

Therapeutic effect of simvastatin combined with vein infusion of hyperoxic fluid on the cardiac function, respiratory mechanics and airway inflammation factor of patients with chronic obstructive pulmonary disease combined with coronary heart disease.

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Abstract

Objective: To observe the therapeutic effect of simvastatin combined with vein infusion of hyperoxic fluid on the cardiac function, respiratory mechanics and airway inflammation factor of patients with Chronic Obstructive Pulmonary Disease (COPD) combined with Coronary Heart Disease (CHD).

Method: 96 patients with COPD combined with CHD who accorded with diagnostic criteria were randomly divided into observation group and control group, each containing 48 patients. The control group was given with vein infusion of hyperoxic fluid, while the observation group was given with simvastatin combined with vein infusion of hyperoxic fluid. The index change of two groups before treatment and 5 d after treatment were compared, including cardiac function (LVEF-Left Ventricular Ejection Fraction and LVDD-Left Ventricular End Diastolic Dimension), blood fat (TC-Total Cholesterol, LDL-Low Density Lipoprotein), oxygenation index ($\text{PaO}_2/\text{FiO}_2$), respiratory mechanical indexes (lung compliance, PIP-peak inspiratory pressure, airway platform pressure, airway resistance), phlegm supernate inflammation factors (IL-8, TNF- α , Neu/Leu%).

Results: 5 d after treatment, LVEF of both groups were increased in different degrees, while LVDD, TC and LDL-C of both groups were decreased ($P<0.05$). After treatment, the LVEF of observation group was significantly higher than that of control group; TC and LDL-C of observation group were significantly lower than that of control group, and the intergroup difference was of statistical significance ($P<0.05$); $\text{PaO}_2/\text{FiO}_2$, Cst, Cdyn of observation group were improved more quickly than control group ($P<0.05$); the PIP, Pplat and RE of observation group were improved more quickly compared with control group ($P<0.05$); the IL-8, TNF- α and Neu/Leu% of observation group were also improved more quickly compared with control group ($P<0.05$).

Conclusion: The combined therapy of simvastatin and vein infusion of hyperoxic fluid can effectively improve the cardiac function, blood lipid level, respiratory mechanics of patients with COPD plus CHD, and effectively reduce level of airway inflammation factors. This combined therapy is an ideal method to treat COPD plus CHD, which should be promoted in clinics.

Keywords: Simvastatin, Vein infusion of hyperoxic fluid, Chronic obstructive pulmonary disease (COPD), Coronary heart disease (CHD), Cardiac function, Respiratory mechanics, Airway inflammation factor.

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Introduction

COPD is a common and frequently-occurring disease. This disease mainly features the occurrence of incomplete invertible airway limitation, causing damage to the cerebrovascular function of patient in certain degree. If timely treatment is not implemented, the health and daily life of patient will be severely impacted. CHD is a common cardiovascular disease for elderly people, which severely affects the life quality of patient. According to relevant researches [1], COPD is prevalent among the elderly people, which easily incur a series of cardiovascular and cerebrovascular diseases in the elderly group. Some scholars believe [2] COPD, as a common risk

factor is correlated with CHD in certain degree. The disease of COPD plus CHD is a torturous disease, which is normally treated with β adrenoceptor agonist, oxygen therapy, anti-infection, phlegm eliminating method. However, the therapeutic effect of this method is poor, and symptoms are insignificantly reduced. More seriously, patients may be easily encountered with complications such as angoria pectoris and myocardial ischemia, and the therapeutic effect can hardly be satisfactory [3,4]. Statins are the most powerful anti-cholesteremic agent at present, which have been widely used in treatment of HLP and CHD [5]. In addition to having lipid-decreasing effect, statins have been proved in recent years to have anti-inflammatory, anti-oxidation function, which can

delay the pulmonary function changes of COPD patients' and reduce the morbidity and mortality [6]. Through vein infusion of hyperoxic fluid, oxygen can be directly introduced into blood circulation to supply oxygen for the whole body tissues, so as to effectively improve the pathogenic histiocyte caused by lack of oxygen and thus realize therapeutic aim [7]. In recent years, our hospital has found a new treatment method for COPD plus CHD, i.e. simvastatin combined with vein infusion of hyperoxic fluid. This combined therapy has achieved satisfactory results in clinically treating COPD plus CHD. Currently, there has been no research reported on treating COPD plus CHD using combined therapy of simvastatin combined with vein infusion of hyperoxic fluid. This study aims to explore the therapeutic effect of such combined therapy on the cardiac function, respiratory mechanics and airway inflammation factors of patients with COPD plus CHD as well as actions mechanism of this combined therapy.

Materials and Method

General information

In this study, 96 patients with COPD plus CHD who had been treated at our hospital from January 2016 to September 2017 were selected as research objects. Among them, there were 54 male patients and 42 female patient, with age varying within 56-74 (averaging at 61.3 ± 1.5 y old), and course of disease ranging within 4 to 12 y (averaging at 6.5 ± 1.2). The COPD diagnostic criteria was based on the COPD guidelines in 2007 revised by the Chronic Obstructive Pulmonary Disease Committee, Respiratory Society, Chinese Medical Association; the CHD diagnostic criteria was based on the coronary arteriography. All selected patients met clinical standard for accepting COPD plus CHD treatment and signed informed consent. Those who did not accept drug therapy and relevant diagnosis or had vital organ (liver, lung) dysfunction combined with severe internal medicine diseases, language barriers, mental disorders, taken the simvastatin in the past three months were excluded.

The 96 patients were randomly divided into control group and observation group, each containing 48. There was no significant difference in gender, age, course of disease between the two groups ($P > 0.05$), as shown in Table 1.

Table 1. Comparison of general data between the two groups.

Group	n	Male/female	Age (y)	Course of disease (y)
Control group	48	28/20	61.1 ± 1.2	6.4 ± 1.1
Observation group	48	26/22	61.5 ± 1.7	6.6 ± 1.4
χ^2/t		0.704	1.015	0.936
P		0.082	0.093	0.145

Treatment method

Both groups were given with conventional treatment approaches, such as airway smoothing, oxygen therapy, anti-infection, eliminating phlegm, cortical hormone, correcting the electrolyte disorder, nutrition support, etc. In addition, the control group was given with vein infusion of hyperoxic fluid, by 500 ml per day, 5 d as a complete course of treatment.

The observation group was given with oral administration of simvastatin (Zhejiang Jingxin Pharmaceutical Co., Ltd., approval number State Food and Drug Administration: H20030207) in addition to vein infusion of hyperoxic fluid. The simvastatin was given by 40 mg per one take, and once a day, 6 weeks as a complete course of treatment.

Observation indexes

Cardiac function and blood lipid index: The two groups were compared in cardiac function (LVEF and LVDD) and blood lipid before and 5 d after treatment. The LVED and LVDD were measured by color Doppler imaging (HD15000). The TC and LDL-C were measured by enzymic method.

Respiratory mechanics index: The oxygenation index ($\text{PaO}_2/\text{FiO}_2$), PIP, Plat pressure (P_{plat}) before and 5 d after treatment were observed. The static compliance (Cst), dynamic compliance (Cdyn) and resistance of expiration (RE) of patients were calculated. According to the calculation formula proposed by Tobin [8], we can obtain $\text{Cst (ml/cmH}_2\text{O)} = \text{VT}/(P_{\text{plat}} - \text{PEEP})$, $\text{Cdyn (ml/cmH}_2\text{O)} = \text{VT}/(P_{\text{max}} - \text{PEEP})$, $\text{RE} = (\text{PIP} - \text{PEEP})/\text{PEF}$ (PEF: Peak Expiratory Flow).

Inflammatory factors of phlegm supernate: Before treatment and 5 d after treatment, the sputum was absorbed *via* trachea cannula, then collected for measuring volume. After that, 0.8% sulfuracol-phosphate buffer (pH7.4) in equal volume concentration was added. Subsequently, the mixture was successively subjected to spiral oscillator mixing for 5 min, and centrifugation at 500 r/min for 20 min at 4°C. Then, the supernate was collected and cool at -70°C for measuring IL-8 and TNF- α . Cell deposit layer was made into cell suspension using HBSS. Then cell counting was performed on cell counter. The cells on smear were counted and classified. The Neu/Leu ratio (%) was recorded. IL-8 ELISA kit was provided by Beijing Kemei Dongya Biotechnology Co., Ltd., TNF- α ELISA kit was provided by BIOSOURCE, USA. The contents of IL-8 and TNF- α were measured with Enzyme Linked Immunosorbent Assay (ELISA) according to kit introduction.

Statistical method

The data were recorded by SPSS 21.0 software. The measurement data that met conditions of normal distribution and homogeneity of variance were subjected to t test; while those that did not meet above conditions were subjected to rank

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sum test or t-test after logarithmic transformation. The comparison of the rate was tested using χ^2 ; exact probability method was adopted when theoretical value was lower than 5 (two-sided test was adopted). $P < 0.05$ means significant difference, and $P < 0.01$ means extremely significant difference.

Results

Comparison of two groups in cardiac function and blood lipid index before treatment and 5 d after treatment

Before treatment, the intergroup differences in LVEF, LVDD, TC, LDL-C were of no statistical significance ($P > 0.05$); 5 d

after treatment, LVEF of both groups were increased in different degrees, while LVDD, TC and LDL-C of both groups were decreased ($P < 0.05$). After treatment, the LVEF level of observation group was significantly higher than that of control group, while TC and LDL-C of observation group were significantly lower than that of control group, the intergroup difference was of statistical significance ($P < 0.05$), as shown in Table 2.

Table 2. Comparison of two groups in cardiac function and blood lipid index before treatment and 5 d after treatment.

Group	n	LVEF (%)		LVDD (mm)		TC (mmol/L)		LDL-C (mmol/L)	
		Before treatment	5 d after treatment	Before treatment	5 d after treatment	Before treatment	5 d after treatment	Before treatment	5 d after treatment
Control group	48	37.12 ± 4.75	39.35 ± 5.04	60.74 ± 8.15	52.41 ± 6.93	5.37 ± 0.81	4.92 ± 0.53	3.15 ± 0.37	2.72 ± 0.21
Observation group	48	36.87 ± 3.96	44.32 ± 5.77	60.35 ± 7.27	53.07 ± 5.44	5.35 ± 0.79	3.81 ± 0.36	3.14 ± 0.35	2.09 ± 0.17
t		1.035	6.742	0.638	0.144	0.922	6.195	0.875	6.004
P		0.064	0.015	0.062	0.053	0.061	0.018	0.054	0.026

Comparison of PaO₂/FiO₂, Cst, Cdyn between two groups before and 5 days after treatment

Before treatment, the difference in PaO₂/FiO₂, Cst, Cdyn between two groups was of no statistical significance ($P > 0.05$);

5 d after treatment, the PaO₂/FiO₂, Cst, Cdyn of observation group was improved more quickly and significantly better than that of control group ($P < 0.05$), as shown in Table 3.

Table 3. Comparison of PaO₂/FiO₂, Cst, Cdyn between two groups before and 5 d after treatment.

Group	n	PaO ₂ /FiO ₂		Cst (ml/cmH ₂ O)		Cdyn (ml/cmH ₂ O)	
		Before treatment	5 d after treatment	Before treatment	5 d after treatment	Before treatment	5 d after treatment
Control group	48	197.25 ± 16.54	243.71 ± 21.36	39.15 ± 3.21	47.33 ± 2.18	35.06 ± 3.22	45.58 ± 2.11
Observation group	48	196.13 ± 15.27	286.33 ± 16.81	39.17 ± 3.46	54.05 ± 2.39	35.04 ± 3.17	50.36 ± 2.45
t		0.265	5.961	0.372	6.002	0.434	6.261
P		0.054	0.037	0.059	0.031	0.057	0.025

Comparison of PIP, Pplat and RE between two groups

Before treatment, the difference in PIP, Pplat and RE between two groups was of no statistical significance ($P > 0.05$); 5 d after

treatment, the PIP, Pplat and RE of observation group was improved more quickly and significantly better than that of control group ($P < 0.05$), as shown in Table 4.

Table 4. Comparison of PIP, Pplat and RE between two groups.

Group	n	PIP (cmH ₂ O)		Pplat (ml/cmH ₂ O)		RE (cmH ₂ O/L·S)	
		Before treatment	5 d after treatment	Before treatment	5 d after treatment	Before treatment	5 d after treatment
Control group	48	29.76 ± 1.36	22.02 ± 1.77	21.04 ± 1.38	19.33 ± 2.02	18.93 ± 1.26	14.46 ± 1.51

Observation group	48	29.81 ± 1.54	19.15 ± 1.63	21.03 ± 1.44	17.26 ± 1.69	18.91 ± 1.38	10.07 ± 1.24
t		0.157	5.496	0.202	6.139	0.524	6.782
P		0.052	0.035	0.057	0.032	0.061	0.023

Comparison of inflammation factors of phlegm supernate between two groups before and after treatment

Before treatment, the difference in phlegm supernate inflammation factors (IL-8, TNF- α and Neu/Leu%) between

two groups was of no statistical significance ($P > 0.05$); 5 d after treatment, the IL-8, TNF- α and Neu/Leu% of observation group was improved more quickly and significantly better than that of control group ($P < 0.05$), as shown in Table 5.

Table 5. Comparison of inflammation factors of phlegm supernate between two groups before and after treatment.

Group	n	IL-8 (ng/L)		TNF- α (μ g/L)		Neu/Leu%	
		Before treatment	5 d after treatment	Before treatment	5 d after treatment	Before treatment	5 d after treatment
Control group	48	1894.52 ± 236.71	873.29 ± 78.64	2.07 ± 0.65	1.76 ± 0.34	78.26 ± 3.08	63.44 ± 2.38
Observation group	48	1905.13 ± 197.55	651.37 ± 65.02	2.08 ± 0.54	1.47 ± 0.23	78.05 ± 2.94	57.15 ± 2.01
t		0.179	5.745	0.218	6.001	0.219	6.492
P		0.062	0.041	0.065	0.037	0.066	0.058

Discussion

COPD combined with CHD is very common in clinics. Patients with COPD combined with CHD have higher risk of cardiac failure, and COPD plus CHD has been regarded an independent risk factor leading to cardiovascular disease and death [9]. In addition, as a pulmonary disease with incompletely invertible airway limitation, COPD normally shows progressive course and has relation with lung's inflammatory response against harmful gases or particles. The main pathological feature of COPD is chronic airway inflammation. According to modern researches [10], COPD chronic airway inflammation is resulted due to mutual inducement and adjustment of complex inflammatory cells and secreted cytokines, wherein IL-8 and TNF- α play significant role. IL-8 is a neutrophil chemotactic factor, which can be synthesized and emitted by various cells such as alveolar macrophage, bronchial epithelia and endothelial cell. As an important media of inflammatory reaction, IL-8 can accumulate within airway, activate neutrophile granulocyte, and induce neutrophile granulocyte to degranulate and release lysosome. According to relevant studies [11], COPD inflammation features polymorphonuclear (PMN) infiltration within lumen and T cell infiltration at tube wall. IL-8 can activate PMN and T cell *via* its receptor, and inhibit PMN apoptosis, thus incurring inflammatory reaction.

Currently, smoking and infection have been confirmed to be two major factors leading to COPD [12]. Relevant studies show that the content of IL-8 in phlegm and BALF (bronchoalveolar lavage fluid) of smoker is higher than that of non-smoker, moreover, the IL-8 level in BALF increases with cigarette amount (number of packets per year) [13]. In

addition, *in vitro* experiment and *in vivo* experiment both indicate bacterial endotoxin can cause increased expression of IL-8 mRNA and IL-8, and effect is dose-dependent. Therefore, it can be known that IL-8 plays an important role in pathological process of COPD. TNF- α is a cytokine generated from activated macrophage, monocyte or T cell under the stimulus of endogenous interferon, bacteria, endotoxin or virus. TNF- α has chemotactic effect to leukocyte. It activates and stimulates endothelial cells to express adhesion molecules, then mediates leukocyte to stick to vascular endothelial cell, so as to concentrate leukocyte at inflammatory site and trigger inflammatory reaction; in addition, TNF- α can amplify COPD airway inflammatory response *via* stimulating the expression of IL-8. According to relevant studies [14], the contents of IL-8 and TNF- α in serum during COPD acute attack period are significantly increased, however only amplifying of systemic inflammatory response can be indicated. This study further verifies that the levels of IL-8, TNF- α and neutrophile granulocyte in sputum of patients with COPD plus CHD also increase, which indicates that the amplifying of systemic inflammatory response is a key factor leading to respiratory failure, and timely controlling of airway inflammatory response can effectively improve respiratory mechanics and oxygenation status of patients.

In the process of treating COPD plus CHD with vein infusion of hyperoxic fluid, due to ultraviolet irradiation and oxygenation, active oxygen which is capable of improving erythrocyte deformability will form in hyperoxic fluid to reduce blood platelet cohesion. In addition, the solubility of fibrous protein is improved and content of calcium ion in cell can be adjusted, which thus effectively prevent ischemic damage of organs. A research shows that [15], statins have

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anti-inflammatory activity and antioxidation function, which can inhibit the expression of various inflammatory factors, reduce many markers of inflammation, inhibit all stages of inflammatory reaction, improve eNOS activity, and promote the generation of NO. According to relevant research [16], statins can reduce the death rate of COPD patients and delay lung function decline. Inflammatory cells and cytokines play significant role in pathogenesis, early diagnosis and prevention and prognosis of patients with COPD plus CHD.

On the basis of clinical practices, this study analyses therapeutic effect of simvastatin combined with vein infusion of hyperoxic fluid in treating patients with COPD plus CHD. Results show that such combined therapy can effectively improve the cardiac function, blood lipid level, respiratory mechanics indexes and oxygenation status and reduce the airway inflammation factor level of patients with COPD plus CHD. This may be due to that: 1. simvastatin can reduce the expression of IL-8 and TNF- α (anti-inflammatory action) and increase NO level (antioxidation effect), so as to improve lung function; 2. Performing vein infusion of hyperoxic fluid allows oxygen to directly enter into blood circulation, so as to directly supply oxygen for whole body tissues; 3. simvastatin combined with vein infusion of hyperoxic fluid achieves a synergistic effect.

The occurrence and development of COPD plus CHD as well as airway limitation is a long-term, repeated and progressive aggravation process, therefore a long-term treatment is required. In view of small sample of this study and insufficient treatment time, a further large-scale clinical research is still needed to verify the results. We hope this study can provide as a new research direction for treating COPD plus CHD by taking the advantage of anti-inflammation and anti-oxidation effect of statins and the direct oxygen supply function of vein infusion of hyperoxic fluid.

Conclusion

The combined therapy of simvastatin and vein infusion of hyperoxic fluid can effectively improve the cardiac function, blood lipid level, respiratory mechanics of patients with COPD plus CHD, and effectively reduce level of airway inflammation factors. This combined therapy is an ideal method to treat COPD plus CHD, which should be promoted in clinics.

Conflict of Interest

The authors declare that there is no conflict of interest to disclose.

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