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Open Access Journal of Pulmonary & Respiratory Sciences
ISSN: 2642-1143

The Expression and Significance of Hypoxia Inducible Factor-1α in Patients with Acute Exacerbation of COPD

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Research Article
Volume 6 Issue 1
Received Date: April 08, 2021
Published Date: April 30, 2021
DOI: 10.23880/oajprs-16000138

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Abstract

Objective: 1) to investigate the expression level and significance of HIF-1 α in COPD stable period, AECOPD and healthy people; 2) to explore the change and significance of HIF-1α expression level at all levels in AECOPD patients; 3) to analyze the relationship between HIF-1α and FEV1%, Hs-CRP, PO2, dioxygen in AECOPD patients. The correlation of carbon partial pressure (PCO2) and the role of HIF-1α in the progression of AECOPD were discussed.

Methods: 180 COPD patients (120 in acute exacerbation stage and 60 in stable stage) from May 2016 to January 2017 in the outpatient or inpatient department of the First People›s Hospital of Yinchuan City were collected, and 60 healthy controls of the same age were enzymatically linked immunosorbent assay (ELISA) to detect the level of HIF-1α in blood, lung function, serum high-sensitivity C-reactive protein, and serum hypersensitivity C-reactive protein. The arterial partial pressure (PO2) and partial pressure of carbon dioxide (PCO2) were measured by arterial blood gas analysis, and their differences and correlation were analyzed.

Results: 1. The levels of HIF-1α and Hs-CRP in AECOPD group, COPD stable group and healthy control group were significantly different ($P < 0.05$). 2. The levels of HIF-1α and Hs-CRP in each grade of AECOPD group increased with the increase of grade, the difference was statistically significant ($P < 0.05$). 3. In AECOPD group, FEV1% was negatively correlated with HIF-1α, Hs-CRP and PCO2 ($p < 0.05$), but positively correlated with PO2 ($r = 0.425$, $P < 0.05$). 4. In AECOPD group, HIF-1α was positively correlated with Hs-CRP ($r=0.209$, $P<0.05$), HIF-1α was negatively correlated with PO2 ($r=-0.198$, $p<0.05$), and HIF-1α was not correlated with PCO2 ($r=0.152$, $p>0.05$).

Conclusion: 1. The level of HIF-1α in AECOPD group and COPD group increased significantly, and the level of HIF-1a increased with the grade of AECOPD. 2. HIF-1a is closely related to FEV1%, Hs-CRP and PO2 in patients with AECOPD, and can reflect the hypoxia and inflammation in patients with AECOPD.

Keywords: COPD; HIF-1alpha; Hypoxia; Inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by persistent airflow restriction. It is associated with abnormal chronic inflammation of airways and lung tissues to harmful gases such as cigarette smoke or harmful particles [1-3]. Chronic hypoxia can induce chronic inflammation of airway, lung parenchyma and pulmonary vessels in COPD patients [4]. Hypersensitive C-reactive protein (Hs-CRP), an inflammatory marker, is an acute phase protein stimulated by inflammatory factors such as IL-6 and TNF-α. Once inflammation occurs, the level of Hs-CRP in blood will increase [5]. Many literatures reported that Hs-CRP has important value in diagnosing acute exacerbation of COPD and reflecting the severity of the disease [6-8]. It can reflect the pulmonary function, nutritional status, acute exacerbation of symptoms, hospitalization rate and mortality rate of patients [9].

Hypoxia-inducible factor-1 (HIF-1) is a heterodimer composed of a hypoxia-regulated functional subunit α subunit and a fixed β subunit [10,11], which can sensitively sense intracellular oxygen Changes in concentration can also regulate hypoxia to regulate nuclear transcription factors and initiate transcription of target genes [12-14]. Under the condition of long-term hypoxia, some inflammatory factors such as TNF-α and IL-6 in chronic inflammation of COPD can activate HIF-1α. Inflammatory factors such as VEGF, transforming growth factor (TGF-β) and NO regulated by HIF-1α also participate in the inflammation of COPD. At the same time, HIF-1α regulates the imbalance of vasoconstrictive substances, the predominance of vasoconstrictive substances, and the persistent contraction of pulmonary vessels, leading to pathological changes. Hypoxic pulmonary hypertension, pulmonary heart disease, respiratory failure, right heart failure to systemic multiple organ failure until death, the formation of hypoxic pulmonary hypertension is the key to the progress of COPD disease [15]. Inflammatory factors have been found to induce the expression of HIF-1α [16] in many cells under hypoxia, which suggests that HIF-1α is closely related to COPD hypoxia and inflammation.

Materials and Methods

The subjects were divided into three groups: group A consisted of 120 cases of acute exacerbation of COPD (30 cases of Grade I, II, III and IV), group B consisted of 60 cases of stable COPD, and group C consisted of 60 healthy persons in the same period as the control group. From May 2016 to January 2017, COPD patients came from the inpatient or outpatient department of the First People's Hospital of Yinchuan City. The control group was healthy people of the same age in the same period.

Selection Criteria

AECOPD Group

A. **Selection Criteria**

1. The selected subjects should conform to the Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD) formulated by the Respiratory Disease Society of the Chinese Medical Association in 2013 and the COPD diagnostic criteria of the European Society of Respiratory Diseases;
2. Typical medical history and confirmed by physical examination and X-ray or chest CT.
3. Pulmonary function index: after inhalation of bronchodilator, the ratio of forced expiratory volume to forced vital capacity (FEV_1 / FVC) in one second was less than 70%.
4. The symptoms of cough, expectoration, chest tightness, shortness of breath, increased sputum, or fever in the near future exceed the daily variation, and need emergency or hospitalization treatment.

B. **Exclusion Criteria**

1. Complicated with other respiratory diseases: patients with bronchial asthma, active pulmonary tuberculosis, lung cancer, primary bronchiectasis, pneumoconiosis and other pulmonary restrictive ventilation dysfunction;
2. Malignant tumors, severe heart failure, connective tissue diseases, metabolic diseases, bone and joint diseases, neuromuscular junction diseases;
3. Received surgical treatment within 6 months;
4. There were myocardial infarction and unstable angina pectoris attacks in the past month.
5. Recent 8 weeks have received antibiotics, inflammatory factor inhibitors, nutritional support and lipid-lowering drugs.

All subjects in group A were grouped according to pulmonary function indicators.

Group I (30 cases): Grade I (mild) FEV_1 / FVC < 70%, FEV_1% of the predicted value (>80%);

Group II (30 cases): Grade II (moderate) FEV_1 / FVC < 70%, 50% less than FEV_1 accounted for less than 80% of the predicted value;

Group III (30 cases): Grade III (severe) FEV_1 / FVC < 70%, 30% less than FEV_1 accounted for less than 50% of the predicted value;

Group IV (30 cases): Grade IV (extremely severe) FEV_1 / FVC < 70%, FEV_1% of the predicted value < 30%, or with chronic respiratory failure.

COPD Stable Group

A. **Selection Criteria**

1. The selected subjects should conform to the Guidelines for the Diagnosis and Treatment of Chronic Obstructive

Pulmonary Disease (COPD) formulated by the Respiratory Disease Society of the Chinese Medical Association in 2013 and the COPD diagnostic criteria of the European Society of Respiratory Diseases;

2. Typical medical history and confirmed by physical examination and X-ray or chest CT;
3. Lung function indicators: after inhalation of bronchodilator, the forced expiratory volume occupied vital capacity ratio (FEV_1 / FVC) in one second was less than 70%.
4. No cough, sputum, wheezing, fever and other symptoms were found in recent January.

B. **Exclusion Criteria**

1. Complicated with other respiratory diseases: patients with bronchial asthma, active pulmonary tuberculosis, lung cancer, primary bronchiectasis, pneumoconiosis and other pulmonary restrictive ventilation dysfunction;
2. Malignant tumors, severe heart failure, connective tissue diseases, metabolic diseases, bone and joint diseases, neuromuscular junction diseases;
3. Received surgical treatment within 6 months;
4. There were myocardial infarction and unstable angina pectoris attacks in the past month.
5. Recent 8 weeks have received antibiotics, inflammatory factor inhibitors, nutritional support and lipid-lowering drugs.

Healthy Control Group

Selection criteria: The same period of physical examination in our hospital, no chronic underlying diseases, no respiratory diseases, related examinations: chest X-ray, lung function, blood gas test normal.

Sample Collection

Inform the patient about the situation, sign the informed consent after obtaining the patient's consent, and take 5 mL peripheral venous blood from the patients into the EDTA tube, and send it to the laboratory within half an hour, centrifuge for 4000 revolutions / minutes, and extract the upper serum after 10 minutes of centrifugation. Store the serum in the refrigerator and wait for detection. The temperature is set to minus 20 degrees Celsius. On the day of hospitalization, patients should take immediate measures.

Detection of HIF-1α: human hypoxia inducible factor-1α (HIF-1α) Enzyme Linked Immunosorbent Assay (ELISA)

Standard: Standard control should be set and standard curve should be calculated. Each standard pore should be added with different concentration of standard 50 μL.

Add sample: set blank hole and sample hole respectively. Add 40 μL diluent into the sample hole, and then add 10 μL sample to be tested. When adding the sample, try not to touch the hole wall, and mix it gently. Enzyme addition: in addition to the blank pore, 100 μL of enzyme standard reagent is added to each pore.

Incubation at constant temperature: incubation at 37 ℃ for 60 minutes.

Solution preparation: dilute the concentrated washing solution for 20 times and then reserve it.

Washing: pour out the liquid, add the diluted washing liquid into each hole, and discard after standing. Repeat for 5 times.

Color developing: add color developing agent A 50 μL and color developing agent B 50 μL into each hole, mix well, react at 37 ℃ for 15 minutes at constant temperature, this process needs to be conducted in dark.

Termination: add 50 μL of termination solution to each hole to terminate the reaction (at this time, the blue color turns to yellow vertically).

Determination: 15 minutes after the termination of the reaction, adjust the blank hole to zero, and measure the absorbance (OD value) of each hole at the wavelength of 450 nm.

Pulmonary function test: after inhalation of bronchodilator, the one second rate (FEV_1 / FVC) and the first second forced expiratory volume (FEV_1) as a percentage of the predicted value (FEV_1%) were detected by pulmonary function instrument.

Detection of serum high-sensitivity C-reactive protein: turbidimetry; arterial blood gas analysis to detect arterial blood pressure (PO_2), carbon dioxide (PCO_2).

Main Experimental Reagents and Instruments

Blood gas analyzer: GEM PREMIER 3000 U.S.A
Pulmonary function instrument: CHESTGRAPH HI-101 CHEST
Company in Japan: Shanghai Mei Lian Biotechnology Co., Ltd.

Human hypoxia inducible factor-1 Kit (ELISA)
Microplate Reader: Labsystems Multiskan MS 352 Finland
Double optical path immunoturbidimeter: Beckman Coulter, Inc.

Statistical Methods

In this study, SPSS22.0 For Windows software package is used for statistical analysis and processing of data. The collected data are grouped by reference to the research content. Each group of continuous variable data is represented by mean ± standard deviation ($\bar{X} \pm s$). Univariate analysis of variance is used for inter group comparison. Q-test is used for inter group comparison. Chi square test is used to analyze the counting data, $P < 0.05$, which is statistically significant Righteousness.

Results

General Information

There was no significant difference between the three groups in terms of height and age ($p > 0.05$). The gender composition ratio of the three groups of males and females was measured by the Chi-square test, and there was no significant difference either ($p > 0.05$). As shown in Table 1 & 2.

	Healthy Control Group (n=60)	COPD Group (n=60)	AECOPD Group (n=120)	p
Age (years)	71.38±9.48	68.92±9.53	68.32±11.85	0.104
Height (cm)	164.13±8.03	165.57±7.9	164.36±7.51	0.533

Table 1: Comparison of three groups of general information.

	Healthy Control Group (n=60)	COPD Group (n=60)	AECOPD Group (n=120)	Chi- Square	p
Male	24	32	64	3.2	0.202
Female	36	28	56		

Table 2: Comparison of the sex composition ratio of the three groups.

There were no significant differences in height and age between different grades in the AECOPD group ($p > 0.05$). There was no significant difference in the composition ratio of males and females between different levels using Chi-Square test, either ($p > 0.05$). As shown in Table 3 & 4.

AECOPD Group	Grade I (n=30)	Grade II (n=30)	Grade III (n=30)	Grade IV (n=30)	p
Age (years)	72.26±11.02	70.23±10.14	73.83±6.70	69.20±9.27	0.232
Height (cm)	164.6±7.88	164.3±7.21	163.7±7.99	164.8±7.27	0.946

Table 3: Comparison of general information at various levels of AECOPD.

AECOPD Group	Grade I (n=30)	Grade II(n=30)	Grade III (n=30)	Grade IV (n=30)	Chi- Square	p
Male	14	19	15	16	1.875	0.599
Female	16	11	15	14		

Table 4: Comparison of male and female composition ratios in each group of AECOPD.

Comparison of HIF-1α, Hs-CRP, PO_2, and PCO_2 in the Three Groups

The blood indicators of the three groups were statistically analyzed. The levels of HIF-1α and Hs-CRP in the three groups of AECOPD group, COPD stable group, and healthy control group were significantly different, the differences were statistically significant ($p < 0.001$). The expression levels of HIF-1α and Hs-CRP in the AECOPD group were the highest, the COPD group was the second, and the healthy control group was the lowest. The PO_2 level in the AECOPD group was significantly lower than that in the healthy control group, and the difference was statistically significant ($p < 0.05$). The PCO_2 level in the COPD group was significantly lower than that in the healthy control group, and the difference was statistically significant ($p < 0.05$). The content of PCO_2 in the AECOPD group was significantly higher than that in the healthy control group, and the difference was statistically significant ($p < 0.05$). The content of the COPD group was significantly higher than that of the healthy control group, and the difference was statistically significant ($p < 0.05$). However, there was no significant difference in the content of PO_2 and PCO_2 between the AECOPD group and the COPD group ($p > 0.05$). As shown in Table 5.

	Healthy Control Group (n=60)	COPD Group (n=60)	AECOPD Group (n=120)	p
HIF-1α (pg/mL)	28.64±9.45	35.72±7.14*	43.09±7.94*#	＜0.001
Hs-CRP (mg/L)	8.62±9.73	22.15±10.7*	30.71±16.79*#	＜0.001
PO2 (mmHg)	83.55±8.42	73.28±16.42*	67.98±13.62*	＜0.05
PCO2 (mmHg)	36.27±5.5	42.63±13.02*	44.54±9.9*	＜0.05

Table 5: Comparison of three groups of HIF-1α, Hs-CRP, PO_2 and PCO_2 indicators.
Note: * indicates $p < 0.05$ compared with the control group.
# indicates $p < 0.05$ compared with the COPD group.

Comparison of HIF-1α, Hs-CRP, PO_2 and PCO_2 Indicators between Different Levels in the AECOPD Group

The levels of HIF-1α, Hs-CRP, and PCO_2 in the AECOPD group gradually increased with the increase of disease grade, and the difference was statistically significant ($p < 0.001$). Further analysis and comparison, for each pair of AECOPD groups, the expression levels of HIF-1α and Hs-CRP were significantly different, and the differences were statistically significant ($p < 0.001$). Compared PO_2 of Grades III and IV with Grades I and II of AECOPD group respectively. PO_2 of Grades III and IV was lower than that of Grades I and II, the difference was statistically significant ($p < 0.05$). Compared with Grades I and II, the PCO_2 levels of Grades III and IV were higher than those of Grades I and II, and the difference was statistically significant ($p < 0.05$). However, when comparing the PO_2 and PCO_2 of Grade III with Grade IV, the difference was not significant ($p > 0.05$). There was also no difference in the expression levels of PO_2 and PCO_2 between Grades I and II ($p > 0.05$). As shown in Table 6.

AECOPD group	Grade I(n=30)	Grade II(n=30)	Grade III (n=30)	Grade IV (n=30)	p
HIF-1α (pg/mL)	38.33±6.60	41.4±8.04	45.16±6.70	47.44±7.44*	＜0.001
Hs-CRP (mg/L)	16.30±9.58	29.36±10.78	30.54±14.66	46.64±15.98*	＜0.001
PO2 (mmHg)	75.33±12.93	71.57±16.04	63.13±12.9#	61.90±6.12#	＜0.05
PCO2 (mmHg)	42.23±7.15	41.47±7.64	46.07±11.7#	48.4±11.01#	＜0.05

Table 6: Comparison of HIF-1α, Hs-CRP, PO_2 and PCO_2 between different levels of AECOPD.
Note: * indicates $p < 0.05$ compared with other groups.
# indicates $p < 0.05$ compared with Grades I and II groups of AECOPD.

Correlation Analysis between FEV_1% and HIF-1α, Hs-CRP, PO_2, PCO_2 in AECOPD Group.

In the AECOPD group, FEV_1% was negatively correlated with HIF-1α ($r = -0.416$, $p < 0.05$), FEV_1% was negatively correlated with Hs-CRP ($r = -0.63$, $p < 0.05$), FEV_1% was positively correlated with PO_2 ($r = 0.425$, $p < 0.05$), FEV_1% was negatively correlated with PCO_2 ($r = -0.208$, $p < 0.05$). As shown in Table 7.

AECOPD	FEV1% r	p
HIF-1α (pg/mL)	-0.416	＜0.05
Hs-CRP (mg/L)	-0.63	＜0.05
PO2 (mmHg)	0.425	＜0.05
PCO2 (mmHg)	-0.208	＜0.05

Table 7: Correlation analysis between FEV_1% and HIF-1α, Hs-CRP, PO_2, PCO_2 in the AECOPD group.

Correlation Analysis of HIF-1α with Hs-CRP, PO_2, and PCO_2 in the AECOPD Group

In the AECOPD group, HIF-1α was positively correlated with Hs-CRP ($r = 0.209$, $p < 0.05$), HIF-1α was negatively correlated with PO_2 ($r = -0.198$, $p < 0.05$), and there was no correlation between HIF-1α and PCO_2 ($r = 0.152$, $p > 0.05$). As shown in Table 8.

AECOPD group	HIF-1α r	p
Hs-CRP	0.209	0.022
PO2	-0.198	0.03
PCO2	0.152	0.097

Table 8: Correlation analysis of HIF-1α with Hs-CRP, PO_2, and PCO_2 in the AECOPD group.

Conclusion

1. The levels of HIF-1α in AECOPD group and COPD group increased significantly.
2. HIF-1α increased with the increase of AECOPD classification.
3. HIF-1α is closely related to FEV_1%, Hs-CRP, and PO_2 in patients with AECOPD, which could reflect hypoxia and inflammation in patients with AECOPD.

Discussion

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory reactive disease characterized by continuous airflow limitation. It not only affects the lungs, but can also affect other organs through inflammation and oxygen imbalance. As the number of acute exacerbations increases, patients' lung function damage and disease progression continue. Hypoxia and inflammation are the key factors driving the progress of COPD disease. Therefore, monitoring of hypoxia and the severity of inflammation in the body can correctly reflect the disease condition. At the same time, it has become a key point for intervention in the progress of COPD disease.

Significance of HIF-1α Expression in Patients with COPD

Regarding the comparison of general data, there were no significant differences in general clinical data such as gender composition ratio, age, and height among patients in the healthy control group, COPD group, and AECOPD group ($p > 0.05$). Eliminate other factors that interfere with the results to facilitate statistical analysis. Make statistical results more reliable and true.

ELISA method was used to detect HIF-1α in healthy control group, COPD group and AECOPD group, and its expression level was AECOPD group > COPD group ＞ Health control group ($p < 0.001$). During the development of COPD disease, HIF-1α was used as a regulator A series of nuclear transcription factors of hypoxic genes, whose expression levels are increased, regulate the body to adapt to the hypoxic environment, and avoid damage caused by hypoxia [17,18], in addition to regulating and regulating hypoxic genes, it also encodes a variety of inflammatory factors gene. Such as VEGF, transforming growth factor (TGF-β), NO, etc. [16], participate in airway, lung tissue and systemic inflammation, while some COPD inflammatory factors can induce high expression of HIF-1α [19,20]. The result of the interaction between the two is that COPD patients' inflammation and hypoxia will continue to increase, forming a vicious cycle to cause further disease progression; in this experiment, the high expression of HIF-1α in the AECOPD group and COPD group, which was found by studies with foreign scholars. The enhancement of transcription and translation in COPD lung tissues is consistent [21]. With the participation of HIF-1α, inflammation in COPD patients is exacerbated. The results of Hs-CRP prove this hypothesis. In healthy control group, COPD group, AECOPD group In the group, the expression level of Hs-CRP was AECOPD group > COPD group > healthy control group ($p < 0.001$). Hs-CRP was higher in the COPD group and AECOPD group than in the control group. There are inflammatory infections in the exacerbation period. Because acute exacerbations of COPD patients are often accompanied by acute upper respiratory infections or airway inflammations, the degree of inflammation in the AECOPD group is more severe, which is consistent with the findings of foreign scholars [22]. At the same time, whether in the stable phase or acute exacerbation phase of COPD, the level of PO_2 in patients was lower than that in healthy people ($p < 0.05$), and PCO_2 was higher than that in healthy people ($p < 0.05$). The content is lower than that of normal people, and hypoxia can cause the level of HIF-1α to increase, which is consistent with the results of HIF-1α in this experiment. Therefore, HIF-1α is closely related to the onset of COPD. You can monitor the patient's hypoxia and inflammation by monitoring the level of HIF-1α to determine whether it is exacerbated, the severity of the disease, and early intervention treatment.

Relationship between HIF-1α and COPD Disease Progression

The levels of AECOPD increased with the severity of the disease, and the level of HIF-1α gradually increased ($p < 0.001$). As mentioned above, HIF-1α is closely related to the inflammation and hypoxia regulation of COPD. In this experiment, the levels of AECOPD were As the grade increased, the level of Hs-CRP gradually increased, and the difference was statistically significant ($p < 0.001$). It shows that as the disease progresses, the inflammatory response gradually increases. As the grade increases, PO_2 gradually decreases, and PCO_2 gradually increases, suggesting that as the disease worsens, hypoxia in the body becomes more and more serious, and carbon dioxide retention occurs; the inflammatory response gradually increases Involving the airway and lung parenchyma, causing airway remodeling and emphysema, the pathological changes of the two can lead to a decrease in FEV_1% and cause impairment of lung function [22]. In the experiment, FEV_1% was negatively correlated with Hs-CRP ($r = -0.63$, $p < 0.05$), the experimental results are consistent with this. COPD disease progresses, the lung structure and function are impaired, resulting in dysfunction of ventilation and ventilation, hypoxemia and hypercapnia in the imbalance of oxygen supply in the body. FEV_1% was positively correlated with PO_2($r = 0.425$, $p < 0.05$), which was consistent with this course change. This experiment confirmed that COPD is mainly caused by hypoxia and

inflammation throughout the disease, which is the key factor that causes COPD disease to be irreversible. In addition, the target genes regulated by HIF-1α include Endothelin-1 (ET-1), Vascular Endothelial Growth Factor (VEGF), etc., which can cause pulmonary vasoconstriction and airway remodeling to cause hypoxic pulmonary hypertension and aggravate the disease deterioration. Combined with the results of this experiment, HIF-1α is closely related to the progress of COPD. In the AECOPD group, FEV_1% was negatively correlated with HIF-1α ($r = -0.416$, $p < 0.05$). At present, the value of FEV_1% is used to classify the degree of lung function damage and reflect the disease progression. HIF-1α is negatively correlated with FEV_1%, which also indicates that HIF-1α can reflect the degree of COPD disease progression.

In the AECOPD group, HIF-1α was not only positively correlated with the FEV_1% of the disease, but also positively correlated with Hs-CRP ($r = 0.209$, $p < 0.05$), indicating that HIF-1α is related to the severity of the body's inflammation level, that is, the patient's inflammation aggravating the severity of lung tissue, leading to hypoxia. At this time, HIF-1α is actively expressed, and related inflammatory factors such as TNF-α, IL-1β can enhance the expression of HIF-1α, and HIF-1α can also regulate a certain The expression of some inflammatory factors such as transforming growth factor (TGF-β), which promote each other, aggravates inflammation and hypoxia. HIF-1α is negatively correlated with PO_2 ($r = -0.198$, $p < 0.05$), which is precisely due to HIF-1α itself is determined by its functional characteristics. It maintains a steady state under hypoxic conditions and adapts to a hypoxic environment. This is a protective response to the body in the early stages of COPD disease. Long-term oxygen homeostasis, HIF-1α and inflammatory effects aggravate hypoxia in the body, causing hypoxic compensatory imbalances, pulmonary vascular remodeling, and disease progression.

In summary, HIF-1α is involved in the pathogenesis of COPD and can promote the disease progression of COPD. It can reflect the hypoxia and inflammation in patients with COPD. In view of this, we can interfere with the process of COPD disease by interfering with HIF-1α targets. At present, it has been found that the NF-κB pathway can regulate the expression of HIF-1α. After giving NF-κb inhibitors (Ammonium pyrrolidine dithiocarbamate, PDTC), the originally increased HIF-1α mRNA in the COPD group was reduced, and the downstream HO-1 and VEGF mRNAs were decreased compared with the previous ones, thus playing a role in intervening the progression of COPD disease [23].

Acknowledgment

Ningxia Hui Autonomous Region Key Research and Development Program, "Clinical study on the effect of hypoxia-inducible factor 1α on the coagulation and fibrinolysis function of COPD and its interaction on the progression of COPD", No.2018BEG03077. Ningxia Medical University Scientific Research Foundation, "Study on the predictive value of NLR and CYSC on COPD", No.XM2020026.

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