Comparison of orally exhaled nitric oxide in allergic versus nonallergic rhinitis

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ABSTRACT

Background: Fractional exhaled nitric oxide (FeNO), a well-known marker of airway inflammation, is rarely evaluated in rhinitis of different etiology. We aimed to compare the eNO levels in allergic rhinitis (AR) and nonallergic rhinitis (NAR) with/without asthma, as well as the contributing factors that interfere with elevated FeNO.

Methods: Patients were enrolled based on chronic nasal symptoms. Orally exhaled NO was measured with the single exhalation method at 50 mL/s. All subjects underwent a panel of tests: skin-prick tests, asthma control test, blood sampling, spirometry, and health-related quality-of-life questionnaires.

Results: The study group consisted of mainly women (130 women/41 men), with a mean age of 32.6 ± 13.2 years. AR was diagnosed in 122 (78.2%), NAR in 34 (21.8%), and 15 subjects were healthy controls. FeNO was insignificantly higher in patients with AR compared with patients with NAR and controls (32.2 parts per billion [ppb] versus 27 and 19.4 ppb), with no difference between genders. NAR + asthma had higher FeNO than those without asthma (40.5 ppb versus 14.9 ppb; $p < 0.03$), whereas accompanying asthma did not affect FeNO levels in the AR group. AR $\pm$ asthma had significantly higher FeNO levels than the NAR-only group ($p < 0.01$). Among AR + asthma, perennial sensitization caused higher FeNO levels than did seasonal allergens (48.5 ± 33.9 and 19.5 ± 13.6 ; $p = 0.003$), whereas FeNO was significantly higher during the allergen season. Nasally inhaled corticosteroids insignificantly reduced FeNO levels in all groups. Severity and seasonality of rhinitis, asthma, and ocular symptoms, but not gender, age, body mass index, Total IgE, forced expiratory volume in 1 second, and smoking, were associated with FeNO.

Conclusion: Rhinitis and comorbid asthma are responsible for increased FeNO, irrespective of atopy. However, NAR without asthma may not be considered as a strong risk factor for airway inflammation.

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The magnitude of nitric oxide (NO) concentration in exhaled breath is believed to increase in proportion with airway inflammation. Measuring fractional exhaled nitric oxide (FeNO) is a validated inflammatory marker in the diagnosis and management of patients with asthma, atopy, and allergic rhinitis (AR).^{1–3} It is a useful, reproducible, noninvasive tool and easy to perform in a short time. However, interpretation is usually difficult because of interfering factors such as height, age, gender, lung function, smoking, and respiratory tract infections.^{4,5}

In healthy subjects most of the bronchial NO production originates from the proximal large airways. Although several studies have shown that patients with atopic asthma have higher levels of FeNO than patients with nonatopic asthma, atopy can not always be a significant predictor of FeNO in asthmatic patients.⁶ The “one-airway, one-disease” concept predicts the inflammation in the upper airways is linked to inflammatory changes in lower airways.⁷ Increased FeNO in patients with AR suggests that either the NO-producing bronchial area is larger in these subjects or that diffusing capacity of NO into the luminal area is augmented due to the physical changes of bronchial mucosa. This might reflect changes induced by subclinical lower airway inflammation in AR.⁸ Although many studies have shown elevated FeNO levels in AR, it was rarely evaluated in non-AR (NAR), with no comparison with AR. Likewise, the relationship between presence of rhinitis and asthma has not been clearly established, as shown by FeNO.

Inhaled corticosteroids (ICSs) are the mainstay of treatment for airway inflammation, but the doses necessary to achieve disease control vary considerably over time. There is a need for an easy, effective, and safe method to guide dose titration. In this regard, measurement of orally eNO has been considered a promising nonin-

vasive biomarker as an adjunct to clinical assessment, not only in asthma but also in patients suffering from chronic rhinitis.⁹

We, therefore aimed to evaluate the airway inflammation with FeNO measurement and the factors influencing its level in patients with rhinitis of different etiology. Moreover, we also investigated the impact of atopy, pollen exposure, and pharmacologic treatment on FeNO production.

METHODS

Orally, eNO was evaluated in a series of consecutive patients referred to an outpatient clinic for persistent rhinitis, lasting >4 days/week for >4 consecutive weeks. Rhinitis was diagnosed if the patients had a history of at least two of the following symptoms: nasal itching, sneezing, rhinorrhea, and/or nasal congestion, as described by the Allergic Rhinitis and Its Impact on Asthma guidelines.¹⁰ Asthma was diagnosed based on symptoms with positive reversibility test. Patients with concomitant nasal polyposis, infectious or occupational rhinitis, major structural nasal abnormalities, current sinusitis, and those who were pregnant or lactating were excluded.

FeNO was measured, before spirometry, with the single-breath exhalation method at a flow rate of 50 mL/s, using a chemiluminescence analyzer (NIOX analyzer; Aerocrine, Solna, Sweden).¹¹ Normal ranges of FeNO level were considered to be from 4 to 25 ppb. After respiratory evaluation with spirometry, an asthma control test (ACT) and blood sampling were performed. Skin-prick tests (SPTs) were done with a battery of common inhalant allergens (ALK, Madrid, Spain). Histamine hydrochloride, 10 mg/mL, and phenolated glycerol-saline served as positive and negative controls. The reaction was regarded as positive if the mean wheal diameter was at least 3 mm greater than negative control. AR was defined as nasal symptoms accompanied by SPT positivity with clinical relevance, whereas NAR was defined as nasal symptoms with negative SPTs. The impact of intranasal corticosteroids on FeNO levels was also evaluated.

Health-Related Quality of Life

The Medical Outcomes Study 36-Item Short-Form Health Survey, minirhinitis quality-of-life (QoL) and miniasthma QoL questionnaires

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Table 1 Characteristics of the study group

	AR <i>n</i> = 95	AR + Asthma <i>n</i> = 27	NAR <i>n</i> = 18	NAR + Asthma <i>n</i> = 16	Controls <i>n</i> = 15	Total <i>n</i> = 171
Female/male gender	65/30	22/5	16/2	15/1	12/3	140/31
Age, yr	30.1 ± 12.7	37.9 ± 13.7	31.6 ± 13.1	43 ± 13.1	32.4 ± 8	32.6 ± 13.2
Body mass index, kg/m ²	24.1 ± 5.2	26 ± 5.7	24.9 ± 5.1	28.3 ± 5.7	25.3 ± 6.6	24.9 ± 5.5
FEV ₁ (% predicted)	—	83.4 ± 15.8	—	79.2 ± 14.4	—	81.8 ± 15.2
Total IgE, kU/L	281.8 ± 355.6	599.4 ± 633.4	96.9 ± 120.3	73.4 ± 63.4	—	299.2 ± 418.2
Smoking (%)						
Nonsmoker	68 (73.1)	18 (69.2)	15 (83.3)	11 (68.8)	10 (66.7)	122 (72.6)
Exsmoker	12 (12.9)	5 (19.2)	2 (11.1)	4 (25)	1 (6.7)	24 (14.3)
Smoker	13 (14)	3 (11.6)	1 (5.6)	1 (6.2)	4 (26.6)	22 (13.1)
Duration of rhinitis, yr	6.5 ± 5.3	9.4 ± 5.8	6.5 ± 8.2	9 ± 6.7	—	7.3 ± 6
Mild/moderate to severe rhinitis	15/79	9/18	7/9	6/10	—	37/116
FeNO, ppb	30.3 ± 23.8	38.8 ± 31.6	14.9 ± 8.2	40.5 ± 44.1	19.4 ± 10.7	40.5 ± 44.1

AR = allergic rhinitis; FeNO = fractional exhaled nitric oxide; FEV₁ = forced expiratory volume in 1 s; NAR = nonallergic rhinitis; ppb = parts per billion.

were used for determining generic and specific health-related QoL (HRQoL).

The protocol for this study was approved by the hospital ethics committee.

Statistical Analysis

Statistical analyses were performed using SPSS Version 18 (SPSS, Chicago, IL). Normality of the distribution for the data was tested with Kolmogorov-Smirnov test. Comparisons between more than two groups for nonparametric variables were performed by the Kruskal-Wallis test and Mann-Whitney *U* test was used for subgroup analysis. The group characteristics were compared using the "Fisher exact test" and the chi-square test. A value of *p* < 0.05 was considered statistically significant.

RESULTS

The Characteristics of the Study Population

A total of 171 participants (130 women/41 men) were assessed: 15 healthy controls and 156 patients, 122 with AR (78.2%) and 34 with NAR (21.8%). All the rhinitis patients underwent a stepwise diagnostic approach of rhinitis according to the Allergic Rhinitis and Its Impact on Asthma, resulting in the following subgroup diagnosis: AR only, NAR only, AR + asthma, and NAR + asthma.

Among patients with NAR the prevalence of asthma was significantly higher (47%) than in patients with AR (22.1%; *p* < 0.04). Demographic characteristics were similar in all groups (Table 1). Patients with AR compared with NAR had more severe disease (*p* = 0.01). Duration of rhinitis in coexisting asthma cases was significantly longer than in patients without asthma (*p* = 0.03).

In general, patients with AR (AR only and AR + asthma) had insignificantly higher FeNO levels compared with patients with NAR (NAR only and NAR + asthma) and controls (32.2 parts per billion [ppb] versus 27 and 19.4 ppb), with no difference between genders. In subgroup analysis FeNO levels (ppb) were 19.4 ± 10.7 (C, control), 30.3 ± 23.8 (AR), 38.8 ± 31.6 (AR + asthma), 14.9 ± 8.2 (NAR), and 40.5 ± 44.1 (NAR + asthma; Fig. 1). Patients with asthma had FeNO values significantly higher than patients without asthma in the NAR group (*p* < 0.03), whereas accompanying asthma did not affect FeNO levels in the AR group. AR ± asthma had significantly higher FeNO levels than the NAR only group (*p* < 0.01). Among AR with asthma, patients sensitized to perennial allergens had significantly higher FeNO levels than did seasonal allergens (48.5 ± 33.9 and 19.5 ± 13.6; *p* = 0.003; Fig. 2 A). Moreover, in atopic patients, FeNO measurement during the allergen season was significantly higher compared with off-season values (AR, *p* = 0.01; asthma + AR, *p* = 0.05; Fig. 2 B). The

Figure 1. Comparison of fractional exhaled nitric oxide (FeNO) in study groups.

difference between AR + asthma and NAR + asthma in terms of inhaled steroid use was not significant, because the first-line treatment in chronic rhinitis is similar between two groups of patients. Nasal steroids caused a reduction in FeNO levels in all patient groups, with no statistical significance (Fig. 3).

A significant correlation was found between FeNO levels and atopic sensitization and total rhinitis symptom score (congestion, rhinorrhea, sneezing, and itching; *r* = 0.215 and *p* = 0.007 and *r* = 0.170 and *p* = 0.03, respectively), but not with increasing age, Total IgE, percent predicted of forced expiratory volume in 1 second, and/or smoking history. FeNO was not correlated with asthma symptom scores and ACT in patients with rhinitis. In a multivariate linear regression analysis, FeNO levels were positively associated with severity and seasonality of rhinitis, asthma comorbidity, and ocular symptoms (Table 2). Furthermore, no significant correlations were found between FeNO and HRQoL, as stated by generic (36-Item Short-Form Health Survey) and specific (minirhinitis QoL and min-asthma QoL) questionnaires (results not shown).

DISCUSSION

Airway inflammation appears to be the most important cause of increased FeNO. Because the factors triggering upper airways may

Figure 2. Comparisons of fractional exhaled nitric oxide (FeNO; parts per billion [ppb]) values according to (A) sensitized allergens and (B) in/off the allergen season in allergic rhinitis (AR).

Figure 3. Effect of nasal glucocorticoid treatment on fractional exhaled nitric oxide (FeNO; parts per billion [ppb]) values.

Table 2 Variables associated with FeNO (ppb) values

Variables	β	SE β	p Value
Severity of rhinitis	11.192	4.627	0.02
Seasonality of rhinitis	8.795	4.169	0.04
Asthma comorbidity	12.027	4.719	0.01
Ocular symptoms score	7.257	2.272	0.002

FeNO = fractional exhaled nitric oxide; ppb = parts per billion; β = regression coefficient; SE β = standard error of β .

also influence lower airways, this favors a strong evidence of a causal relationship between rhinitis and asthma.^{12,13}

The aim of the present study was to investigate FeNO levels in patients with rhinitis of different etiology (allergic versus nonallergic), as well as the influencing factors. We also evaluated the impact of asthma on rhinitis in airway inflammation, measured as FeNO.

Generally, in all AR patients, FeNO was slightly but not significantly higher than in all patients with NAR. However, when subgroup analysis was performed AR with/without asthma had significantly higher FeNO levels than only patients with NAR without asthma. Subjects with NAR and asthma exhibited elevated FeNO levels, similar to AR. Our study has a limitation, because the distribution of different subpopulations is not homogeneous concerning the number of patients. However, this is the first investigation—to our knowledge—that compares the airway inflammation between atopic and nonatopic patients by means of FeNO values, in an adult population with chronic rhinitis. Copenhagen Prospective Study on Asthma in Childhood birth cohort showed that only children with AR had elevated FeNO.³ Our findings of elevated FeNO levels in patients with AR is not in accordance with findings of children consistently showing a higher FeNO measurement in AR (with or without asthma) compared with NAR. Jouaville *et al.* have not only shown that nonasthmatic atopic subjects had higher eNO than nonatopic subjects, but also among nonatopic children, the eNO level increased in atopic patients who had rhinitis.¹⁴

FeNO was usually found to be implicated in allergic inflammatory mechanisms. Increased expression of inducible NO synthase was shown to have a role both in the development of allergic inflammation in upper and lower airways and in comorbidity of AR and asthma.^{15–17} In contrast, Giannesi *et al.* found a relationship between the increase in NO synthase expression and the damage in the nasal mucosa of NAR patients.¹⁸ As was shown in our recent study, NAR was around one-fifth of the population with chronic rhinitis.¹⁹ In our present study, higher asthma comorbidity in NAR patients may have been responsible for the insignificant difference compared with AR, using a validated marker of asthma-related inflammation, FeNO. Previous studies showed that those with rhinitis and asthma had significantly higher FeNO values compared with those without asthma.^{9,16,20} In this study, patients with AR but no asthma were still shown to have elevated FeNO levels, as was observed in the Copenhagen Prospective Study on Asthma in Childhood birth cohort.³ Elevated FeNO in patients with AR, irrespective of asthma comorbidity, suggests an increased airway inflammation even in the absence of asthma, whereas the presence of asthma significantly contributes to increased FeNO levels in NAR.

The single exhalation flow rate of 50 mL/s, as recommended by the American Thoracic Society/European Respiratory Society standardizations, is low enough to cause the NO concentration to be predominantly of central airway origin.²¹ However, reference values and determinants of FeNO levels are defined in only certain populations. The geometric mean of FeNO was found to be 17.9 ppb with a 90% confidence interval, in the interpretation of FeNO measurements in white adults.²²

The power of the present study is that many variables are considered in the same cohort. Because spirometry appears to reduce eNO

levels, we performed FeNO measurements before spirometry. Multiple potential influencing factors that can modify FeNO were also evaluated. Although duration of rhinitis does not seem to be an important factor in determining elevated FeNO, severity and seasonality of rhinitis as well as coexisting asthma and ocular symptoms were found to be associated with FeNO, in our atopic and nonatopic patients. Dressel *et al.* suggested that respiratory allergy, smoking, respiratory tract infection, male gender, and height are independent factors of increased FeNO levels,²³ and others explained the association between FeNO and gender by differences in height.²⁴ Conversely, gender, but not height, has been reported as a determinant of FeNO in adults.²⁵ Likewise, there are conflicting data regarding the age effect on FeNO levels. In our study population, no difference was observed for FeNO values in terms of age, smoking history, gender, and body mass index.

We also documented reliable information whether subjects with seasonal allergies were examined in their respective season. This is of interest, because FeNO values that were lower in AR compared with asthma were shown to reach similar levels after allergen exposure.²⁶ Natural pollen exposure was found to cause a significant FeNO elevation in allergic individuals. Thus, IgE-mediated allergy has been reported to be responsible for elevated FeNO.²⁷ We have shown that a significant increase of eNO during the pollen season in atopic rhinitis patients influences the impact of inflammation on the upper airways. Our results are consistent with earlier reports by Henriksen *et al.*²⁸ They found that an increase in eNO on allergen exposure, particularly in hyperresponsive subjects, may be suggestive of airway inflammation and an increased risk for developing asthma in AR. Moreover, elevated FeNO in the nonpollen season, especially in perennially sensitized subjects, increased further in the pollen season, in their study.

The effects of topical nasal glucocorticoids in FeNO are controversial, although most investigations showed that nasal NO levels were significantly lower in treated patients, when compared with untreated groups.²⁹ Ohkura *et al.* found that eNO was not a risk factor for longitudinal decline in forced expiratory volume in 1 second in asthma patients even if their asthma was stable and well controlled by ICSs.³⁰ However, in difficult-to-treat asthma, use of eNO measurement to guide asthma management, and maintenance would be beneficial in increasing asthma control and would result in reduced cost as well.³¹ In an adult study, FeNO could be decreased in a dose-dependent manner by inhaled corticosteroids,³² but nasal corticosteroid treatment was not found to lower airway inflammation in a pediatric population.⁷ The short duration of pharmacotherapy may have explained such conflicting effects. On the contrary, neither antihistamines nor leukotriene antagonists have effect on FeNO in allergic rhinitis patients.³³ Our observation of insignificant reduction in FeNO measurements after nasal steroids is in agreement with other reports that could not detect any decrease in airway inflammation.³⁴ The patients may have had a moderate-to-severe degree of rhinitis, which did not give enough response to ICSs. Another explanation is that no improvement in airway inflammation after nasal glucocorticoid in patients with comorbid asthma suggests a bidirectional link between upper and lower respiratory tract, because a majority of our patients with asthma were already under treatment with inhaled steroids.

Although impairment in QoL was also found to be significantly associated with FeNO in a pediatric population,³⁵ QoL was not found to be directly related in our group of adult patients. Likewise, we did not find an association between FeNO and ACT results, as was reported by Quaedvlieg *et al.*³⁶ in uncontrolled asthma.

Our results emphasize the determination of FeNO levels in rhinitis with nonallergic etiology may provide an early diagnosis of comorbid asthma, because both allergic and NAR have been associated with increased prevalence of asthma. The functions exerted by NO release require further investigation. Thus, elevated levels of FeNO can therefore be regarded as a noninvasive potential clinical tools to monitor

not only asthma, but also rhinitis of different etiology. Such advances will probably enable to more appropriately exploit NO for the diagnosis, treatment, and monitoring of relevant upper respiratory disorders, as well as lower respiratory diseases.

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