ANALYSIS OF THE CORRELATION BETWEEN FRACTIONAL CONCENTRATION OF EXHALED NO, CLEARANCE RATE OF BLOOD LACTIC ACID AND LACTIC ACID AND THE SEVERITY OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

Wei Zhao, Panxin Hu*
Emergency Department, Taizhou First People's Hospital

ABSTRACT

Objective: *To study the correlation between the fractional concentration of exhaled nitric oxide (FENO), clearance rate of blood lactic acid, and lactic acid and the severity of patients with acute respiratory distress syndrome.*

Methods: *Seventy-six patients with acute respiratory distress syndrome admitted to the intensive care unit of our hospital from June 2017 to August 2019 were selected as the study group. The patients were divided into mild (36 cases), moderate (26 cases), and severe (14 cases) groups according to the difference of oxygenation index (OI) and were placed into survival (60 cases) and death (16 cases) groups according to the different prognosis of patients. Twenty-five healthy subjects who underwent a physical examination in our hospital during the same period were selected as the normal group. The severity of the patients was evaluated by their APACHE II score. The FENO of each group using an exhaled nitric oxide (NO) analyzer was determined. The levels of blood lactate at 0 and 24 h in each group were determined with a blood gas analyzer. Pearson correlation analysis was used to determine the relationship between FENO, clearance rate of blood lactic acid, and lactic acid and the severity of patients with acute respiratory distress syndrome.*

Results: *Compared with the normal group, the FENO, blood lactic acid at 0 and 24 h, and APACHE II scores in the study group were significantly increased, and the lactic acid clearance rate was significantly reduced (P<0.01). With the increase of disease severity, the FENO, blood lactic acid at 0 and 24 h, and APACHE II scores were significantly increased, and the lactic acid clearance rate was significantly reduced (P<0.01). Compared with the survival group, the FENO, blood lactic acid at 0 and 24 h, and APACHE II scores in the death group were significantly increased, and the lactate clearance rate was significantly reduced (P<0.01). Pearson correlation analysis showed that FENO and blood lactate were positively correlated with the severity of the patients (P<0.05); lactic acid clearance rate was negatively correlated with the severity of the patients (P<0.05).*

Conclusion: *The FENO and blood lactate levels of patients with acute respiratory distress syndrome were significantly higher than those of healthy subjects, and the lactate clearance rate was significantly lower, which can be used as important indicators for evaluating patients' severity and prognosis.*

Keywords: *Fractional concentration of exhaled NO, blood lactic acid, lactic acid clearance rate, patients with acute respiratory distress syndrome, severity of disease, correlation.*

DOI: 10.19193/0393-6384_2021_5_458

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Acute respiratory distress syndrome is a type of diffuse pulmonary interstitial and alveolar edema. It is caused by damage to pulmonary capillary endothelial cells and alveolar epithelial cells during non-cardiogenic diseases, such as severe infection, shock, trauma, and burns, resulting in acute hypoxic respiratory insufficiency or failure with the main clinical manifestations of progressive hypoxemia and respiratory distress. The main pathophysiological characteristics are reduced lung volume, decreased lung compliance, and severe ventilation/blood flow ratio imbalance[1]. Some studies have found that the nature of the onset of acute respiratory distress syndrome is the systemic inflammatory response caused by the proinflammatory reaction dominating the body[2]. The fractional concentration of exhaled

NO (FENO) has been confirmed by many studies as a noninvasive biomarker that can quantify airway inflammation directly and is significantly positively correlated with eosinophilic inflammation. As one of the clinically critical diseases, acute respiratory distress syndrome has the characteristics of rapid disease progression, poor treatment effect, extremely high mortality, and poor prognosis, etc., all of which seriously affect people's health and quality of life[3].

Therefore, it has an important role in evaluating the condition and prognosis of patients with acute respiratory distress syndrome in a timely and correct manner. Studies have found that arterial blood lactic acid level can be used as an important indicator of systemic tissue perfusion and oxygen metabolism[4]. The detection of blood lactic acid and blood lactic acid clearance rate is essential for understanding the severity of the patient's condition and guiding treatment. This study analyzed the relationship between FENO, clearance rate of blood lactic acid, and lactate and the severity of the disease in patients with acute respiratory distress syndrome.

Materials and methods

Basic information

This study was approved by the hospital ethics committee and was in accordance with the medical ethics of fairness, respect for patients, and the interests of patients. Seventy-six patients with acute respiratory distress admitted to the intensive care unit of our hospital from June 2017 to August 2019 Syndrome patients were selected as a research group randomly. According to the patients' oxygenation index (OI), patients were divided into mild (36 cases, 200mHg <OI ≤300mmHg, with positive end-expiratory pressure or continuous positive airway pressure ≥5cmH_2O), moderate (26 cases, 100 <OI ≤200mmHg, with positive end-expiratory pressure ≥5cmH_2O), and severe (14 cases, OI ≤100mmHg, with positive end-expiratory pressure ≥5cmH_2O) groups. According to the different prognosis of patients, they were divided into survival (60 cases) and death (16 cases) groups.

Inclusion criteria:

• All patients met the diagnostic criteria of the "Berlin Definition" in 2012[5];

• All patients were over 20 and under 80 years old;

• All patients had clinical onset or respiratory symptoms that newly developed or worsened within 1 week;

• The patient and their family members were informed and signed an informed consent form;

• The patients had normal chest radiograph or CT.

Exclusion criteria:

• The patient's medical records were incomplete, or they withdrew from the study for some reason;

• The patient's mental state was good, and there was no related mental disease;

• The patient died within one week;

• Patients with hematological diseases such as leukocyte or myelodysplastic syndrome;

• Pregnancy or lactation patients.

Those who had undergone health examinations in our hospital at the same time were selected as the normal group. There were 46 males and 30 females in the study group, aged 47-79 years, with an average age of 65.24±4.77 years.

A total of 25 healthy subjects who underwent a physical examination in our hospital during the same period were selected as the normal group, including 14 males and 11 females, aged 44-78 years, with an average age of 64.22±4.14 years.

There was no significant difference in the basic data such as age and gender between the two groups (P>0.05).

Experimental equipment

Exhaled nitric oxide analyzer (Beijing Bain United Technology Development Co., Ltd., model: ANALYZER CLD 88 sp with DENOX 88); low-temperature high-speed centrifuge (Hunan Hengnuo Instrument Equipment Co., Ltd., model: MiniStar); -80 °C ultra-low temperature refrigerator (Nanjing Vedeng Medical Co., Ltd., model: MDF-C8V); blood gas analyzer (Shanghai Hanfei Medical Instrument Co., Ltd., model: BGA-101).

Observation indicators

All subjects did not drink for 4 hours and fasted for more than 10 hours after admission. Five mL of fasting median venous blood was taken on the morning of the following day. Serum and blood cells were separated using a cryogenic high-speed centrifuge, and the supernatant liquid was stored at -80°C for inspection.

The acute physiology and chronic health II (APACHE II) score is often used to evaluate the severity of patients' clinical conditions, including acute physiological rating (APS), age, and chronic health status. APACHE II score = APS + age + chronic health status.

FENO determination

The FENO concentration of each group was tested by the exhaled NO analyzer. The research subject was in a quiet state within 30 minutes before the test. First, the medical staff explained and demonstrated the test method to the tester, then allowed them to eliminate the gas in their lungs as much as possible during the calm breathing state. After that, they wrapped their lips around the mouthpiece tightly and inhaled the treated gas. After eliminating the effect of the original NO in the environment, they immediately exhaled with a constant air flow of 50 ml/s for 10 s so that the exhaled air reached a stable plateau. Finally, the measurement results were obtained. They rested for 30s, repeated the measurement 3 times, and the average was taken.

Determination of clearance rate of blood lactic acid and lactic acid

a blood gas analyzer was used to measure the levels of blood lactic acid at 0 and 24 h in each group, and the blood lactic acid clearance at 24 h was calculated according to the formula: 24 h blood lactate clearance rate = (0 h blood lactate – 24 h blood lactate) ÷ 0 h blood lactate × 100%.

Correlation analysis

Pearson correlation analysis was used to determine the relationship between FENO concentration, blood lactic acid, and lactic acid clearance rate and the severity of patients with acute respiratory distress syndrome.

Statistical methods

In this study, the comparisons of measurement data were tested by single-factor analysis of variance and an LSD t-test and were expressed as ($\bar{x}\pm s$). The APACHE II score was used to evaluate the severity of the patient's condition.

The FENO concentration of each group was determined using the exhaled NO analyzer. The blood gas analyzer was used to determine the levels of blood lactate at 0 and 24 h in each group. Pearson correlation analysis was used to determine the relationship between FENO concentration, blood lactic acid, and lactic acid clearance rate and the severity of patients with acute respiratory distress syndrome.

SPSS 18.0 software was used for statistical data analysis, and P<0.05 was regarded as being statistically significant.

Results

Comparison of FENO concentration, blood lactic acid, and lactic acid clearance rate and APACHE II score between study and normal groups

Compared with the normal group, the FENO concentration, blood lactic acid at 0 h, blood lactic acid at 24 h, and APACHE II scores of the study group were significantly increased, and the lactic acid clearance rate was significantly reduced (P<0.01). See Table 1.

Groups	Cases (n)	FENO (ppb)	Blood lactic acid at 0 h (mmol/L)	Blood lactic acid at 24 h (mmol/L)	Lactic acid clearance rate (%)	APACHEII-score (points)
Study group	76	42.48±4.28	7.55±1.82	6.43±1.68	14.83±3.69	24.41±3.57
Normal group	25	12.37±4.83	1.53±0.34	0.95±0.25	37.26±2.59	12.56±3.11
t		29.549	16.391	16.197	28.153	14.837
P		<0.001	<0.001	<0.001	<0.001	<0.001

Table 1: Comparison of FENO concentration, blood lactic acid, and lactic acid clearance rate and APACHE II score between study and normal groups ($\bar{x}\pm s$).

Comparison of FENO concentration, blood lactic acid, lactic acid clearance rate, and APACHE II score of patients with different severity

With the increase of disease severity, the FENO concentration, blood lactic acid at 0 h, blood lactic acid at 24 h, and APACHE II scores were significantly increased, and the lactic acid clearance rate was significantly reduced (P<0.01). See Table 2.

Groups	Cases (n)	FENO (ppb)	Blood lactic acid at 0 h (mmol/L)	Blood lactic acid at 24 h (mmol/L)	Lactic acid clearance rate (%)	APACHEII-score (points)
Mild group	36	31.50±8.53	4.32±1.01	3.50±0.89	19.36±2.16	13.06±1.58
Moderate group	26	46.38±10.59	8.41±1.64	7.47±1.52	11.41±1.74	17.57±2.39
Severe group	14	76.47±11.43	11.21±1.33	10.60±1.31	5.52±1.57	22.14±2.73
F		106.02	145.37	194.81	298.27	100.14
P		<0.001	<0.001	<0.001	<0.001	<0.001

Table 2: Comparison of FENO concentration, blood lactic acid, lactate clearance rate, and APACHE II score of patients with different severity ($\bar{x}\pm s$).

Comparison of FENO concentration, blood lactic acid, lactic acid clearance rate, and APACHE II scores of patients with different prognosis

Compared with the survival group, the FENO, blood lactic acid at 0 h, blood lactic acid at 24 h and APACHE II scores in the death group were significantly increased, and the lactate clearance rate was significantly reduced (P<0.01). See Table 3.

Groups	Groups	Cases (n)	FENO (ppb)	Blood lactic acid at 0 h (mmol/L)	Blood lactic acid at 24 h (mmol/L)	Lactic acid clearance rate (%)
Survival group	60	43.29±9.57	6.36±2.92	5.53±2.88	15.37±6.45	15.59±3.97
Death group	16	67.33±9.33	10.33±1.87	9.63±1.96	7.23±3.86	20.28±3.32
t		8.973	5.150	5.360	4.809	4.333
P		<0.001	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of FENO concentration, blood lactic acid, lactic acid clearance rate, and APACHE II scores of patients with different prognosis ($\bar{x}\pm s$).

Relationship between FENO concentration, blood lactic acid, and lactic acid clearance rate and severity of patients with acute respiratory distress syndrome

Pearson correlation analysis showed that FENO concentration and blood lactate were positively correlated with APACHE II score, which was positively correlated with the severity of the patient's condition (P<0.05); lactate clearance rate was negatively correlated with APACHE II score, which was negatively correlated with the severity of the patient's condition (P<0.05). See Table 4.

Indicators	APACHEIIscore	
	r	*P*
FENO	0.731	<0.05
Blood lactic acid at 24h	0.949	<0.05
Lactate clearance rate	-0.316	<0.05

Table 4: Correlation analysis.

Discussion

Acute respiratory distress syndrome refers to an acute respiratory failure caused by various non-internal and external pathogenic factors. It is characterized by diffuse alveolar-capillary membrane injury, mainly manifested as intractable hypoxemia and respiratory distress. Acute respiratory distress syndrome has a rapid onset and progress that can often cause the original disease to become more serious and complicated, representing one of the most common diseases in intensive care departments[6]. Acute respiratory distress syndrome has many pathogenic factors, including intrapulmonary factors such as pneumonia, lung contusion, and aspiration, as well as extra-pulmonary factors such as multiple trauma, postoperative surgery, drug poisoning, and shock. When two or more risk factors appear at the same time, the disease incidence increases significantly, and the longer the risk factors last, the worse the patients' prognosis[7]. Currently, acute respiratory distress syndrome is a highly debated point of contention in clinical critical illness research; the pathogenesis is intricate, and so far, there is no definite conclusion. Studies have shown that inflammatory cytokines and inflammatory mediators play an important role in the pathogenesis of acute respiratory distress syndrome[8].

NO is widely present in human tissues and is mainly produced by nitric oxide synthase (NOs), catalyzing the multi-step oxidation-reduction reaction of L-arginine and oxygen molecules[9]. NOs are divided into endothelial (eNOs), neuronal (nNOs), and inducible (iNOs) forms. The distribution of the three types is different. eNOs are mainly found in neurons, and iNOs are found in immune cells such as macrophages and neutrophils, and they are key enzymes of NO. Because NO carries free radicals, its chemical properties are highly active, and the half-life is short. Studies have found that NO is mainly derived from epithelial cells of the respiratory system, and a few are derived from airway nerves, inflammatory cells, and smooth muscle cells[10]. Under normal circumstances, a small amount of NO protects the body by relaxing the airway smooth muscle and fighting against airway hyperresponsiveness[11].

During inflammation, iNOs are expressed in the cells rapidly and produce higher than eNOs and nNOs. At this time, toxic free radicals and inflammatory mediators are induced, resulting in increased bronchial blood flow and vascular permeability and bronchial epithelial cells shed, mediating the inflammatory response, which eventually aggravates and amplifies the inflammatory response[12]. Therefore, detecting the level of NO in the airway can determine whether there is an inflammatory response and assess the degree of inflammation of that response to a certain extent.

Lactic acid is an intermediate product of the body's metabolism. The concentration of blood lactic acid mainly depends on its synthesis and metabolic rates. Studies have found that patients will have respiratory distress and hypoxemia that are difficult to correct when acute respiratory distress syndrome occurred, and the tissue's oxygen supply is severely insufficient, resulting in disturbances in the body's environment and metabolism and, subsequently, the production of a large amount of lactic acid[13]. Previous studies have shown that metabolic disorders caused by ischemia and hypoxia

often develop earlier than the changes in clinical hemodynamic indicators because changes in clinical routine hemodynamic indicators often lag behind the increase in blood lactic acid levels. The level of blood lactic acid can reflect the severity of patients with acute respiratory distress syndrome earlier and can be used as an index to evaluate the prognosis of patients with sepsis[14].

APACHE II scoring is a non-specific scoring system that is widely used and recognized by scholars for its advantages of simplicity and reliability and because it can be quickly obtained by the bed. The APACHE II score is closely related to the severity and prognosis of patients with acute respiratory distress syndrome and can be used as an important indicator to judge the severity and prognosis of patients[15]. This study found that the concentration of FENO, blood lactic acid, and lactic acid clearance rate were significantly related to the severity of patients with acute respiratory distress syndrome. With the increase of the severity of the patient's condition, the FENO concentration and blood lactic acid level increased significantly, and the lactic acid clearance rate decreased significantly.

In summary, the FENO concentration and blood lactate level of patients with acute respiratory distress syndrome were significantly higher than those of healthy subjects, and the lactate clearance rate was significantly lower than that of healthy subjects. The above indicators were significantly related to the disease severity of the patients and can be used as highly suitable indicators to determine the severity and prognosis of patients.

References

1) Derwall M, Martin L, Rossaint R. The acute respiratory distress syndrome: pathophysiology, current clinical practice, and emerging therapies. Expert Rev Respir Med 2018; 12: 1021-1029.
2) Khorashadi M, Bokoch MP, Legrand M. Is nitric oxide the forgotten nephroprotective treatment during cardiac surgery? Ann Intensive Care 2020; 10: 22.
3) Zhu H, Zhang R, Hao C, Yu X, Tian Z, et al. Fractional Exhaled Nitric Oxide (FeNO) Combined with Pulmonary Function Parameters Shows Increased Sensitivity and Specificity for the Diagnosis of Cough Variant Asthma in Children. Med Sci Monit 2019; 25: 3832-3838.
4) Yuan WH, Zeng LK, Cai BH, Liu XY, Wang S, et al. [Value of arterial blood lactic acid in the evaluation of disease severity and prognosis in neonatal shock]. Zhongguo Dang Dai Er Ke Za Zhi 2018; 20: 17–20.
5) Hirshberg EL, Majercik S. Isn't It Just Very Low Tidal Volume Ventilation? Ann Am Thorac Soc 2020; 17: 557-558.
6) Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. New Engl J Med 2017; 377: 562-572.
7) GY Jiao, LY Hao, Chen L, Gao CE, Feng R, et al. High levels of PEEP preserve diaphragm contractility during acute respiratory distress syndrome in rats. Exp Physiol 2015; 100: 967-976.
8) Vasques F, Duscio E, Cipulli F, Romitti F, Quintel M, et al. Determinants and Prevention of Ventilator-Induced Lung Injury. Crit Care Clin 2018; 34: 343-356.
9) Monsalve-Naharro JÁ, Domingo-Chiva E, García Castillo S, Cuesta-Montero P, Jiménez-Vizuete JM. Inhaled nitric oxide in adult patients with acute respiratory distress syndrome. Farm Hosp 2017; 41: 292-312.
10) Pan JZ, Peng ML, Liao C, Hu X, Wang AM, et al. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. Medicine (Baltimore) 2019; 98: 14453.
11) Tremblay J, Couture ÉJ, Albert M, Beaubien-Souligny W, Elmi-Sarabi M, et al. Noninvasive Administration of Inhaled Nitric Oxide and Its Hemodynamic Effects in Patients With Acute Right Ventricular Dysfunction. J Cardiothorac Vasc Anesth 2019; 33: 642-647.
12) Oliynyk OV, Savchuk SO, Korobko DB. Peculiarities of lipid peroxidation in conditions of acute respiratory distress syndrome and its correction. J Virol 2015; 17: 4074-4082.
13) Ghadimi K, Rajagopal S. Nasally Inhaled Nitric Oxide for Sudden Right-Sided Heart Failure in the Intensive Care Unit: NO Time Like the Present. J Cardiothorac Vasc Anesth 2019; 33: 648-650.
14) Smith MM, Kor DJ, Frank RD, Weister TJ, Dearani JA, et al. Intraoperative Plasma Transfusion Volumes and Outcomes in Cardiac Surgery. J Cardiothorac Vasc Anesth 2020; 34: 1446-1456.
15) O'Doherty J, Leader LFW, O'Regan A, Dunne C, Puthoopparambil SJ, O'Connor R. Over prescribing of antibiotics for acute respiratory tract infections; a qualitative study to explore Irish general practitioners' perspectives. BMC Fam Pract 2019; 20: 27.

Corresponding Author:
Panxin Hu
Email: gy05dq@163.com
(China)