE index changes in the case and control groups after intervention

| Variable                | Average Change(SD) | Average Difference (SD) | p-value |
|-------------------------|--------------------|-------------------------|---------|
| Δ BMI (Kg/m²)           |                    |                        |         |
| Case                    | 0.18 (0.27)        | 0.00 (0.00–0.93)b       | 0.0005**|
| Control                 | -0.02(0.05)        | 0.00 (-0.19–0.00)       |         |
| Δ %VEP1 (%)             |                    |                        |         |
| Case                    | 1.45(3.51)         | 2.98 (1.31–4.64)        | 0.005*  |
| Control                 | -1.53(2.03)        |                        |         |
| Δ MMRC                  |                    |                        |         |
| Case                    | -1.67(0.56)        | -2.00 (-2.00–0.00)      | 0.000** |
| Control                 | -0.42(0.50)        | 0.00 (-1.00–0.00)       |         |
| Δ UJ6M (m)              |                    |                        |         |
| Case                    | 66.40(21.51)       | 70.00 (35.00–135.00)    | 0.000** |
| Control                 | -5.08(23.40)       | 0.00 (-40–35)           |         |
| Δ BODE index            |                    |                        |         |
| Case                    | -1.96(1.04)        | -2.00 (-4–0)            |         |
| Control                 | -0.13(0.68)        | 0.00 (-1–1)             |         |

*unpaired T test; **Mann-Whitney test

After both groups had received their interventions, results indicated that the case group had experienced changes in their BMI scores. The case group had an average increase of 0.18 Kg/m², while the control group decreased by an average of 0.02 Kg/m². For % VEP1, the average increase of the case group was 2.98% higher than in the control group. In the case group, the MMRC score decreased by 2 units, though it remained the same in the control group. Additionally, in the case
group, the UJ6M variables had a median difference of 70 m, while the control group showed a median decrease of 5.08 m. Side effects identified over the course of the study included pain at the pricking site in 2 of 24 (8.33%) subjects and lower leg pain in 4 of 24 (16.67%) subjects. Other side effects such as hematoma, acushock, infection, or allergic reaction were not found during this study. Non-inflammatory subcutaneous nodules were identified in 1 of 24 (4.17%) subjects.

3.2 Discussion

This is the first Indonesian study to apply acupoint-catgut embedment to COPD patients and the first to analyze the BODE index as an outcome measure. This study differs from those conducted by Li et al. [7] and Jaroen suk and Sittimart [8]; while those studies did examine acupoint-catgut embedment in COPD patients, they diverge from the current research in terms of the acupuncture points used, the therapy intervals applied, and the outcome measures analyzed. Regarding the results of a clinical research study, it is necessary to consider the clinical significance of the analyzed outcomes as well as their statistical significance [9,10]. Minimum clinical improvements that are considered clinically significant are referred to as MCID (minimum clinically important difference scores); this concept was first introduced by Jaeschke et al. The BODE index MCID data regarding COPD was obtained from multiple sources; the UJ6M variables = 54–80 m, the MMRC = 1 unit, and the BODE index = 1 unit. However, the MCID for the % VEP1 and BMI variables could not be determined [5]. The results showed a mean decrease of BODE index scores in the case group; after intervention, the index score was 1.96 (1.04) units. Considering each of the BODE index variables: BMI demonstrated a mean increase of 0.18 (0.27) kg/m$^2$, % VEP1 had an average increase of 1.45 (3.51)%, UJ6M showed a mean increase of 66.40 (21.51) meters, and the MMRC scores decreased by an average of 1.67 units. Based on the MCID values of the BODE index for COPD, the average changes in the BODE index as well as in the UJ6M and MMRC variables were statistically significant and demonstrated clinical significance.

In this study, changes in the BMI and %VEP1 variables were rated the lowest as compared to the other BODE index compiler variables. The same occurred during a case series conducted by Suzuki et al. [11] and during clinical trials performed by Suzuki et al. [12]. A review of clinical trials conducted in an effort to determine the effects of medications on changes to lung function, a four-year UPLIFT (Understanding Potential Long-Term Impact on Function with Tiotropium) study involving 5,993 respondents across 37 countries showed that the use of tiotropium may improve lung function, enhance quality of life, and reduce exacerbation frequency, though it did not significantly inhibit the rate of VEP1 decrease. It was reported that a large increase in VEP1 occurred after four years of study (figures increased from 87 to 103 ml [p < 0.001]) [13,14]. A TORCH (Toward a Revolution on COPD Health) study—a multi-center, clinical trial that lasted for three years and involved 6,112 respondents—recorded a change in the VEP1 value over the course of a three-year (93%) combination of LABA and ICS bronchodilators (p < 0.001) [13]. The duration of therapy required to increase the VEP1 value was estimated according to the parenchymal lung damage that occurred and to the fibrosis that led to the airway remodeling of the respiratory tract and COPD [15]. The superiority of catgut embedment techniques as compared to manual acupuncture lies in its use of fewer acupuncture points, longer-lasting stimulation, and less frequent therapy requirements [6]. To this end, Suzuki et al. [11] performed a series of experiments on 26 patients with COPD. The study subjects continued to receive standard COPD treatment as well as manual acupuncture at the LU1 Zhongfu, LU9 Taiyuan, LI18 Futu, CV4 Guanyuan, CV12 Zhongwan, ST36 Zusanli, Taixi KI3, GB12 Wangu, BL13 Feishu, BL20 Pishu, and BL23 Shenshu points. Therapy was performed once a week for 10 weeks. Following the application of these interventions, the study reported an average decrease in BODE index scores of 1.54 units (p < 0.05). This study, in contrast, was conducted over a period of 30 days and involved two acupuncture acts of unilateral catgut embedment; after intervention, results revealed a decrease in BODE index scores of 1.96 units (p = 0.000).

Research conducted by Tai et al. [16], highlighted the role of acupuncture in improving mucocilliary clearance and found that it helps to normalize the inflammation that occurs in a patient's
airways. It is now known that the mucus production regulation associated with mucociliary clearance is affected by PPAR-\(\gamma\), which is also described as a form of anti-inflammatory, immunomodulating, and suppressing pulmonary fibrosis. The Fenglong ST40 point was chosen because it has been shown in several studies to play a role in lipid metabolism involving PPAR-\(\gamma\) [17,18]. Various inflammatory pathways, to include several inflammatory cells and inflammatory mediators (lipid mediators, cytokines, chemokines, growth factors, and proteases), are involved in the peripheral inflammation of lung tissues and the respiratory tract or in the systemic inflammation that occurs in people with COPD. This leads to the advent of a medical approach that targets only an individual cytokine or a specific chemokine receptor, thus leading to an unsatisfactory clinical outcome [19]. Furthermore, the response to steroid use is different in COPD patients than in asthma patients. The use of inhaled steroids as a monotherapy or in combination with other treatments should be cautiously administered to COPD patients due to the various side effects that can be induced [20]. Studies have shown that the use of inhaled steroids to reduce the frequency of exacerbations indicates an effectiveness that is not significantly different from that of inhaled beta2-agonists [21]. Inhaled steroids were also reported to play no role in significantly reducing mortality [22].

The oxidative environments of the tissues and organ systems of people with COPD and the variety of inflammatory pathways active in COPD patients are also thought to be factors that lead to glucocorticoid resistance in COPD patients [22]. Phosphodiesterase-4 (roflumilast) inhibitors are broad-spectrum anti-inflammatory substances developed for COPD patients, though some disturbing side effects such as nausea limit the doses that can be administered orally [23]. Inhaled phosphodiesterase-4 inhibitors are now being developed in an effort to reduce these side effects during long-term use [19]. The results of Laforest et al. [24] study of patient adherence to COPD drug consumption showed that 45% of patients forgot that regular COPD drugs must be taken daily, while 30% stopped taking their medications because they felt that the drugs did not lead to clinical benefits. The risk of discontinued drug use is found to increase when a patient complains that they are asked to consume ‘too many’ drugs on a daily basis. Naturally, this adds to the list of problems to be solved in the management of COPD and the reduction of mortality and progression rates. In response to this condition, and based on data from the results of this study, the mean BODE index score decreased by 1.83 units; this decrease was greater in the case group, wherein patients received a combination of medical and acupuncture therapies (\(p = 0.000\)). Additionally, minimal adverse effects were found in the recording data during this study. Thus, the utilization of acupuncture as a treatment therapy for COPT management should be considered.

In studies conducted by Li et al. [8], Suzuki et al. [12], and Jaroensuk and Sittimart [9], as well as in this study, acupoint-catgut embedment was shown to reduce symptoms of breathlessness and to increase the capacity for physical exercise in people with COPD. In various studies, acupuncture has been shown to increase endogenous NO production. Acupuncture prickling stimulates the vlPAG (ventro-lateral periaqueductal gray), an important element of the brain that regulates autonomic nerve outflow; this element in turn sends impulse signals to the rVLM (rostral ventro-lateral medulla), an integral region of the sympathetic outcome, and stimulates the formation of Cnos [24]. Based on an analysis of the relatively complex role of NO in COPD patients, and of the role of acupuncture in COPD treatment, it has been found that acupuncture can act as an anti-inflammatory, antioxidant, and antifibrosis measure; thus, the iNOS formation process can be suppressed, and nNOS and eNOS production can be improved. By normalizing the balance between Th1 and Th2 [18], cell acupuncture can suppress the production of various inflammatory cytokines such as TNF-\(\alpha\), interferon-\(\gamma\), and IL-1\(\beta\) and can increase the production of 16 anti-inflammatory mediators such as IL-6 and IL-10; furthermore, it can stimulate endogenous antioxidants such as SOD and GPx [24]. This condition is advantageous to NO metabolism, as it leads to the formation of eNOS and nNOS, which play positive roles in the formation of NO; NO, in turn, impacts bronchodilation and decreases mucus secretion, airway remodeling, and the vasodilation of pulmonary and bronchial vessels [25]. This study is limited by its brief research period, which prevented clinical monitoring of the duration of catgut embedment's effects and precluded an analysis of whether those effects can survive in are search subject. Therefore,
the optimal number and frequency of acupoint-catgut embedment treatments for COPD patients has yet to be determined. A longer study time is needed to observe the effects of catgut embedment on the four BODE index variables, especially VEP1 and BMI.

4. Conclusion
Acupoint-catgut embedment combined with medical treatment was shown to more effectively lower the BODE index scores of COPD patients as compared to medical treatment alone. There was a significant difference in the mean BODE index scores of the two groups; for instance, index scores were 1.83 units higher in the case group than in the control group (p = 0.000).

References
[1] Antariksa B, Yunus F, et al. 2011 Diagnosis dan penatalaksanaan penyakit paru obstruktif kronik (PPOK). (Jakarta: Perhimpunan Dokter Paru Indonesia (PDPI)) [In Indonesian]
[2] Clark J. An introduction to saturated vapour pressure [Internet]. 2014 [cited 2015 14 November]. Available from: http://www.chemguide.co.uk/physical/phaseeqia/vapourpress.html.
[3] Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease updated 2014.
[4] Badan penelitian dan pengembangan kesehatan 2013 Riset Kesehatan Dasar 2013. (Jakarta: Kementrian Kesehatan RI) [In Indonesian]
[5] Lan L T T and Dinh-Xuan A T 2013 Pathophysiology updates for chronic obstructive pulmonary disease. Curr. Respir. Care Rep. 2 139-44.
[6] Fu P K and Hsieh C L 2013 Acupuncture for attenuating dyspnea in patients with chronic obstructive pulmonary disease. OA Evid.-Based Med. 1 1-8.
[7] Kang S-G, Zhang M-L, Duan X-D, Zhang X-P, Zhang X-D, Zhang X et al. 2012 Exploration to the disease spectrum of acupoint catgut-embedding therapy. World J. Altern. Med. 22 53-8.
[8] Li J, Zhou Y, Tang J, Yang P, Huang H, Shen Y, et al. 2011 Efficacy observation of chronic obstructive pulmonary disease due to lung and kidney deficiency treated with acupointcatgut-embedding therapy combined western medication. Zhongguo Zhen Jiu 31 26-30.
[9] Jaroensuk C and Sittimart P 2013 Catgut embedding technique at selected acupoints in patients with chronic obstructive pulmonary disease. J. Thai Tradit. Alternat. Med. 11 152-61.
[10] Cook C E 2008 Clinimetrics corner: The minimal clinically important change score (MCID): a necessary pretense. J. Man. Manip. Ther. 16 E82-3.
[11] Glaab T, Vogelmeier C and Buh R 2010 Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. Respir. Res. 11 1-11
[12] Suzuki M, Namura K, Ohno Y, Egawa M, Sugimoto T, Ishizaki N et al. 2012. Combined standard medication and acupuncture for COPD: a case series. Acupunct. Med. 30 96-102.
[13] Suzuki M, Muro S, Ando Y, Omori T, Shiota T, Endo K, et al. 2012 A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD) - the COPD-acupuncture trial (CAT). Arch. Intern. Med. 172 878-86.
[14] Miravitlles M and Anzueto A. 2009 Insights into interventions in managing COPD patients: lessons from the TORCH and UPLIFT® studies. Int. J. Int. COPD. 4 185-201.
[15] Tashkin D P, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M et al. 2008 A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N. Engl. J. Med. 359 1543-54.
[16] Tai S, Wang J, Sun F, Xutian S, Wang T and King M. Effect of needle puncture and electroacupuncture on mucociliary clearance in anesthetized quails. BMC Complement. Alternat. Med. 2006 6 1-6.
[17] Ngai S P, Jones A Y, Hui-Chan C W, Ko F W, Hui D S, et al. 2013 An adjunct intervention for management of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). J. Alternat. Complement. Med. 19 178-81.
[18] Ngai SP, Jones AY and Hui-Chan CY 2011 Acu-TENS and postexercise expiratory flow volume in healthy subjects. *Evid.-based Complement. Alternat. Med.* **726510** 1-7.

[19] Li M and Zhang Y 2007 Modulation of gene expression in cholesterol-lowering effect of electroacupuncture at Fenglong acupoint (ST40): A cDNA microarray study. *Int. J. Mol. Med.* **19** 617-29.

[20] Liang F, Chen R, Nakagawa A, Nishizawa M, Tsuda S, Wang H *et al.* 2011 Low-frequency electroacupuncture improves insulin sensitivity in obese diabetic mice through activation of SIRT1/PGC-1α in skeletal muscle. *Evid.-Based Complement. Alternat. Med.* **735297** 1-9.

[21] Barnes P J 2014 Cellular and molecular mechanisms of chronic obstructive pulmonary disease. *Clin. Chest Med.* **35** 71-86.

[22] Price D, Yawn B, Brusselle G and Rossi A 2012 Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim. Care Respir. J.* **21** 92-100.

[23] Lin J G and Chen W L 2008 Acupuncture analgesia: a review of its mechanisms of actions. *Am. J. Chin. Med.* **36** 635-45.

[24] Laforest L, Denis F, Van Ganse E, Ritleng C, Saussier C, Passante N *et al.* 2010 Correlates of adherence to respiratory drugs in COPD patients. *Prim. Care Respir. J.* **19** 148-54.

[25] Fabio L, Sterk P J, Gaston B, Folkerts G *et al.* 2004 Nitric oxide in health and disease of the respiratory system. *Physiol. Rev.* **84** 731-65.