Original Article
The clinical study of serum hs-CRP, TNF-α, PCT and IL-6 in patients with acute exacerbation of chronic obstructive pulmonary disease

Yajun Song, Yaokang Liu, Zhehui Zhou, Wenwei Yang, Yan Zhou

Department of Respiratory, Shanghai Huangpu District Center Hospital, Shanghai 200002, China

Abstract: To investigate the serum levels of hs-CRP, PCT, IL-6 and TNF-α in patient with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and their relationship with gas analysis test and COPD assessment test (CAT). 80 cases of AECOPD patients were collected in experimental group, and another 80 cases of COPD patients in stable stage was treated as control group. Then, serum levels of hs-CRP, PCT, IL-6 and TNF-α, gas analysis test in artery and CAT scores were measured in the two groups. Results showed that serum levels of hs-CRP, PCT, IL-6 and TNF-α, $PaCO_2$ and CAT scores of patients in experimental group were significantly elevated compared with that of control group (P<0.0001). For experimental group, levels of hs-CRP, PCT, IL-6 and TNF-α, $PaCO_2$ and CAT in prior treatment patients were higher than that of post-treatment patients (P<0.0001). PaO_2 of pre-treatment patients were lower than that of control patients. Furthermore, PaO_2 levels could be significantly increased by treatment compared with that of pre-treatment patients (P<0.0001). Levels of hs-CRP, PCT, IL-6 and TNF-α were positively correlated with $PaCO_2$ and CAT score, the difference was statistically significant, and they have negative correlation with the level of PaO_2, the difference was statistically significant. The measure of hs-CRP, PCT, IL-6 and TNF-α combined with CAT score and gas analysis test may be a good assessment and disease monitoring in AECOPD.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD), hypersensitive C-reactive protein (hs-CRP), procalcitonin (PCT), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), gas analysis test in artery, COPD assessment test (CAT)

Introduction

The chronic obstructive pulmonary disease (COPD) is one of the common chronic lung diseases with the characteristic of continuing airway limitation [1, 2]. So far, the patho-mechanism of COPD is still not clear, and it generally considered that airway inflammatory reactions are closely related to the COPD [3, 4]. In recent years, the epidemic disease investigations indicated that there is an increasing incidence rate for the COPD due to the deteriorating environmental situations, in particular the air pollution. It's reported that COPD has a high incidence in old people of the Asian-pacific region (morbidity is approximate 6.2%) [5, 6]. Importantly, COPD has an incidence rate of 8.2% for the people over 40 years old in China [7].

In 2014, European respiratory society (ERS) defined that the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a diagnosis by exclusion, and obvious acute exacerbation would be observed in the respiratory system of COPD patients, including dyspnea, cough, excessive phlegm and purulent sputum, etc [8, 9]. Furthermore, the most common reason for AECOPD is airway inflammatory reactions due to virus or bacteria [10]. In addition, COPD is also considered as a systemic inflammatory disease [11], and its severity could be reflected by levels of oxidative stress, inflammatory mediators, and hypersensitive C-reactive protein (hs-CRP) [3, 12]. Thus, this work was designed to explore the changes of hs-CRP, PCT, IL-6 and TNF-α in AECOPD patients; furthermore, we analyzed the clinical significance of hs-CRP, PCT, IL-6 and TNF-α for AECOPD, which could be beneficial for evaluating the severity and prognosis of AECOPD patients.

Table 1. General information of patients in the two groups (n=80)

	Experimental	Control	P
Age (year)	71.55±9.92	71.71±10.15	0.9186
Sex (male/female)	45/35	47/33	0.7491

Chi-Square analysis was used to compare the general information between the two groups.

Materials and methods

Subjects

In this study, 80 patients with definite diagnosed AECOPD in Shanghai Central Hospital of Huangpu district from Jan. 2015 to Jun. 2016 were enrolled (Experimental group); in addition, another 80 patients in stable phase of COPD were served as the control subjects. The protocols of this investigation were approved by the Ethics Committee of the Shanghai Central Hospital of Huangpu district, and all the subjects were required to sign the informed consents.

Inclusion criteria

All patients collected in this study followed the criteria: 1) all the AECOPD and stable COPD patients were accorded to the chronic obstructive pulmonary diseases diagnosis and treatment guideline of China; 2) AECOPD and stable COPD patients must had the abilities of reading, writing and communicating; 3) no other active chronic respiratory diseases.

Exclusion criteria

Patients would be excluded as: 1) treatment with antibiotic within 15 days; 2) patients with bacterial infection besides respiratory system; 3) acute exacerbation was over 3 days; 4) had other serious diseases such as hypertension, diabetes mellitus, coronary disease, liver diseases, kidney disease, tumor, blood diseases and connective tissue diseases; 5) patients with surgery recently; 6) patients currently treated with immunosuppressor.

Experimental protocols

In the present investigation, AECOPD patients were treated by anti-infection combined other AECOPD therapies (ceftizoxime sodium, *ivgtt*, 2g, q12h; doxofylline, *ivgtt*, 0.3, qd; salbutamol, *ivgtt*, 200 μg, bid; ambroxol, *ivgtt*, 30 mg, bid)

for 15 days. Venous blood and radial artery bloods samples were collected before treatment and after treatment. Then, the serum levels of hs-CRP, PCT, IL-6 and TNF-α were determined in the venous blood samples, and blood gas analysis was performed using the radial artery bloods samples. In addition, the serum levels of hs-CRP, IL-6 and TNF-α were determined by using commercial ELISA kits (Shanghai Meiyuan Biotech, Shanghai, China), and the PCT was assayed by using Immunogold labeling kit (Wuhan Easydignosis Biomedicine Co., Wuhan, China). Blood gas analysis was carried out by using an ABL80 bloodgas analyzer (Radiometer Co., Copenhagen, Denmark). COPD assessment test (CAT) was carried out based on the general information of the collected subjects.

Statistical analysis

Data were expressed as Mean ± standard deviation (SD), and analyzed by using SAS 9.1 software, $P<0.05$ was considered as significance. Correlation analysis was performed by using the Pearson rectilinear correlation analysis.

Results

Results of the general data of patients

In the experimental group, the general information of the subjects were described in **Table 1**, there were 80 subjects enrolled with an average age of 71.55±9.92 years old; 45 of the subjects were male (56.25%) and 35 of the subjects were female (43.75%). In the control group, the average age was 71.71±10.15 years old, and the male and female patients were 47 (58.75%) and 33 (41.25%) respectively. Based on the analysis results, we could find that there was no obvious difference in the general data of patients between the two groups (P>0.05).

Changes of the serum levels of hs-CRP, PCT, IL-6 and TNF-α

As shown in **Table 2**, serum levels of hs-CRP, PCT, IL-6 and TNF-α of AECOPD patients were significant higher than that of stable COPD patients (P<0.0001, P<0.0001, P<0.0001 and P<0.0001, respectively). Furthermore, after treatment, the serum levels of hs-CRP, PCT, IL-6 and TNF-α of AECOPD patients significantly decreased (P<0.0001, P<0.0001, P<0.0001 and P<0.0001, respectively).

Table 2. Levels of hs-CRP, PCT, IL-6 and TNF-α of patients in the two groups

		hs-CRP (mg/L)	PCT (ng/ml)	IL-6 (ng/L)	TNF-α (ng/L)
Experimental	Pre-treatment	39.51±15.26	2.43±1.29	90.09±17.77	41.45±10.84
	Post-treatment	22.95±10.30	0.67±0.45	54.96±13.38	25.79±5.51
Control		8.01±2.69	0.20±0.13	31.98±9.70	16.33±4.76
P_1		<0.0001	<0.0001	<0.0001	<0.0001
P_2		<0.0001	<0.0001	<0.0001	<0.0001

The *t*-test was used to compare the difference. P_1: Pre-treatment vs. Post-treatment; P_2: Pre-treatment vs. control.

Table 3. Results of evaluations of PaO_2, $PaCO_2$ and CAT of patients in the two groups

		PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	CAT
Experimental	Pre-treatment	62.68±11.39	59.14±16.51	19.91±5.64
	Post-treatment	80.32±7.42	47.69±9.21	12.41±4.68
Control		82.15±5.20	43.21±5.53	12.03±3.51
P_1		<0.0001	<0.0001	<0.0001
P_2		<0.0001	<0.0001	<0.0001

The *t*-test was used to compare the difference. P_1: Pre-treatment vs. Post-treatment; P_2: Pre-treatment vs. control.

Table 4. Correlative analysis between levels of hs-CRP, PCT, IL-6, TNF-α and lung functional parameters & CAT

		hs-CRP	PCT	IL-6	TNF-α
CAT	r	0.678	0.668	0.729	0.715
	p	<0.0001	<0.0001	<0.0001	<0.0001
PaO_2	r	-0.464	-0.461	-0.514	-0.393
	p	<0.0001	<0.0001	<0.0001	0.0003
$PaCO_2$	r	0.544	0.533	0.621	0.545
	p	<0.0001	<0.0001	<0.0001	<0.0001

Results of the evaluation of PaO_2, $PaCO_2$ and CAT

Results of the evaluation of PaO_2, $PaCO_2$ and CAT were showed in **Table 3**, and it indicated that $PaCO_2$ (P<0.0001) and CAT (P<0.0001) were significantly increased compared with that of stable COPD patients, whereas the PaO_2 was obviously decreased (P<0.0001). In contrary, after treatment, the $PaCO_2$ (P<0.0001) and CAT (P<0.0001) were significantly decreased compared with that of pre-treatment, whereas the PaO_2 (P<0.0001) was obviously increased.

Results of the correlation analysis

As can be seen in **Table 4** and **Figures 1-3**, results of the correlation analysis were showed.

Our results revealed that serum levels of hs-CRP, PCT, IL-6 and TNF-α are positively correlated with the $PaCO_2$ and CAT, whereas has a negative correlation with PaO_2.

Discussion

It's reported that airway inflammation is one of the important characteristics of COPD, and the inflammatory cytokines have been aroused considerably attention [4]. PCT, the propeptide of serum calcitonin, could be secreted to the blood by various cells under bacterial infection and septicopyemia [13, 14]. PCT could detected from 3 hours after infection, and reach at the peak value during 6 to 12 hours after infection. Compared with other traditional biomarker of inflammation, PCT has a longer half-time (approximate 24 h), and could not be reflected by renal functions and hormonotherapies [15]. Thus, it's recognized that the sensitiveness and specificity of PCT is better than that of other biomarkers (such as CRP and lactic acid) for infectious diseases [16]. In addition, previous reports have demonstrated that dynamic monitoring of PCT is beneficial for early diagnosis of various infectious diseases, antibiotic therapy and assessment of prognosis of diseases in clinical, etc. IL-6 plays important roles in immune responses of body under infectious diseases [17, 18]. IL-6 is considered as an effective early predicted biomarker of infection, and could be also used to evaluate or predict the infection severity and prognosis. However, IL-6 is not a specific marker of infection, and various factors could arouse the increase of IL-6 such as bacterial infection, autoimmunity and [19, 20]. Thus, PCT combined with IL-6 could be better for diagnosis of infection.
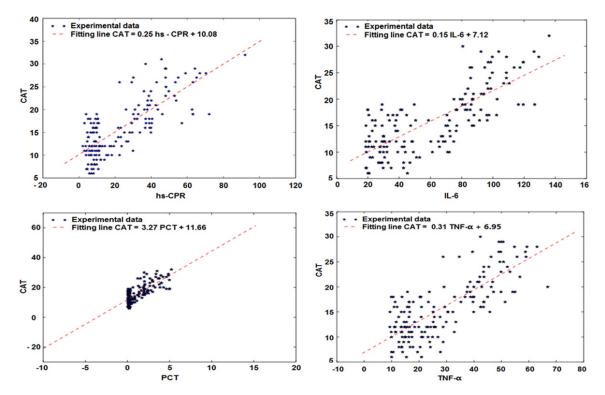
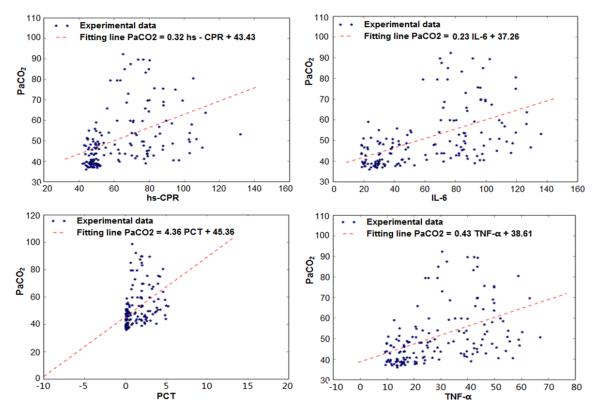**Figure 1.** Results of the analysis between hs-CRP, PCT, IL-6 & TNF-α and CAT.

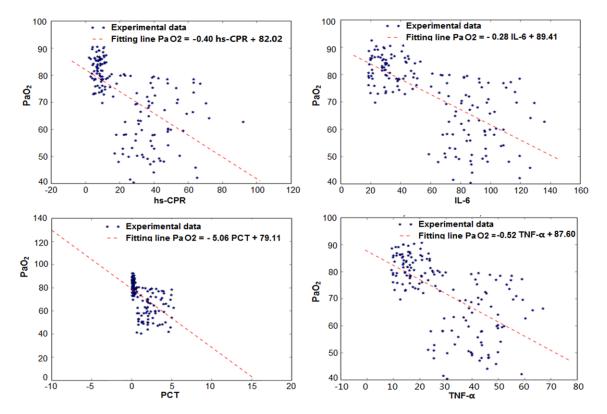**Figure 2.** Results of the analysis between hs-CRP, PCT, IL-6 & TNF-α and PaCO$_2$.

Figure 3. Results of the analysis between hs-CRP, PCT, IL-6 & TNF-α and PaO_2.

CRP, the acute phase serum protein, could active complement system and bind to the Fc receptor, and it's known that the significant increase of CRP indicates inflammation [21]. The hs-CRP is a sensitive biomarker of systemic inflammation, and it's also reported that serum level of hs-CRP has a closely correlation with the development, severity and prognosis of COPD [22, 23]. TNF-α, also an early inflammatory cytokines released by the mononuclear leucocytes and macrophagocytes, could active the neutrophile granulocytes, inducing the releases of IL-8 [24, 25]. TNF-α could result in the damage of lysosome, leading to damages of alveolar cells. In addition, serum levels of TNF-α could be used to evaluate the severity of COPD, and could be recognized as an important biomarker for evaluation of the prognosis of COPD [25, 26].

CAT score is a recommended index for evaluation of the severity of COPD in clinic [27, 28]. Furthermore, arterial blood gas analysis is another commonly used clinical application for diagnosis and prognosis evaluation of AECOPD [29, 30]. In our present study, we analyzed the serum levels of hs-CRP, PCT, IL-6 and TNF-α in AECOPD patient and their relationship with gas analysis test and CAT. Our results revealed that serum levels of hs-CRP, PCT, IL-6 and TNF-α are positively correlated with the $PaCO_2$ and CAT, whereas has a negative correlation with PaO_2. We think that evaluating hs-CRP, PCT, IL-6, TNF-α combined with CAT score and gas analysis test may be a good assessment and disease monitoring in AECOPD.

Disclosure of conflict of interest

None.

Address correspondence to: Yajun Song, Department of Respiratory, Shanghai Huangpu District Center Hospital, No. 109, Sichuan Road, Shanghai 200002, China. Tel: +86-021-65086803; Fax: +86-021-65086803; E-mail: songyajunhpu@126.com

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