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Predictive and Diagnostic Value of Fractional Exhaled Nitric Oxide in Patients with Chronic Rhinosinusitis

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Fractional exhaled nitric oxide (FeNO) participates in the local defense of the upper respiratory tract. Abnormal FeNO level is directly related to the occurrence of nasal diseases. However, the clinical value of FeNO in the upper airway is limited, which greatly impedes the diagnosis and treatment of nasal diseases. Here, we assessed the level of FeNO and evaluated the diagnostic accuracy of FeNO for chronic rhinosinusitis.

Material/Methods: We enrolled 35 patients with confirmed nasal inflammation and 30 healthy subjects from December 2016 and June 2017. The FeNO level was measured using a fractional exhaled nitric oxide detector. The level of FeNO in patients with different clinicopathological factors was compared. The diagnostic potential of FeNO for chronic rhinosinusitis was evaluated by receiver operating characteristic (ROC) curve analysis.

Results: FeNO level was significantly lower in patients with nasal inflammation than in healthy subjects ($P<0.05$). For nasal inflammation diagnosis, FeNO had the highest area under the curve (AUC) at 0.760, with a sensitivity of 93.30% and a specificity of 68.60%. FeNO level was significantly downregulated in chronic rhinosinusitis patients relative to chronic rhinitis patients ($P<0.05$). FeNO had a good ability to discriminate between chronic rhinosinusitis patients and chronic rhinitis patients, with higher AUC, sensitivity, and specificity of 0.760, 93.30%, and 68.60%, respectively. However, FeNO levels were not significantly different between different histological types of chronic rhinosinusitis ($P>0.05$).

Conclusions: Our results show that FeNO is a useful marker for discriminating chronic rhinosinusitis, and has potential to provide valuable information in the early diagnosis of chronic rhinosinusitis.

MeSH Keywords: Chronic Disease • Nasopharyngeal Diseases • Nitric Oxide

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Background

Chronic rhinosinusitis, a common disease in otolaryngology and head and neck surgery, is a chronic inflammatory disease occurring in the nasal-paranasal mucosa [1,2]. Its clinical manifestations includes nasal obstruction, runny nose, headache, and loss of smell [3,4]. Epidemiological research shows that the incidence of chronic rhinosinusitis is more than 10% in China [5]. Because of the high incidence of chronic rhinosinusitis and its enormous social and economic burden [6], the prevention, diagnosis, and treatment of chronic rhinosinusitis has gradually become a global public health problem.

Nitric oxide (NO), catalyzed by nitric oxide synthase (NOS) *in vivo*, is a physiologic messenger molecule that plays an essential role as a regulator in many biological processes, including regulating blood flow, platelet function, immunity, and neurotransmission [7–9]. NO is present in exhaled gases, most of which in healthy people come from the upper respiratory tract, and very few come from the lower respiratory tract and lungs [10]. Under physiological conditions, NO is very important to maintain normal function of the nasal cavity, including the regulation of nasal mucosal blood flow, gland secretion, cilium movement, and antibacterial and antiviral action [11,12]. However, abnormal levels of NO are directly related to the occurrence of nasal diseases [13,14]. NO, an extremely active free radical, may activate cyclooxygenase or lipoxygenase to cause tissue damage [15,16]. In addition, the peroxide nitrite produced by NO and peroxides is toxic to tissue [17]. The downregulation of NO weakens the body's defenses against pathogens, vasodilatation, and mucociliary activity of mucous membrane, which causes the occurrence of disease in the nasal cavity and the whole respiratory tract [18,19]. In cavitary organs, NO is produced from the surface structure of the mucosa and diffuses into the cavity [20]. Detection of fractional exhaled nitric oxide (FeNO) by collecting gas in the cavity is a new noninvasive airway inflammation detection technique [21–24]. It has the advantages of being quantitative, non-invasive, easy to use and safe, and has high specificity and sensitivity [25–28]. By detecting rhinogenous NO of exhaled gas in patients, the noninvasive, accurate, rapid, and early diagnosis of sinusitis or even the diagnosis of rhinitis caused by different etiologies is achieved at the molecular level.

In the present study we investigated the FeNO levels in 35 patients with nasal inflammation and 30 healthy subjects. The diagnostic value of FeNO was evaluated in chronic rhinitis patients and chronic rhinosinusitis patients, which, to the best of our knowledge, has not been previously performed.

Material and Methods

Patients

The ethical approval in this cross-sectional study was granted from the ethics and scientific committees at Daqing Oilfield General Hospital, Daqing, China. In order to participate in our study, all patients and healthy subjects had to provide written informed consent. From December 2016 and June 2017, 35 patients with confirmed nasal inflammation and 30 healthy subjects were recruited into this study. Before FeNO detection, a complete baseline diagnostic evaluation was performed, including anterior nasal endoscopy, nasal secretion smear pathogenic bacteria detection, and CT diagnosis of paranasal sinuses. Further examinations, including position drainage and X-ray nasolacrimal duct angiography, were performed if clinically indicated. The definitions of 'chronic rhinitis', 'chronic rhinosinusitis', and 'chronic rhinitis with chronic rhinosinusitis' were based on previous guidelines for diagnosis and treatment of chronic rhinosinusitis [29]. According to the diagnostic criteria, 13 patients were diagnosed with chronic rhinosinusitis including chronic rhinosinusitis with nasal polyp (6 patients) and fungal rhinosinusitis (3 patients), 6 patients were diagnosed with chronic rhinosinusitis with nasal polyp, and 3 patients were diagnosed with fungal rhinosinusitis. According to the guidelines for diagnosis and treatment of chronic rhinosinusitis [29], 16 patients were diagnosed with chronic rhinitis and 6 patients were diagnosed with chronic rhinitis with chronic rhinosinusitis. All candidates met the requirements of FeNO detection. We excluded patients and healthy subjects who had upper and lower respiratory tract infection within the past month, or who had allergic disease, nasal surgery, paranasal sinus cyst, nasal tumor, or nasal polyp. There were no patients who had systemic or topical medication within the last 2 weeks or who had serious systemic diseases. We excluded patients and healthy subjects who smoked tobacco or drank alcohol. Women who were menstruating or pregnant were also excluded. A summary of the baseline characteristics of patients and healthy subjects is presented in Table 1.

FeNO detection

All tests were carried out indoors with no smell of flowers, dust, furniture, or wall paint and other decorations. The indoor temperature was 20°C to 28°C and the humidity was 20% to 60%. Within 2 h before testing, all patients and healthy subjects were fasted and did not consume coffee, tea, carbonic acid, soy milk, or overcooled/overheated drinking water, and did not perform any vigorous exercise or engage in active or passive smoking. The FeNO level was measured using a Nanocoulomb nitric oxide analyzer (Sunvou, Shanghai, China). The patients and subjects were seated without a nasal clip. After exhaling to the residual gas position, they held the mouthpiece and

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Table 1. Clinicopathological characteristics of nasal inflammation patients and healthy subjects.

Clinical characteristic	Patients (n=35)	Healthy subjects (n=30)	*P* value
Gender			
Male	19	16	>0.05
Female	16	14	
Age (year)			
Mean age	40.74±15.22	42.16±16.83	>0.05
Smoking			
Current	12	10	
Former	7	6	>0.05
Never	6	4	
Side			
Left	17	15	>0.05
Right	18	15	
Course of disease (month)			
Median time	31.53±45.98	/	
Symptom			
Rhinobyon	32	/	
Purulent nasal mucus	17	/	
Headache	11	/	
Position			
Maxillary sinus	19	/	
Ethmoid sinus	17	/	
Frontal sinus	8	/	
Sphenoid sinus	6	/	
Nasal septum	33	/	
Inferior turbinate	28	/	
Middle turbinate	10	/	
Nasal polyp	7	/	

inhaled to make NO-free air enter the lungs and reached the total lung volume, then exhaled at about 10 mL/s for about 10 s. Using animated demo program monitoring, the whole breath process of patients and subjects were kept in the green area until the end of the display time. The FeNO value was recorded and measured continuously 3 times.

Statistical analysis

In this study, Statistical Product and Service Solutions (SPSS) 23.0 statistical software (IBM, Armonk, NY) was used for all statistical analyses. Data are presented as mean ±SD. The significance of mean values was analyzed by *t* test. The chi-square test was used to evaluate the constituent ratios in both groups. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic potential of FeNO for chronic rhinitis and chronic rhinosinusitis. A *P* value <0.05 was considered significant.

Results

The discernment of FeNO in patients with nasal inflammation

To assess differences in FeNO between healthy subjects and patients with nasal inflammation, the level of FeNO was measured using a Fractional Exhaled Nitric Oxide Detector. As shown

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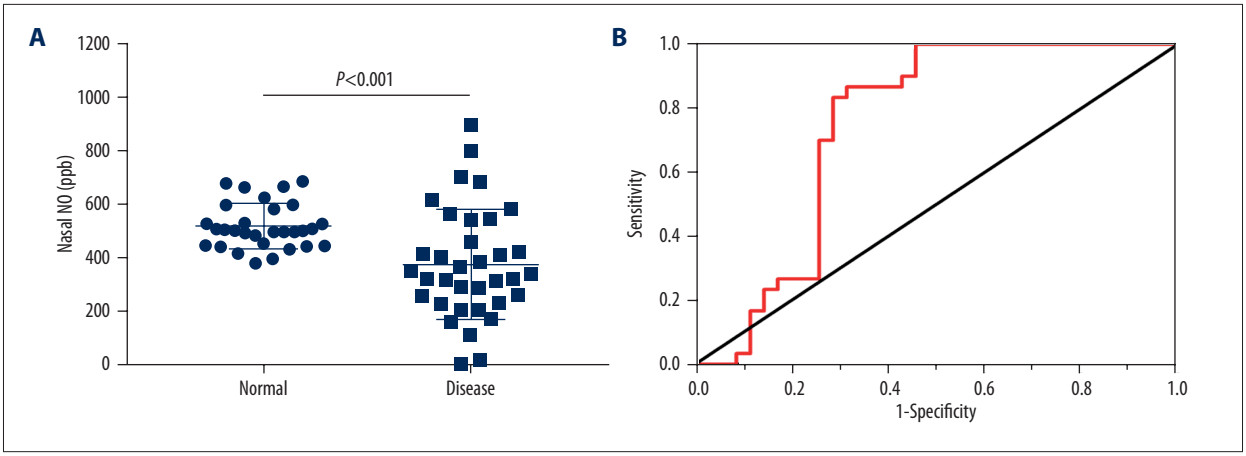

Figure 1. The diagnostic potential of FeNO for nasal inflammation. (**A**) The level of FeNO in nasal inflammation patients and healthy subjects. (**B**) ROC curve of FeNO was used as a biomarker for nasal inflammation diagnosis.

Table 2. Clinicopathological characteristics of 35 patients with nasal inflammation.

Clinical parameter	H-FeNO group (n= 11)	L-FeNO group (n= 24)	*P* value
Gender			
Male	6	13	>0.05
Female	5	11	
Age (year)			
Mean age	38.27±16.21	41.88±14.97	>0.05
Course of disease (month)			
Median time	50.18±47.26	44.63±68.28	>0.05
NO rate			
Mean NO rate	2159.79±978.20	5454.77±1731.59	<0.05
Side			
Left	3	14	>0.05
Right	8	10	
Symptom			
Rhinobyon (Y/N)	11/0	21/3	>0.05
Purulent nasal mucus (Y/N)	4/7	13/11	>0.05
Headache (Y/N)	0/11	11/13	<0.05

as in Figure 1A, we found the level of FeNO in patients with nasal inflammation was significantly lower than in healthy subjects. The ROC curve was used to estimate the diagnostic value of FeNO. The ROC curve (Figure 1B) showed that the AUC was 0.760 (95% confidence interval (CI): 0.632–0.888). FeNO level was selected as the critical value of nasal inflammation diagnosis when the Youden index (the sensitivity plus the maximum –1 value) was the largest. The cut-off value of FeNO was 412.73 ppb, and its sensitivity and specificity were 93.30% and 68.60%, respectively. Collectively, these data demonstrated that FeNO had a higher resolution in identifying nasal inflammation.

The relationship between FeNO level and clinicopathological factors in rhinitis patients

According to the cut-off value of ROC curve of FeNO in expiratory air, the 35 patients with rhinitis were classified into 2 groups: the L-FeNO group (n=24, FeNO level ≤412.73 ppb) and the H-FeNO group (n=11, FeNO level ≥412.73 ppb). The clinical and pathological data of 35 patients with rhinitis listed in this study were compared by chi-square test and are displayed in Table 2. The FeNO level was correlated with NO rate ($P<0.05$) and headache ($P<0.05$). However, no relationship between FeNO level and other factors such as gender,

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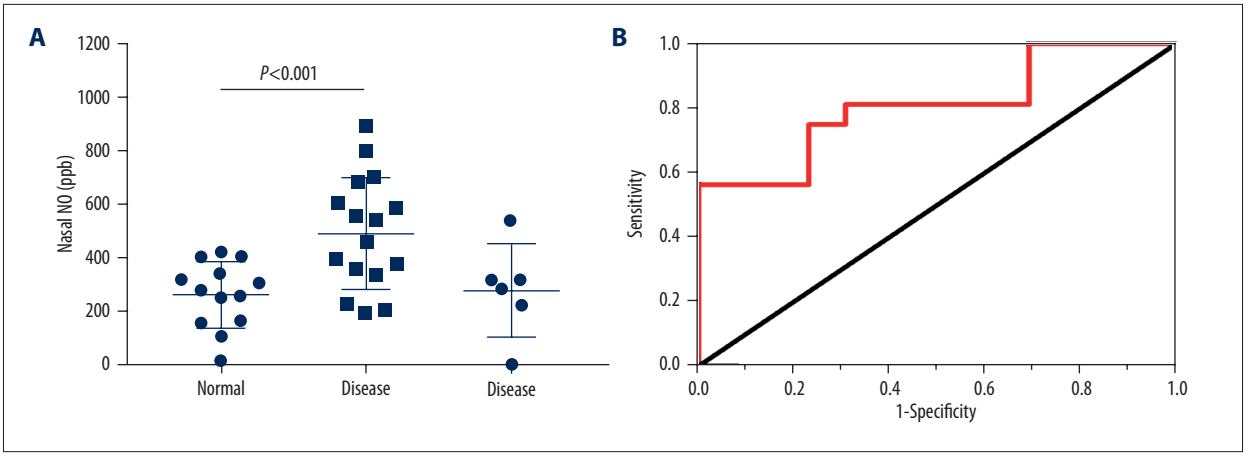

Figure 2. The diagnostic potential of FeNO for chronic rhinosinusitis. (**A**) The level of FeNO in chronic rhinosinusitis (CRS), chronic rhinitis (CR), and chronic rhinitis with chronic rhinosinusitis (CRwCRS). (**B**) ROC curve analysis of FeNO was used for discriminating chronic rhinosinusitis patients from rhinitis patients.

mean age, course of disease, side, rhinobyon, and purulent nasal mucus was found.

Evaluation of the diagnostic potential of FeNO for chronic rhinosinusitis

To verify the utility in distinguishing between chronic rhinosinusitis patients and chronic rhinitis patients, the FeNO levels and the ROC curves were further assessed. The results in Figure 2A show that the level of FeNO in patients with chronic rhinosinusitis was significantly lower than that of patients with chronic rhinitis. However, no significant differences between patients with chronic rhinosinusitis and patients with chronic rhinitis and chronic rhinosinusitis (CRwCRS) were seen. As shown in Figure 2B, the cut-off value of 329.00 ppd was equal to sensitivity+specificity–1, which was maximal for FeNO. At the cut-off value of 329.00 ppd for FeNO, the sensitivity was 81.30% and the specificity was 69.20% with an AUC of 0.808 (95% CI=0.649–0.966). Taken together, these data suggest that FeNO is a useful marker for discriminating chronic rhinosinusitis patients from chronic rhinitis patients.

Evaluation of the relationship between FeNO level and histological type of chronic rhinosinusitis

We further assessed the ability to distinguish between different histological types of chronic rhinosinusitis. The results in Figure 3 show there were no significant differences in FeNO level between chronic rhinosinusitis and other classifications such as chronic rhinosinusitis complicated with nasal polyp, fungal rhinosinusitis, or chronic rhinosinusitis with chronic rhinitis ($P>0.05$). The results showed that FeNO has poor ability to distinguish between different histological types of chronic rhinosinusitis.

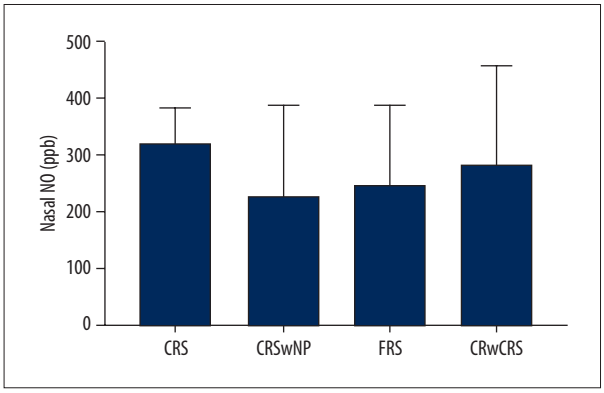

Figure 3. The level of FeNO in different histological type of chronic rhinosinusitis. chronic rhinosinusitis (CRS), chronic rhinitis (CR), chronic rhinosinusitis with nasal polyp (CRSwNP), and chronic rhinitis with chronic rhinosinusitis (CRwCRS).

Discussion

The level of NO in the oral and transnasal exhalation is an indicator of the degree of inflammation in the upper and lower airway [30]. Wang et al. [31] reported that the degree of FeNO changes reflect the severity of different respiratory disease. Therefore, FeNO may have a maximum accuracy in early diagnosis of sinusitis or even in the diagnosis of sinusitis caused by different etiologies. FeNO detection technology was developed in recent years and can detect nasal NO. In the present study, we investigated the levels of FeNO in nasal inflammation patients and evaluated the diagnostic value of FeNO in nasal inflammation patients. Our study found that FeNO levels were significantly lower in nasal inflammation patients than in healthy subjects and in chronic rhinosinusitis patients relative to chronic rhinitis patients. ROC curve analysis showed that FeNO had a higher resolution in identifying nasal inflammation

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and FeNO was a useful marker for discriminating chronic rhinosinusitis patients from chronic rhinitis patients. However, FeNO had a poor ability to distinguish different histological types of chronic rhinosinusitis. The evidence shows that FeNO has potential as a diagnostic marker of chronic rhinosinusitis.

Chronic rhinosinusitis is a chronic inflammation of the nasal sinuses caused by repeated attacks of acute sinus infections, in which the mucosa of the nasal sinuses undergoes pathological changes and loses ciliary epithelium function [32,33]. Chronic rhinosinusitis can result from mechanical obstruction, allergic reactions, bacterial or fungal infections, and other chronic diseases [34,35]. Clinical manifestations of chronic rhinosinusitis are similar to the symptoms of rhinallergosis, influenza, and hypertrophic rhinitis, and were not distinguished easily, which cause a variety of complications, including orbital wall osteitis, periostitis, retrobulbar optic neuritis, epidural abscess, and purulent meningitis [36,37]. Therefore, accurate diagnosis of sinusitis or even the diagnosis of rhinitis caused by different etiologies is of great significance. The level of NO is closely related to many pathological processes [30]. In clinical guidelines based on the ATS/ERS consensus, rhinogenic NO levels below 125 ppb (10 mL/s) suggest Kartagener syndrome, primary ciliary dyskinesia, or cystic fibrosis [38]. In this study, we found that FeNO levels in patients with nasal inflammation were significantly downregulated. Increasing evidence shows that the level of eNOS is decreased in nasal polyps epithelial cells, glandular epithelial cells, and infiltrating inflammatory cells, resulting in decreased levels of NO [39]. Low NO levels reduce blood flow and secretion of nasal glands, as well as weakened ciliary movement and antibacterial effects, which cause nasal inflammation [40]. ROC curve analysis showed FeNO had a higher resolution in identifying nasal inflammation, with higher AUC and sensitivity. While, the specificity was not very high. However, high levels of NO, an extremely active free radical, promote inflammation or cytotoxicity of non-injured cells, and exacerbate autoimmune tissue damage. Therefore, we hypothesized that high levels of NO cause deviation of the nasal septum and further causes nasal inflammation. Some patients with nasal inflammation have lower levels of NO, while some patients with nasal inflammation have higher levels of NO. Follow-up studies and clinical sampling are needed to confirm this hypothesis. Nasal inflammation patients can be distinguished by their higher or lower levels of NO.

Further analysis indicated that there are differences in NO levels between chronic rhinitis and chronic sinusitis patients. This might be due to the different locations and cause of disease. However, we found no significant differences between patients with chronic rhinitis with chronic rhinosinusitis and those with chronic rhinitis or chronic rhinosinusitis, possibly because our sample size was too small. Significantly, ROC curve analysis showed that FeNO is a useful marker for discriminating chronic rhinosinusitis patients from chronic rhinitis patients, which could assist in early diagnosis and treatment of chronic sinusitis and overcomes the need for additional multiple diagnoses. However, FeNO does not have a high specificity, which may be due to a variety of causes. We further found that FeNO had poor ability to distinguish between different histological types of chronic rhinosinusitis, perhaps due to the insufficient sample size and differences inf pathogenic factors and clinical symptoms.

Conclusions

Our study shows that there is a downregulated level of FeNO in rhinitis patients and in chronic rhinosinusitis patients. Furthermore, our results highlight that FeNO is a useful marker for discriminating between rhinitis and chronic rhinosinusitis, and may offer valuable information in the early diagnosis of chronic rhinosinusitis.

Conflict of interest

None.

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