Effects of electroacupuncture at Zusanli (ST36) on inflammatory cytokines in a rat model of smoke-induced chronic obstructive pulmonary disease

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OBJECTIVE: Improvement in lung function was reported after acupuncture treatment of chronic obstructive pulmonary disease (COPD), but little is known about the underlying mechanisms. Because an immune response imbalance could be seen in COPD, we hypothesize that electroacupuncture (EA) may play a role in regulating inflammatory cytokines and contribute to lung protection in a rat model of smoke-induced COPD.

METHODS: A COPD model using male Sprague-Dawley rats exposed to cigarette smoke was established. The rats were randomly divided into four groups (control, sham, COPD, and COPD plus EA), and COPD model was evaluated by measuring pulmonary pathological changes and lung function. EA was applied to the acupuncture point Zusanli (ST36) for 30 min/d for 14 d in sham and COPD rats. Bronchoalveolar lavage fluid (BALF) was used to measure levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and malonaldehyde (MDA).

RESULTS: Compared with the control rats, COPD rats had significant changes in lung resistance (R_l) and lung compliance (C_l) (both $P<0.01$), bronchi and bronchiole airway obstruction ($P<0.01$), and levels of MDA, TNF-α, and IL-1β ($P<0.01$). There were no significant differences between the control and the sham groups. Compared with the COPD rats, the COPD plus EA rats had decreased $R_l$ and increased $C_l$ (both $P<0.05$), and reduced bronchi and bronchiole airway obstruction ($P<0.05$, $P<0.01$, respectively), while levels of TNF-α, IL-1β, and MDA in BALF were lowered ($P<0.05$ and $P<0.01$, respectively). However, TNF-α and IL-1β levels of the EA group rats remained higher than those of the control group ($P<0.05$).

CONCLUSION: EA at ST36 can reduce lung injury in a COPD rat model, and beneficial effects may be related to down-regulation of inflammatory cytokines. The anti-inflammatory and antioxidant effects may prolong the clinical benefit of EA.

KEYWORDS: chronic obstructive pulmonary disease; electroacupuncture; anti-inflammatory; antioxidant; Zusanli (ST36); rats

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive limitation in airflow¹,². It is predicted that by 2020, COPD will rank third as the cause of death worldwide (an increase from sixth place in 1990), while the social burden of COPD will rank fifth
(an increase from twelfth place in 1990). Smokers make up 90% of patients with COPD in Western countries, thus smoking has become one of the most important pathogenic factors in this disease. COPD is thought to be caused by inflammation induced by inhaled smoke and particulates, leading to structural changes in airways and alveoli, resulting in airflow limitation. The pathology of COPD involves small airways and lung parenchyma, with chronic inflammation leading to luminal obstruction, thickening of the airway wall by increased deposition of matrix molecules and proliferation of mesenchymal cells, and narrowing of the airway by fibrosis, causing a decrease in lung function.

The aetiology of COPD is not completely clear. Smoke, environmental pollution, airway hyper-reactivity, age, and genetic predisposition are known risk factors. Development of COPD may be caused by various harmful gases and particulates that are inhaled into the airway, leading to an inflammatory response in the lungs. A number of inflammatory cells, including macrophages, neutrophils, T cells, B cells, eosinophils, and epithelial cells are involved in the disease process. These inflammatory cells may induce immune responses, resulting in changes in a large number of inflammatory mediators, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, the levels of which were found to be significantly increased in induced sputum samples from patients with COPD. COPD is a complex chronic inflammatory disease, and the long-term imbalances in immune regulation may result in lung tissue remodeling or damage, leading to decline in lung function. Oxidant-antioxidant imbalance also causes inflammation and destruction of lung tissue. It is anticipated that methods to reduce pulmonary inflammation will provide effective, disease-modifying therapies.

Reactive oxygen species (ROS) plays an important role in the COPD process. Tobacco smoke not only is as one of exogenous ROS, but also induces the airway epithelial cells and inflammatory cells to produce large amounts of endogenous ROS in response to cigarette smoke. So tobacco smoke will produce a large number of ROS.

Malonaldehyde (MDA) is a natural product of lipid oxidation. The gradual decomposition of some fatty acid oxidation results in a series of complex compounds, including MDA. The level of MDA can be a marker of the level of lipid oxidation, thus determination of MDA is widely used as an indicator of lipid oxidation.

There are some different therapies for COPD. The anti-inflammatory therapy is one choice for COPD. Targeting oxidative stress with antioxidants is likely to be beneficial in the treatment of COPD. Acupuncture has been used as a clinical treatment for various diseases in traditional Chinese medicine for a long time, and is being increasingly accepted by practitioners and patients in the Westen countries as well. Although acupuncture can improve exercise capacity, respiratory function and respiratory muscle strength in patients with COPD, its mechanisms of action are still unclear.

The aim of this study was to investigate the pathogenesis of COPD and the effect of electroacupuncture (EA) in reducing lung injury and its possible anti-inflammatory and antioxidant mechanisms in COPD. We therefore devised a cigarette smoke-induced experimental model of COPD. This model is well established, with concomitant pathological change in the lung and airways. This experiment determined the levels of TNF-α, IL-1β and MDA in the bronchoalveolar lavage fluid (BALF).

2 Materials and methods

2.1 Animals and COPD model

All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals, and efforts were made to minimize the number of animals and any discomfort to them.

Male Sprague-Dawley (SD) rats weighing 180–200 g were used in the experiments (Shanghai Laboratory Animal Center, Shanghai, China). Rats were housed in an environment with relative humidity of 50%±5% and 12-h light/dark cycles at (22±1) °C, and given ad libitum access to food and water.

We divided 28 rats randomly into four groups (n = 7 in each group), namely, control, sham, COPD and COPD plus EA.

The experimental model of COPD was established as we described previously. Rats in groups 3 and 4 were exposed to cigarette smoke for 1 h twice daily for 12 weeks. After each period of exposure, rats were placed back into their cages. Animals in groups 1 and 2 underwent the same procedure but without cigarette smoke exposure.

2.2 EA treatment

EA stimulation was applied to the sham and the COPD plus EA groups (after cigarette smoke exposure in the morning). The rats were given mild anesthesia with 6% chloral hydrate (4 mL/kg, less than the normal dose of 7 mL/kg), which left them able to crawl when given appropriate stimulation, and they recovered completely from the anesthetic within about 30 min.

A pair of stainless-steel needles (4–5 cm, 0.3 mm diameter; Suzhou Medical Appliance Factory, China) was inserted bilaterally into the acupuncture points Zusanli (ST36) located 5 mm below and lateral to the anterior tubercle of the tibia, at a depth of 3 mm, for 30 min daily. After insertion, the needles were held in place by plastic adhesive tape. Both needles were connected to the output terminals of an EA apparatus (Model G-6805-1; Shanghai Medical Electronic Apparatus Company, Shanghai, China). Alternating strings of dense-sparse frequencies (60 Hz for...
1.05 s and 2 Hz for 2.85 s alternately) were selected. The stimulating intensity was adjusted until it induced slight muscle contraction of the hind limb (≤1.5 mA)\(^{[18]}\).

2.3 Measurement of lung function

Changes in lung function are one of the key features of COPD, so we measured lung resistance (\(R_L\)) and lung compliance (\(C_L\)) to reflect the degree of airway obstruction and the extent of bronchial fibrosis. Rats were anesthetized by intraperitoneal injection with 7 mL/kg composite anesthetic agent (140 g urethane, 7 g chloralose, and 7 g borax in 1 L of normal saline). Tracheal intubation was performed to allow measurement of airflow and tidal volume, and the tube was connected to a flow transducer of a pneumotachograph (Godart, Bilthoven, the Netherlands). A saline-filled soft oesophageal cannula was connected to a pressure transducer of a Physiological Signal-Processing System (Model SMUP, Department of Physiology and Pathophysiology, Shanghai Medical College of Fudan University, Shanghai, China). The output of the pneumotachograph was also imported to this SMUP processing system for simultaneous recording. The signals for oesophageal pressure and airway flow were recorded consecutively for 5 min. The \(R_L\) and \(C_L\) values were calculated using a computerized respiratory analyzer as reported previously\(^{[19,20]}\) with modifications.

2.4 Bronchoalveolar lavage fluid

The lungs were removed en bloc and tubing was inserted into the trachea and secured. The right lung was clamped at the bronchus to prevent the lavage fluid entering the right lung, so that it could be used for other measurements. The left lung was lavaged three times with 2 mL of normal saline as described previously\(^{[21]}\).

2.5 Histopathological examination

At the end of the 12th week, the pathological changes and function were evaluated. The right lower lobe was excised and immersed with 10% formalin for 24 h. Fixed and function were evaluated. The right lower lobe was clamped at the bronchus to prevent the lavage fluid entering the right lung, so that it could be used for other measurements. The left lung was lavaged three times with 2 mL of normal saline as described previously\(^{[21]}\).

The histological changes in the lungs were scored by a slight modification of a previously described method\(^{[22]}\). For each animal, 24 areas of lung parenchyma were observed under a microscope at \(\times 10\) magnification. Airway obstruction was evaluated. For each animal, 15 bronchi and 30 bronchioles were assessed, and the percentage of cross-sectional area (0-100%) obstructed was estimated. The result was recorded as the mean percentage of cross-sectional area of the airway that was obstructed.

2.6 Measurement of MDA in BALF

Because there is an imbalance between the oxidant and antioxidant response in patients with COPD, we hypothesized that EA might regulate this response. The level of MDA in BALF was determined by thiobarbituric acid-reactive substance assay in accordance with the manufacturer’s instructions (Nanjing Jiancheng Biochemistry Co., Nanjing, China). The MDA content in the supernatant was measured using a commercial kit\(^{[23,24]}\).

2.7 Measurement of IL-1β and TNF-α in BALF

Because there is an inflammatory and anti-inflammatory imbalance in patients with COPD, we hypothesized that EA might regulate this response. Levels of IL-1β and TNF-α were measured in BALF with a commercial enzyme-linked immunosorbent assay (ELISA) kit (Bender, Austria), following the manufacturer’s instructions\(^{[25]}\).

2.8 Statistical analyses

Data were expressed as mean ± standard error of mean. One-way analysis of variance was used to compare the means among the four groups, and least-significant difference test was used to compare the means between two groups. \(P<0.05\) was considered significant. SPSS software (SPSS for Windows, statistics version 17.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

3 Results

3.1 Lung histopathology of the COPD model

The COPD model was evaluated by lung histopathology. The photomicrographs of the HE-stained sections showed that the bronchi and bronchioles were obstructed by larger infiltrates of neutrophils and there was greater shedding of bronchial epithelial cells, mucous, and fibrin in the COPD group (Figures 1E and 1F) than in the control group (Figures 1A and 1B; \(n=7\), \(P<0.01\); Table 1). In the COPD plus EA group, the average level of obstruction of both bronchi and bronchioles decreased compared with the COPD group (\(P<0.05\) and \(P<0.01\), respectively; Table 1).

3.2 Lung function in the COPD model

The COPD model was also evaluated using the lung function test, which showed that \(R_L\) increased and \(C_L\) decreased in the COPD group compared with the control group (\(n=7\) for each, both \(P<0.01\); Table 2). The lung function of the COPD plus EA group was improved compared with the COPD group, with evidence of decreased \(R_L\) and increased \(C_L\) (\(n=7\) for each, both \(P<0.05\); Table 2).

3.3 TNF-α and IL-1β levels in BALF of the COPD model

The ELISA results showed that the levels of TNF-α and IL-1β in BALF were markedly increased in the COPD group compared with the control group (\(n=7\) for each, both \(P<0.01\); Table 3), whereas they were decreased in the COPD plus EA group compared with the COPD group (\(n=7\) for each, both \(P<0.05\); Table 3). However, the levels of both TNF-α and IL-1β were still higher in the COPD plus EA group than in the control group (\(n=7\), \(P<0.05\); Table 3).

3.4 MDA level in BALF of the COPD model

Compared with the control group, the MDA level in
BALF was significantly increased in the COPD group ($n=7$, $P<0.01$; Figure 2). Measurement of MDA in BALF revealed negligible oxidative injury in the COPD plus EA group, thus EA treatment significantly decreased the MDA level in the COPD plus EA group compared with the COPD group ($n=7$, $P<0.01$; Figure 2).

**Table 1** Effects of EA on lung function

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>$R_L$ (mmHg/(mL·s))</th>
<th>$C_L$ (mL/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>0.35±0.04</td>
<td>0.22±0.03</td>
</tr>
<tr>
<td>Sham</td>
<td>7</td>
<td>0.37±0.01</td>
<td>0.18±0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>7</td>
<td>0.68±0.07**</td>
<td>0.12±0.01**</td>
</tr>
<tr>
<td>COPD plus EA</td>
<td>7</td>
<td>0.46±0.04</td>
<td>0.18±0.01</td>
</tr>
</tbody>
</table>

$** P<0.01$, vs control group; $^\triangle P<0.05$, $^\triangle\triangle P<0.01$, vs COPD group. COPD: chronic obstructive pulmonary disease; EA: electroacupuncture.

**Table 2** Effects of EA on lung histopathological sections

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Bronchi obstruction</th>
<th>Bronchiole obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>23.57±2.10</td>
<td>18.14±0.77</td>
</tr>
<tr>
<td>Sham</td>
<td>7</td>
<td>27.50±2.81</td>
<td>19.50±1.20</td>
</tr>
<tr>
<td>COPD</td>
<td>7</td>
<td>38.00±2.62**</td>
<td>28.86±1.16**</td>
</tr>
<tr>
<td>COPD plus EA</td>
<td>7</td>
<td>27.71±2.58</td>
<td>21.00±1.50</td>
</tr>
</tbody>
</table>

$^** P<0.01$, vs control group; $^\triangle P<0.05$, $^\triangle\triangle P<0.01$, vs COPD group. COPD: chronic obstructive pulmonary disease; EA: electroacupuncture.

**Table 3** Effects of EA on TNF-α and IL-1β levels

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>TNF-α (ng/L)</th>
<th>IL-1β (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>25.97±3.15</td>
<td>67.87±9.41</td>
</tr>
<tr>
<td>Sham</td>
<td>7</td>
<td>30.40±1.47</td>
<td>80.02±8.98</td>
</tr>
<tr>
<td>COPD</td>
<td>7</td>
<td>45.92±2.80**</td>
<td>187.60±21.90**</td>
</tr>
<tr>
<td>COPD plus EA</td>
<td>7</td>
<td>36.47±1.60**</td>
<td>112.90±12.56**</td>
</tr>
</tbody>
</table>

$^P<0.05$, $^** P<0.01$, vs control group; $^\triangle P<0.05$, vs COPD group. COPD: chronic obstructive pulmonary disease; EA: electroacupuncture; IL: interleukin; TNF: tumor necrosis factor.

**Figure 1** Lung histopathological sections of rats in different groups

A and B: control; C and D: control plus EA; E and F: COPD; G and H: COPD plus EA. Hematoxylin and eosin (Light microscopy; original magnification: A, C, E and G, $\times$100 and B, D, F and H, $\times$400). COPD: chronic obstructive pulmonary disease; EA: electroacupuncture.

**Figure 2** Effects of EA on level of MDA

Data are expressed as mean±standard error of mean, $n=7$; $^** P<0.01$, vs control group; $^\triangle P<0.05$, vs COPD group. COPD: chronic obstructive pulmonary disease; EA: electroacupuncture; MDA: malondialdehyde.

4 Discussion

COPD is one of the major causes of chronic morbidity and mortality worldwide. The etiology of COPD is not completely clear, but it may be caused by various harmful gases and particulates in the airway. Cigarette smoke-
induced COPD is emerging as a growing health problem in China, but the condition has not received enough attention compared with coronary heart disease and cancer. Reasons for this include the complex pathogenesis of COPD and lack of reliable model for the condition. We have been focusing on research to understand the pathogenesis of COPD and establish an appropriate animal model for the disease. A number of animal studies of COPD have been performed over the years, which have differed in the type of cigarettes used, the length of exposure, and the age at which the animals should be exposed to smoke. In the present study, we exposed rats to cigarette smoke starting from age of 8 weeks and continuing for a 12-week period to mimic a 10-year smoking history in humans (assuming a life span of 80 years). The rats were exposed to cigarette smoke twice daily for 7 d per week until the end of week 12, which was different from other models in which exposure occurred for 3 or 5 d per week. We believe that this model is a better reflection of smoking habits, as the vast majority of smokers will smoke cigarettes every day, not only 3 or 5 d a week. Using a model with intermittent smoke exposure may result in the accumulated molecules being discharged from the airways during the resting period. The detail steps of establishing our model were the same as we described previously. Besides, the pathological and functional changes in this model without death mimic those in patients with COPD. Thus we believe that the COPD model procedure used in the current study is a better model for the study of cigarette smoke-induced COPD in rats. This COPD model resulted in a pulmonary inflammatory response, leading to production of inflammatory cells involved in the disease process, such as macrophages, neutrophils, T cells and B cells, eosinophils and epithelial cells. These inflammatory cells may induce immune responses, resulting in an increase in a number of inflammatory mediators, including IL-1β and TNF-α. TNF-α has been shown to play an important role in the pathogenesis of COPD. Levels of TNF-α are increased in blood, sputum and BALF in patients with COPD compared with healthy subjects. TNF-α is a cytokine that is predominantly produced by the macrophage, and it has extensive biological activities, including involvement in inflammation-induced tissue injury.

IL-1β is also associated with COPD, and the level of IL-1β in blood and BALF is raised in patients with COPD. IL-1β is closely involved in the occurrence and development of COPD, and is an important target for COPD treatment. In this study, we found that TNF-α, IL-1β and MDA were significantly increased in BALF of smoke-exposed COPD rats.

Although EA has been practiced for more than 4 000 years, its biological basis was difficult to establish. We found that the response to EA in our study varied in individual rats. For example, there was a large decrease in IL-1β level in BALF for most rats (one rat had a decrease of 70.6%), but this change in that was much less (e.g. 29%) in some other rats, and it even increased by 45% in one rat. A similar pattern was seen with other factors such as MDA. These findings suggest that the effects of EA depend on the individual immune response and body state, with individual differences occurring with the same acupuncture stimulation, which also occurs in clinical practice.

In the theoretical system of traditional Chinese medicine, ST36 is an important acupuncture point for good health care. Recent studies have shown that EA at ST36 could regulate the nerve-endocrine-immune network. EA at ST36 can regulate a wide variety of diseases caused by inflammation, and can also modulate TNF-α and IL-1β levels. Various reports have indicated that acupuncture can improve lung function, quality of life, exercise capacity and respiratory muscle strength in patients with COPD. Suzuki et al. reported treatment of a 66-year-old patient with COPD by acupuncture and moxibustion (burning of the herb mugwort) therapy, which resulted in an improvement in the patient’s respiratory function and physical strength, thus acupuncture therapy may be an effective treatment methods for COPD. However, the mechanisms of EA are still unclear, therefore it is important to study the pathogenesis of COPD and the biological effect of EA.

We treated COPD model rats with EA for two weeks and measured the lung pathology and lung function, as well as the levels of IL-1β, TNF-α and MDA in BALF, to evaluate the effects of EA on this model and to elucidate its anti-inflammatory and antioxidant mechanisms.

We found that lung function decreased while the bronchial and bronchiolar obstruction increased in the COPD model rats. EA treatment improved lung function, and decreased the bronchial and bronchiolar obstruction. Exposure to cigarette smoke increased the levels of MDA and the inflammatory cytokines IL-1β and TNF-α in BALF, while EA decreased the levels of all above.

Studies have confirmed that ROS generated by cigarette smoke can stimulate an inflammatory reaction in the airway. IL-1β and TNF-α, which are generated in response to ROS, can increase mucus secretion in the airway, resulting in airway obstruction, indicating that decreasing the ROS level could be an effective way to treat COPD.

In this study, we found that EA treatment reduced the severity of lung injury in the COPD model rats, and this observation was supported by the histological findings and lung function results. In addition, EA treatment decreased the levels of MDA, TNF-α and IL-1β in the lung. These results indicate that EA treatment may improve lung function through an antioxidant mechanism.

Recent research has shown that acupuncture exhibits a variety of neuromodulating functions throughout the
body. EA has been shown to have some interesting neuroimmuno-modulating functions, suggesting that it suppresses the increase in apoptosis induced by the stress of surgical trauma, possibly through modulating Fas-protein expression. Some researchers have suggested that the cholinergic anti-inflammatory pathway could therefore provide a very plausible physiological mechanism for the reported anti-inflammatory actions of acupuncture.

Our study suggests that EA treatment has an antioxidant effect and it may be another mechanism for the anti-inflammatory actions of acupuncture in the COPD model. Acupuncture seems to stabilize disordered lipid peroxide processes and improved the antioxidant status of erythrocytes. EA was shown to increase the lung content of saturated phosphatidylcholine and total phospholipids in rat fetuses, but could also decrease the antioxidant enzyme activities. The results from the present study confirm that EA can decrease ROS and improve the antioxidant status of erythrocytes, but EA can also decrease the activity of antioxidant enzyme. Thus, the mechanism of the antioxidant effect of EA is complex, and more studies are needed to confirm its antioxidant effects and elucidate the mechanism behind them.

Our study has some limitations. A flaw in the experiment is that it lacked a sham acupuncture point in the COPD rats. There were no significant differences between the sham (with acupuncture at ST36) and the control rats in the lung tissue and function and the levels of MDA, TNF-α and IL-1β in the BALF in this study. EA did not cause harm to rats in this study, to say the least. The COPD rat model of cigarette smoking was successful, but there are still a percentage of COPD cases that developed without cigarette smoke. In addition, the rat model is different from the COPD patients. Therefore, more studies are needed to confirm the effects of EA in clinical application, and to identify how EA exerts antioxidant and anti-inflammatory effects.

5 Conclusion

EA treatment at ST36 attenuated the lung injury induced by cigarette smoke through anti-inflammatory and antioxidant mechanisms, which suggests this method has potential for the treatment of COPD. Acupuncture is a simple and non-invasive method, making it a very attractive adjunctive therapy for a number of chronic inflammatory and autoimmune diseases, including COPD. We hope our results will stimulate future clinical studies to validate the use of EA for COPD.

6 Funding

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7 Competing interests

The authors declare that they have no competing interests.

REFERENCES

5 Teramoto S. 1. COPD pathogenesis from the viewpoint of risk factors. Intern Med. 2007; 46(2): 77-79.
14 Rahman I. Antioxidant therapies in COPD. Int J Chron Obstruct...
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