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The correlation between FeNO and nNO in allergic rhinitis and bronchial asthma

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Abstract

This study aimed to evaluate the correlation between fractional exhaled nitric oxide (FeNO) and nasal nitric oxide (nNO) in allergic rhinitis (AR) and patients with or without bronchial asthma (BA).

A total of 90 patients who were diagnosed with persistent AR (AR group, $n=30$), BA (BA group, $n=30$), or allergic rhinitis with bronchial asthma (AR-BA) (AR-BA group, $n=30$), were enrolled in this study, along with 30 healthy adult volunteers (control group, $n=30$). The participants were further divided into 2 groups based on the results of a skin-prick test (SPT): a highly atopic group (SPT=3+ and above) and a moderately atopic group (SPT=2+ and below). All participants underwent FeNO and nNO measurement, an absolute blood eosinophil count, total serum immunoglobulin measurement, and horizontal baseline lung capacity determination.

The results showed that the FeNO levels in the 3 observation groups were significantly higher than those in the control group ($P<.01$), and in the BA group they were significantly higher than in the AR-BA group ($P<.01$). The levels of nNO in both the AR group and the AR-BA group were higher than those in the control group and the BA group ($P<.01$), but there was no significant difference between the AR group and the AR-BA group ($P>.05$). The levels of nNO in the BA group were also significantly different from those in the control group ($P<.01$).

FeNO and nNO are positively correlated with the degree of AR in patients with BA; therefore, nNO levels can be used as an inflammatory marker of AR in patients with BA. FeNO can also be used as an inflammatory marker of AR in patients complicated with BA as a warning indicator of asthma.

Abbreviations: AR = allergic rhinitis, AR-BA = allergic rhinitis with bronchial asthma, BA = bronchial asthma, EOS = absolute eosinophil count, FEF = medium/forced expiratory volume, FeNO = fractional exhaled nitric oxide, FEV1 = forced expiratory volume per second, FVC = forced vital capacity, IgE = total serum immunoglobulin, nNO = nasal nitric oxide, NO = nitric oxide, PEF = peak expiratory volume, SPT = skin-prick test.

Keywords: allergic rhinitis, atopic status, bronchial asthma, FeNO, nNO

1. Introduction

Nitric oxide (NO) is widely distributed in the tissues of all organisms and is a type of biological messenger molecule.[1] It is mainly dependent on NO synthase production in the epithelial and inflammatory cells of inflammatory airway diseases.[2–4] It is also an important endogenous mediator in the upper and lower respiratory tract.[5] Gustafsson et al[6] first demonstrated the presence of NO in oral exhalation (fractional exhaled nitric oxide [FeNO]) in 1991 and found a significant increase in FeNO content in asthmatic patients in 2010.[7] The measurement of FeNO has been gradually standardized, and has now become a non-invasive method for the diagnosis and evaluation of respiratory diseases.[8] Nose breath NO (nasal nitric oxide [nNO]) is mainly produced in the epithelial cells of the sinus mucosa cilia and can increase the cilia activity.[9,10] Although it has been used in some clinical reports, the clinical application value of nNO has not yet received broad recognition.[11–14]

Allergic rhinitis (AR) is a common disease that affects approximately 25% of the world's population. It continues to increase in prevalence[15] and is strongly associated with asthma.[16] Most asthmatic patients have associated AR, and up to 40% of AR patients suffer from asthma.[17] In patients with AR —particularly those who are highly reactive—the increase of nNO may indicate an increased risk of airway inflammation and asthma.

The present study aimed to analyze the correlation between FeNO and nNO in patients with AR with or without bronchial asthma (BA) in order to evaluate the value of FeNO and nNO in the diagnosis and treatment of AR.

2. Materials and methods

2.1. Participants

In this study, 90 cases of persistent AR (AR group, $n=30$), allergic BA (BA group, $n=30$), or allergic rhinitis with bronchial

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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asthma (AR-BA group, $n=30$) and 30 healthy adult volunteers (control group) were enrolled between January 2019 and October 2019. The enrolled patients included 78 males (65%) and 42 females (35%) and were aged between 18 and 66, with an average age of 39.9 years. The 4 groups were further divided into 2 groups based on the results of skin-prick test (SPT): a highly atopic group (SPT = 3+ and above) and a moderately atopic group (SPT = 2+ and below). All patients with AR were sensitized by dust mites and had no obvious anatomical abnormalities, such as a deviated nasal septum. All patients in the observation groups were in the stage of attack, had no history of nasal surgery, and had not received any systemic or topical medication in the 4 weeks prior to the study. The diagnosis of BA was based on the recommended standards of BA prevention and treatment of the Asthma Group of the Respiratory Society of the Chinese Medical Association (2016).[18]

All subjects underwent a series of investigations, including FeNO and NNO measurement, an allergen SPT, absolute blood eosinophil count, total serum immunoglobulin (IgE) measurement, and horizontal baseline lung capacity determination. Subsequent analysis was conducted in accordance with the Guidelines for the Diagnosis and Treatment of Allergic Rhinitis (2009), the diagnostic criteria of Wuyishan,[19] and Allergic Rhinitis and its Effect on Asthma (2010 revision).[20]

All subjects provided written informed consent, and the research plan was approved by the Ethics Committee of our hospital.

2.2. Inclusion and exclusion criteria

Inclusion criteria: patients who were diagnosed with AR; patients who were diagnosed with asthma; patients aged 18 years or older.

Exclusion criteria: patients who had an obvious deviation of the nasal septum; patients who had abnormal anatomical structures.

2.3. The SPT

Fourteen different standardized inhalation origin spines (German Allergo) were used for the SPT: household dust mites, dust mites, dog epithelium, cat epithelium, *Alternaria*, *Cladosporium herbarum*, *Aspergillus fumigatus*, hay dust, willow, pine, *Firmiana simplex* pollen, ragweed, mugwort, and cockroaches. Normal saline and histamine (54.3 mmol/L) were used as negative and positive controls respectively, and a result of at least 1 allergen SPT $\geq$ + was considered a positive reaction.[21] The SPT was conducted by dropping a small amount of highly purified allergen fluid onto the patient's forearm and gently penetrating the skin surface with a prick needle. If the patient was allergic to the allergen, the presence of an allergic disease was determined by the presence of a mosquito bite, an itchy response, or a change in color within 15 minutes.

2.4. Measurement of FeNO and nNO

FeNO and nNO were measured using a nano-Coulomb expiratory meter (Sunvou Medical Electronics) according to the standards of the American Thoracic Society.[24] The average value of nNO in both nasal cavities was taken. The patient was not permitted to eat or undertake any strenuous exercise for 3 hours prior to measurement. A nasal or pharyngeal examination was performed by the same examiner within 1 hour prior to FeNO and nNO measurement.

2.5. Determination of total serum IgE and absolute eosinophil count

Total IgE concentration in the peripheral blood was measured using a Siemens BN^{TM} II special protein analyzer (Siemens), and peripheral absolute eosinophil count (EOS) was measured using a Sysmex XN-1000 eosinophil analyzer (Sysmex).

2.6. Examination of lung function

Spirometry was assessed at room temperature using a Jaeger Masterscreen Body (Wurzburg, Germany), during which the patient was seated upright with a nose clamp. The best of at least 3 consecutive measurements for each patient was recorded. The measurements included forced vital capacity (FVC), forced expiratory volume per second (FEV1), medium/forced expiratory volume (FEF-25%–75%), peak expiratory volume (PEF), and FEV1/FVC. The results were expressed as percentages of the predicted value.

2.7. Statistical analysis

SPSS software (version 15; SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables were expressed as mean $\pm$ standard deviation. Discontinuous variables were expressed as a percentage (%). When data conformed to a normal distribution, comparisons between 2 values were undertaken using an analysis of variance test. Non-normally distributed continuous data were compared using non-parametric tests. Counting data were tested using a χ^2 test. The correlation between variables was evaluated by Pearson coefficient. A value of $P<.05$ was considered statistically significant.

3. Results

3.1. General characteristics (Tables 1 and 2)

This study included 90 patients who were diagnosed with persistent AR ($n=30$), BA ($n=30$), and AR with BA ($n=30$) and 30 healthy adult volunteers. The overall sample consisted of 78 males (65%) and 42 females (35%). The enrolled patients were aged between 18 and 66, with an average age of 39.9 years. There were no significant differences in gender, age, height, weight, or Body Mass Index between the 4 groups ($P>.05$).

3.2. FeNO and nNO determination (Table 3)

The FeNO levels of all 3 observation groups were significantly higher than those of the control group ($P<.01$), and in the AR-BA group and BA group they were significantly higher than in the

Table 1

The description of research participants.

	Research subjects	Control group
Gender [n (%)]		
Male	59 (66)	19 (63)
Female	31 (34)	11 (37)
Age (yr)		
Range	18–66	21–55
Average	39.9	35.5
Course (yr)		
Range	0.5–30	0.5–12
Average	1	1.5

Table 2

Demographic characteristics.

Group	N	M/F	Age	Height	Weight	BMI
BA	30	20/10	46.53 ± 14.08	1.66 ± 0.09	64.48 ± 10.05	23.44 ± 2.79
AR	30	19/11	37.6 ± 14.76	1.66 ± 0.09	65.77 ± 13.74	23.79 ± 3.88
AR-BA	30	19/11	42.07 ± 17.78	1.67 ± 0.08	69.4 ± 11.16	24.68 ± 3.24
Control	30	21/9	33.43 ± 16.2	1.68 ± 0.11	64.73 ± 13.79	22.59 ± 3.21

AR = allergic rhinitis, AR-BA = allergic rhinitis with bronchial asthma, BA = bronchial asthma, BMI = body mass index.

Table 3

FeNO and nNO measurements.

	FeNO			nNO		
	Value	T	*P*	Value	T	*P*
BA	92.8 ± 49.33	8.350	.000*	225.57 ± 68.53	1.169	.248
AR	21.6 ± 6.32	2.734	.008*	684.4 ± 258.95	9.434	.000*
AR-BA	50.9 ± 29.11	6.222	.000*	596.27 ± 213.23	9.043	.000*
Control	16.77 ± 7.7	/	/	192.11 ± 113.13	/	/

AR = allergic rhinitis, AR-BA = allergic rhinitis with bronchial asthma, BA = bronchial asthma, FeNO = fractional exhaled nitric oxide, nNO = nasal nitric oxide.
* $P<0.01$

AR group ($P < .01$). The FeNO levels of the BA group were also significantly higher than those of the AR-BA group ($P < .01$).

The nNO levels of the AR group and AR-BA group were significantly higher than those of the control group and BA group ($P < .01$); although the nNO levels of the AR group were slightly higher than those of the AR-BA group, there was no significant difference between them ($P > .05$). There was also no significant difference between the BA group and the control group in nNO levels ($P > .05$).

3.3. SPT results and NO levels (Table 4)

The evaluation criteria (using histamine as the standard) were ++ + regardless of the size of the pimple caused by histamine, ++++ for a dermicula larger than the histamine, +++ for a dermicula as large as the histamine, and ++ and + for a dermicula smaller than the histamine. The longest diameters and the vertical transverse diameters of the wheal and redness were measured separately with a straightedge. And the average was taken after adding the two, which was called the average diameters (in principle, the wheal reaction prevailed, while the redness reaction was only used for reference). In order to record the reaction form, 2 circles can be drawn with a ballpoint pen according to the outer edge of the wheal and redness, with a solid line for the inner circle of the wheal and a dashed line for the outer circle of the redness. Then use transparent tape to flatten on the wheal and redness, make the circle color stick to the tape, remove it and transfer it to the calculation paper as a record.[22,23]

In the BA group, AR group, and AR-BA group, the FeNO values were significantly higher in patients with SPT results of > +++ than in those with SPT results of +/++ ($P < .05$). In the AR group and AR-BA group, the nNO values were significantly higher in patients with SPT results of > +++ than in those with SPT results of +/++ ($P < .01$), but the differences between these groups and the BA group were not statistically significant ($P > .05$).

3.4. Total serum IgE and EOS detection results and NO levels (Tables 5 and 6)

The total serum IgE and EOS levels in the BA, AR, and AR-BA groups were significantly higher than those in the control group ($P < .01$). nNO level was significantly correlated with total serum IgE level ($P < .01$), while FeNO level was not ($P > .05$). FeNO and nNO level were both significantly correlated with EOS level (both $P < .01$).

3.5. Spirometry

There was a significant decrease in lung function parameters, including FEV1, PEF, FEV1/FVC, FEF-25%, and FEF-50% in the BA and AR-BA groups compared with the AR and control groups. However, FEV1, FVC, and FEV1/FVC were not significantly correlated with FeNO and nNO levels.

4. Discussion

The present study found that the FeNO levels in the 3 observation groups were significantly higher than those in the control group,

Table 4

Skin-prick test results and NO.

		BA	AR	AR-BA	Control
FeNO	+/++	77.58 ± 39.82*	14.21 ± 5.32**	65.92 ± 23.21*	16.77 ± 7.22
	>+++	102.55 ± 42.35	23.35 ± 4.43	98.21 ± 22.30	
nNO	+/++	212.32 ± 45.82	494.15 ± 148.35*	443.21 ± 132.23*	192.11 ± 113.13
	>+++	236.25 ± 32.11	720.21 ± 94.42	614.25 ± 162.25	

AR = allergic rhinitis, AR-BA = allergic rhinitis with bronchial asthma, BA = bronchial asthma, FeNO = fractional exhaled nitric oxide, nNO = nasal nitric oxide, NO = nitric oxide.
* $P<0.01$
** $P<0.05$

Table 5

IgE and EOS detection results.

	BA	AR	AR-BA	Control
IgE (IU/mL)	202.20 ± 145.98**	462.87 ± 472.57**	220.69 ± 138.08**	58.27 ± 27.80
EOS (10^{-9}/L)	0.46 ± 0.23**	0.44 ± 0.13**	0.42 ± 0.16**	0.21 ± 0.09

AR = allergic rhinitis, AR-BA = allergic rhinitis with bronchial asthma, BA = bronchial asthma, EOS = absolute eosinophil count, IgE = total serum immunoglobulin.
** Compare to control group, $P < .01$.

and the FeNO levels in the BA group were significantly higher than in the AR and AR-BA groups. FeNO measurement is a commonly used and effective method for the diagnosis and evaluation of asthma. Because of its non-invasive characteristics, it is also being increasingly applied to the evaluation of the diagnostic and therapeutic effects on patients. nNO testing has also become an important method of assessing the degree of AR. The present study found that the nNO value of patients with AR was significantly higher than that of healthy people and patients with BA. Therefore, nNO can be used as a biomarker and therapeutic evaluation index for the diagnosis of allergic and non-allergic diseases of the nose.[18]

Previous studies[18,21,22] have found that the FeNO values of patients with asthma and those with asthma combined with AR are significantly higher than those of healthy adults or patients with only AR. Consistent with these findings, the present study found that the FeNO levels in the BA group and AR-BA group were higher than those in the control group and AR group (both $P < .01$), but there was no statistically significant difference between the AR group and the control group. There was, however, a statistically significant difference between the FeNO levels of the moderately atopic patients and the control group ($P < .05$) but no statistically significant difference between the highly atopic patients and the control group ($P > .05$). There was also a significant difference in gender between the highly atopic and moderately atopic groups ($P < .05$). These results suggest that an increase in allergy in patients with asthma leads to gradually aggravated nasal airway inflammation and an increased risk of AR. Therefore, FeNO levels can be used as a biomarker to predict the risk of AR in asthmatic patients. With the continuous increase of FeNO level, the possibility of AR also increases. Prevention and treatment measures should therefore be given in advance.

The present study also found that patients with AR and those with AR combined with BA had significantly higher nNO levels than healthy adults and patients with only BA, but there was no significant difference between the AR group and AR-BA group. The elevated nNO levels in patients with AR are caused by the elevated expression of NO synthase, a mechanism that is similar to that of the elevated NO levels in patients with BA. Furthermore, the present study found that the nNO levels in asthmatic patients increased with the increase of atopic degree, and there was a significant difference between the nNO levels of the highly atopic group and the moderately atopic group. With the aggravation of asthma, nasal airway inflammation gradually aggravates, making AR more likely to occur. Therefore, nNO levels can be used to predict the risk of AR in patients with asthma. The findings of Williamson et al[23] are consistent with these results. However, nNO is not as stable as FeNO and may be affected by many factors. Over time, the characteristics of the disease begin to change, so a change of 20% to 25% or less is considered a normal fluctuation rather than a disease state.[24] For some diseases, such as primary ciliary dyskinesia and cystic fibrosis, however, nNO levels are extremely low and nNO measurement can therefore be a useful screening tool.[25]

Table 6

The correlation analysis between FeNO, nNO and IgE, EOS.

	Correlation coefficient	
	IgE (IU/mL)	EOS (10^{-9}/L)
FeNO	0.068	0.482**
nNO	0.370**	0.252**

EOS = absolute eosinophil count, FeNO = fractional exhaled nitric oxide, IgE = total serum immunoglobulin, nNO = nasal nitric oxide.
** $P < .01$.

The elevated nNO levels identified in the patients with AR in the present study suggest that nNO levels may be an important marker of upper respiratory tract inflammation. Kumar et al[26] and Strunk et al[27] showed that the degree of a positive SPT result was proportional to FeNO levels. Consistent with these findings, the present study also found that the FeNO levels in the AR-BA group were positively correlated with the degree of a SPT positive response, and FeNO levels were found to increase with the aggravation of the degree of allergy. Furthermore, the present study identified a significant correlation between nNO levels and a positive SPT test result. However, Moore et al[28] found that the FeNO levels in patients with asthma were not always positively correlated with the degree of a positive SPT result.

The present study had several limitations. First, the trial was not randomized and controlled. Second, it was a single-center trial, and the sample size was limited. The correlation between FeNO and nNO levels in AR and BA should therefore be studied further with larger sample sizes in multicenter trials.

5. Conclusion

The present study found that the FeNO levels in patients with BA were significantly higher than those of healthy adults, the nNO levels of patients with AR were significantly higher than those of healthy adults, and both the FeNO and nNO levels in patients with in AR combined with BA were higher than those of healthy adults. The test results were also positively correlated with the atopic degree of the patients. A patient's FeNO level reflects the degree of inflammation in the lower respiratory epithelial cells, which can be used in the clinical diagnosis and evaluation of the therapeutic effect of BA.

The results of the present study suggest that lung function and FeNO measurement may be useful for the diagnosis of asthma in children and adolescents. It was found that lung function parameters FEV1, PEF, FEV1/FVC, FEF-25%, and FEF-50% were significantly decreased in patients with BA and BA combined with AR compared with healthy adults and patients with only AR. However, the parameters FEV1, FVC, and FEV1/FVC had no significant correlation with FeNO and NNO levels.

FeNO and nNO both have a certain clinical value in the diagnosis and evaluation of therapeutic effect in patients with AR or BA, as a patient's atopic status affects their FeNO and nNO levels. Therefore, both FeNO and nNO levels can be used for the early identification of airway inflammation, as well as in the diagnosis of BA and AR and the evaluation of therapeutic efficacy. They can both be used as an inflammatory marker of AR in patients with BA, while FeNO levels can be used as an early warning indicator of BA.

Author contributions

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