ORIGINAL ARTICLE

Correlation Analysis and its Significance of Serum N-terminal Pro b-type Natriuretic Peptide, Potential of Hydrogen Value and Carbon Dioxide in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: *To explore the correlation analysis of serum N-terminal pro b-type natriuretic peptide (NT-proBNP), potential of hydrogen (pH) value and carbon dioxide ($PaCO_2$) in patients with different degrees of chronic obstructive pulmonary disease (COPD) and their significances.*

Methods: *Clinical data were collected from 126 patients with chronic obstructive pulmonary disease. The correlation analysis of NT-proBNP, pH-value and $PaCO_2$ in patients was performed and compared with 50 patients of the same period. The serum NT-proBNP concentration was measured by using bidirectional lateral flow immunoassay, pH-value was detected with the ion electrode selection method and $PaCO_2$ was detected with the gas sensitive electrode method.*

Results: *The concentration of serum NT-proBNP and $PaCO_2$ in COPD patients was significantly higher than those in the healthy group. The pH-value in COPD patients was lower than that in the healthy group ($p < 0.05$). The concentration of serum NT-proBNP and $PaCO_2$ in Grades 1 and 2 COPD patients was higher than those in the healthy control group. The pH-value was lower than that in the healthy control group. But the difference was not statistically significant ($p > 0.05$). The concentration of serum NT-proBNP and $PaCO_2$ in Grades 3 and 4 COPD patients were higher than those in the healthy control group. The pH-value was lower than that in the healthy control group ($p < 0.05$). The linear correlation analysis showed that serum NT-proBNP was negatively correlated with pH-value and positively correlated with $PaCO_2$ in COPD patients.*

Conclusion: *The regular detection of serum NT-proBNP, pH-value and $PaCO_2$ in COPD patients can detect earlier disease progression in COPD patients, which is conducive to the active treatment of COPD and with change of life style, can improve the quality of life of patients.*

Keywords: Chronic obstructive pulmonary disease (COPD), NT-proBNP, pH-value, $PaCO_2$

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Análisis e Importancia de la Correlación del Péptido Natriurético N-terminal pro tipo-B Sérico, el Potencial del Valor del Hidrógeno y el Dióxido de Carbono en Pacientes con la Enfermedad Pulmonar Obstructiva Crónica

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RESUMEN

Objetivo: *Explorar el análisis de la correlación del péptido natriurético N-terminal pro-tipo-B sérico (NT-proBNP), el potencial del valor del hidrógeno (pH) y la presión parcial de dióxido de carbono ($PaCO_2$) en pacientes con diferentes grados de enfermedad pulmonar obstructiva crónica (EPOC) y sus significados.*

Métodos: *Los datos clínicos fueron recogidos a partir de 126 pacientes con EPOC. El análisis de la correlación NT-proBNP, valor de pH y $PaCO_2$ en los pacientes fue realizado y comparado con 50 pacientes del mismo período. La concentración NT-proBNP del suero fue medida usando el inmunoensayo de flujo lateral bidireccional, el valor de pH fue detectado con el método de electrodos selectivos de iones, y el $PaCO_2$ se detectó con el método de electrodos sensibles al gas.*

Resultados: *La concentración de NT-proBNP y $PaCO_2$ en suero en los pacientes con EPOC fue significativamente mayor que en el grupo sano. El valor de pH en los pacientes con EPOC fue más bajo que en el grupo sano (*$p < 0.05$*). La concentración de NT-proBNP y $PaCO_2$ en suero de los pacientes con EPOC de grado 1 y grado 2 fue más alta que la del grupo de control sano. El valor de pH fue más bajo que en el grupo de control sano. Pero la diferencia no fue estadísticamente significativa (*$p > 0.05$*). La concentración de NT-proBNP y $PaCO_2$ en suero en los pacientes con EPOC de grado 3 y grado 4 fue más alta que en los del grupo de control sano. El valor de pH fue más bajo que en el grupo de control sano (*$p < 0.05$*). El análisis de la correlación linear mostró que el NT-proBNP en suero guardaba una correlación negativa con el valor de pH y una correlación positiva con $PaCO_2$ en los pacientes con EPOC.*

Conclusión: *El análisis regular de NT-proBNP en suero, valor de pH, y PaCO2 en los pacientes con EPOC puede detectar una progresión temprana de la enfermedad en pacientes con EPOC, y por ende conducir al tratamiento activo de EPOC y a un cambio de estilo de vida, que finalmente mejore la calidad de vida de los pacientes.*

Palabras clave: Enfermedad pulmonar obstructiva crónica (EPOC), NT-proBNP, valor de pH, $PaCO_2$

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) comprises of chronic bronchitis and (or) emphysaema characterized by airflow obstruction and can further develop into pulmonary heart disease, respiratory failure and other chronic diseases. Its onset is related to abnormal inflammatory response due to the harmful gas and the harmful agents (*eg* smoke, particles). Its disability rate and death rate are very high. The incidence rate in persons over 40 years old has been as high as 9% –10% worldwide (1, 2).

In recent years, the diagnosis and treatment of COPD have improved. The airflow limitation is completely irreversible and progressive. So the overall outcome is still not unsatisfactory (3). Recent clinical studies showed that the clinical test of NT-proBNP (B-type natriuretic peptide precursor) can diagnose and treat COPD patients. The NT-proBNP concentration was an important index which could objectively reflect the severity of disease and heart function of COPD patients (4). To study the clinical test significance of NT-proBNP and the correlation analysis of pH-value and $PaCO_2$ in

different degrees of COPD, the clinical data of 126 cases of COPD patients were retrospectively analysed and compared with 50 healthy patients.

SUBJECTS AND METHODS

General data

One hundred and twenty-six patients with COPD in our hospital Respiratory Department were studied from July 2009 to July 2014, there were 65 males and 61 females. The ages ranged from 42–67 years and the average age was (51.47 ± 8.79) years. The average duration was (37.7 ± 7.3) months. The patients with congenital heart disease and kidney disease were excluded. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Xinxiang Central Hospital. Written informed consent was obtained from all participants.

COPD classification standard

In accordance with classification standard formulated by the Chinese Medical Association COPD research group, the severity grading standards of 126 COPD patients were as follows: Grade 1: mild, forced expiratory volume-one second/ forced vital capacity (FEV1/FVC) 80% predicted value, with or without chronic cough and expectoration. Grade 2: moderate, FEV1/FVC < 70%, 50% < FEV1< 80% predicted value, with or without chronic cough and expectoration. Grade 3: severe, FEV1/FVC < 70%, 30% < FEV1 < 50% predicted value, with or without chronic cough and expectoration. Grade 4: extremely severe, FEV1/FVC < 70%, FEV1< 30% or FEV1< 50% predicted value, accompanied by chronic respiratory failure or clinical signs of right heart failure. The above FEV1 values referred to FEV1 after treatment by bronchodilator. Respiratory failure was PaO_2 < 60 mmHg when breathing air at sea level, with or without arterial blood $PaCO_2$ > 50 mmHg (5). According to this standard, there were 33 cases of Grade 1, 31 cases of Grade 2, 35 cases of Grade 3 and 27 cases of Grade 4 in 126 cases of COPD patients.

Detection method

One hundred and twenty-six patients with COPD underwent venous blood collection, 3 mL fasting venous blood was collected from each. The venous blood was stored in an aseptic Eppendorf tube (EP), as a sample containing 0.5 mL NT-proBNP inhibitor. The sample was immediately centrifuged by 2000 r/minutes for 10 minutes in high speed centrifugation. The supernatant was frozen and stored at -70 °C in a refrigerator. The concentration of serum NT-proBNP was detected by liquid-liquid extraction, high performance liquid chromatography and radioimmunoassay methods (Model: EALABS; Shenhua Biotechnology Co, Guangzhou, China). Then 2 mL of arterial blood of each patient was collected, stored in sterile tubes containing 0.5 mL heparin. The blood gas analysis was conducted immediately. The pH-value was detected by an ion electrode selection method (Model: i-STAT 300; Abbott, Chicago, USA) and $PaCO_2$ was detected by a gas sensitive electrode method (Model: M362536/ReLIA; Xihuayi Co, Guangzhou, China) and whether acid-base balance disorder existed, hypoxia and the degree of hypoxia in the body were determined. The concentration of serum NT-proBNP, pH-value, $PaCO_2$ and other indicators in COPD patients and the healthy group were detected and compared.

Statistical analysis

All the data were analysed by statistical analysis software SPSS 14.0 (SPSS Inc, Chicago, IL, USA). All the parameters were shown with mean ± standard deviation (x ± s), *t* and χ^2 tests were used $p < 0.05$ showed that the difference had statistical significance.

RESULTS

Comparison of the concentration of serum NT-proBNP, pH-value and $PaCO_2$ between COPD patients and those in the healthy group

Statistical analysis showed that the concentration of serum NT-proBNP and $PaCO_2$ in COPD patients were significantly higher than those in the healthy group, pH-value was lower than that in healthy group. The difference was statistically significant [$p < 0.05$] (Table 1).

Table 1: Comparison of NT-proBNP, pH-value and $PaCO_2$ between different degrees of COPD patients and healthy people ($\bar{x}$ ± s)

Groups	Cases	NT-proBNP (pg/mL)	pH-value	$PaCO_2$
Healthy group	50	146.4 ± 19.2	7.42 ± 0.08	38.2 ± 3.1
COPD group	126	347.3 ± 47.5	7.15 ± 0.07	46.7 ± 5.5
t		7.058	1. 46	2. 17
p		0.004*	0.046*	0. 032*

Note: * showed that the difference was statistically significant between the two groups ($p < 0.05$). NT-proBNP: N-terminal pro b-type natriuretic peptide; pH: potential of hydrogen value; PaCO2: carbon dioxide; COPD: chronic obstructive pulmonary disease

Comparison of the concentration of serum NT-proBNP, pH-value and $PaCO_2$ among the different degrees of COPD patients

According to the degree, the COPD patients were divided into four groups. The concentration of serum NT-proBNP, pH-value, $PaCO_2$ and other detection indicators were collected from the four groups of COPD patients and compared with the healthy group. The results showed that the concentration of serum NT-proBNP and $PaCO_2$ in Grades 1 and 2 COPD patients were higher than those in the healthy control group; pH-value was lower than that in the healthy control group, but the difference was not statistically significant ($p > 0.05$). The concentration of serum NT-proBNP and $PaCO_2$ in Grades 3 and 4 COPD patients were higher than those in the healthy control group; pH-value was lower than that in the healthy control group. The difference was statistically significant ($p < 0.05$, Table 2).

Table 2: Comparison of the concentration of serum NT-proBNP, pH-value and $PaCO_2$ between the different degrees of COPD patients ($\bar{x} \pm s$)

Groups	Cases	NT-proBNP (pg/mL)	pH-value	$PaCO_2$
Healthy group	50	146.4 ± 19.2	7.42 ± 0.08	38.2 ± 3.1
Grade 1	33	155.3 ± 22.7	7.39 ± 0.08	40.2 ± 3.8
Grade 2	31	162.8 ± 24.6	7.31 ± 0.06	42.9 ± 3.9
Grade 3	35	269.6 ± 42.1*	7.19 ± 0.05*	48.1 ± 5.3*
Grade 4	27	612.2 ± 67.4*	7.08 ± 0.05*	54.4 ± 6.9*

Note: *Compared to the healthy group, the difference was statistically significant ($p < 0.05$).

Correlation between NT-proBNP, pH-value and $PaCO_2$ in COPD patients

The correlation between NT-proBNP, pH-value and $PaCO_2$ in COPD patients was analysed. The results showed that serum NT-proBNP in COPD patients was negatively correlated with pH-value (R = -0.723, p = 0.013) and positively correlated with $PaCO_2$ (R = 0.648, p = 0.026). They were statistically significant (Figs. 1, 2).

DISCUSSION

Chronic obstructive pulmonary disease is a lung disease characterized by airflow limitation, that is completely irreversible and progressive. The overall outcome is still unsatisfactory (6). N-terminal pro b-type natriuretic peptide is a chemical substance released in the blood by the heart when the heart enlarges to make-up for the weak contraction of the stretched heart-wall. The release level of NT-proBNP has a direct correlation with the heart burden level. The guidelines for the diagnosis and treatment of acute heart failure in our country has mentioned the increase of NT-proBNP concentration as a recognized objective index to diagnose heart failure and indeed it is a key indicator of the clinical diagnosis of heart failure in recent years. N-terminal pro b-type natriuretic peptide was approved by the Food and Drug Administration (FDA) for the diagnosis and assessment of patients with heart failure and risk assessment of acute coronary syndrome in the United States of America. The evidence showed that NT-proBNP had important prognostic value to evaluate the increased prognostic risk and mortality from COPD (7).

The stability of NT-proBNP *in vitro* is good and blood half-life is long. Once heart failure occurs in patients, the level of NT-proBNP will increase significantly. Along with the aggravation of disease in COPD patients, the concentration of serum NT-proBNP is also increased. In this study, statistical analysis showed that the concentration of serum NT-proBNP, pH-value and $PaCO_2$

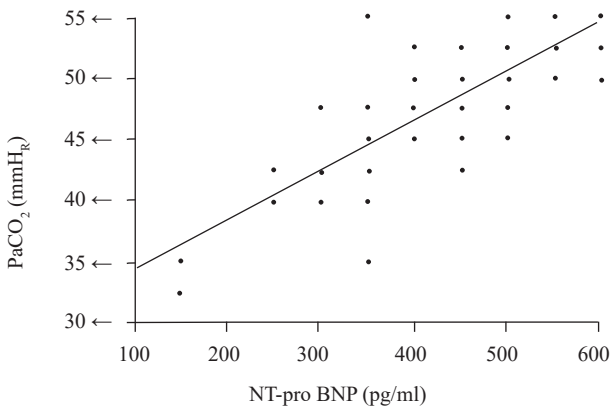

Fig 1: The serum NT-proBNP in chronic obstructive pulmonary disease patients was negatively correlated with pH-value, which had statistical significance (p = 0.013).

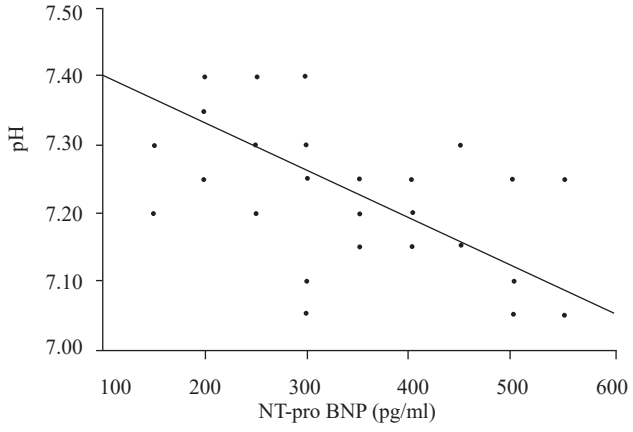

Fig 2: The serum NT-proBNP in chronic obstructive pulmonary disease patients was positively correlated with $PaCO_2$, which had statistical significance (p = 0.026).

in COPD patients were significantly higher than those in the healthy group and the difference was statistically significant (p = 0.004, 0.046, 0.032). According to the degree of the disease, the COPD patients were divided into four Groups.

The concentration of serum NT-proBNP, pH-value, $PaCO_2$ and other indicators were collected from four Groups of COPD patients and compared with the healthy group. The results showed that the concentration of serum NT-proBNP in Grades 1 and 2 in COPD patients showed no statistical significance compared with the control group. The concentration of serum NT-proBNP in Grades 3 and 4 in COPD patients was significantly higher than those in the control group and the difference was statistically significant ($p < 0.05$).

In addition, the linear correlation analysis on NT-proBNP, pH-value and $PaCO_2$ in COPD patients was conducted. The results showed that serum NT-proBNP in COPD patients was negatively correlated with pH-value (R = -0.723, p = 0.013) and positively correlated with $PaCO_2$ (R = 0.648, p = 0.026). They both had statistical significance, suggesting that NT-proBNP was an important diagnostic index of COPD patients. In clinical practice, we should make full use of its advantages to provide fast and accurate detection of disease, and timely adjustment of the therapeutic schedule of COPD patients (8).

With the progression of disease, $PaCO_2$ and pH-value in COPD patients will also change. Both are important indices in the development and prognosis of COPD. The airflow limitation in COPD patients can cause severe hypoventilation, causing hypoxaemia. The reason is that the physiological dead space (TD) of patients increases, causing the effective ventilatory capacity to decline. Hyperinflation causes flatness of the diaphragm and the tidal volume is not easy to increase compensatorily (9, 10). The increase of long-term airway resistance can cause respiratory muscle fatigue. The airway inflammation, soft palate collapse and hypotonia of the upper airway muscle group cause increase of upper airway resistance, upper airway obstruction and potential respiratory apnoea (11, 12). The test results of $PaCO_2$ also verified the decrease of ventilation function in COPD patients. Meanwhile, the increase of cardiac output can increase arteriovenous shunt and also aggravate hypoxaemia. With aggravation of the patient's disease, obvious hypoxia and carbon dioxide retention occur in the patients and arterial blood oxygen partial pressure (PaO_2) decreases, $PaCO_2$ increases, decompensated respiratory acidosis appears and pH-value reduces (13). In this study, there was a difference in pH-value and $PaCO_2$ in Grades 1 and 2 COPD patients compared with the health control group, but the difference was not statistically significant. The difference was statistically significant in pH-value and $PaCO_2$ in Grades 3 and 4 COPD patients compared with the health controls ($p < 0.05$). In addition, whether there was a correlation between the concentration of serum NT-proBNP, pH-value and $PaCO_2$ also was investigated in the different degrees of COPD patients in this research. The linear correlation analysis was performed on NT-proBNP, pH-value and $PaCO_2$ in COPD patients. The results showed that serum NT-proBNP was negatively correlated with pH-value in COPD patients, and positively correlated with $PaCO_2$. They both were statistically significance ($p < 0.05$).

Respiratory acidosis and decreased pH will appear in COPD patients due to the decreased PaO_2 and increased $PaCO_2$. The patients with severe disease have difficulty breathing, cardiac palpitations, shortness of breath, and weakness (14) and also orthopnea. If the right heart failure is accompanied by a significant, increase of serum NT-proBNP level, the patients would lose appetite, and develop nausea, abdominal distension and other digestive system congestive symptoms, cyanosis, increase of heart rate, P2 hyperthyroidism, systolic murmur in three tricuspid area and right heart dysfunction. Finally, this will greatly affect quality of life of patients (15, 16).

Based on the above research, we advised that the level of serum NT-proBNP, $PaCO_2$ and pH-value in those above Grade 2 COPD patients or accompanied by digestive system congestion; incomplete right cardiac insufficiency, should be regularly monitored, which can help to judge and predict the future progress of COPD patients, including heart failure and cardiovascular events. NT-proBNP can pick-up early deterioration of COPD patient's disease, and is conducive to the active treatment and the transformation of life style in COPD, thereby to terminate or relieve the progress of heart failure in COPD patients. Finally the survival of patients can be prolonged and their quality of life of patients can be significantly improved.

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