

Exhaled and Nasal Nitric Oxide – Impact for Allergic Rhinitis

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Summary

FeNO measurement is a validated non-invasive technique, which is used for diagnosis and monitoring of asthma. It would be desirable to find a reliable method to monitor allergic rhinitis (AR) via measurement of FeNO, and/or nasal nitric oxide (nNO). The aim of our study was the assessment of the efficacy of FeNO and nNO as markers in AR treatment. FeNO and nNO were measured with the portable NO analyser (NIOX MINO®) in healthy participants and in patients with AR. The patients were examined during the pollen season and out of it. The effect of local corticosteroids and antihistamine therapy was observed in patients with AR during pollen season after three weeks of therapy. There are significant differences between FeNO and nNO in patients with AR compared to healthy controls at all set points of measurements. While FeNO responded well to the treatment with both antihistamines and combined therapy, nNO decreased only after combined therapy with antihistamines and nasal corticosteroids. nNO monitoring alone is not a suitable method to monitor inflammation of the upper airways in AR and its suppression by anti-allergic treatment and should be correlated with other markers as FeNO or symptom scores.

Key words

Nitric oxide • Allergic rhinitis • Inflammation • Pharmacotherapy

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Introduction

Allergic rhinitis (AR) is the most common allergic disease in both adult and paediatric population. It is frequently under-diagnosed, and therapy is often insufficient. Untreated AR is a risk factor for onset and progression of lower airway diseases, therefore effective treatment of the upper airway inflammation is a preventive measure towards lower airways pathology (Corren 1998).

Nitric oxide (NO) plays a substantial role in airways. It regulates bronchial muscle tone, blood flow and immune response in the lower airways, controls the motion of cilia and regulates defence processes in the upper airways (Struben *et al.* 2006, Antosova *et al.* 2017a). Its concentration increases due to eosinophilic inflammation in the airways what makes the detection of NO perfect diagnostic tool (Jatakanon *et al.* 1998).

While method of exhaled NO (FeNO) measurement reached the clinical practice relatively quickly becoming a reliable tool in the management of asthma (Balbi *et al.* 2007), detection of nNO is not a routine diagnostic method so far, except ciliary disorders (Leigh *et al.* 2013). The reason is an ambiguous approach to detection technology, the difference in devices used for detection, insufficient information about factors that affect nNO (Jorissen *et al.* 2001) together with high inter-individual variability, over-time variation

and lack of universal standardization of testing procedure (Kharitonov *et al.* 1997). There is evidence about the role of NO in the pathogenesis of allergic rhinitis and asthma (Alving *et al.* 1993, Bergmann-Hug *et al.* 2009), however, detection of nNO as a marker in allergic rhinitis is still not validated (Antosova *et al.* 2017b). Some authors suggest, that monitoring of nNO as non-invasive and easy-to-perform techniques can be useful to monitor AR and its clinical course. Our study was aimed to measure FeNO and nNO in healthy volunteers and patients with allergic rhinitis to assess effects of allergen exposure and pharmacotherapy (antihistamines and local corticosteroids) on levels of both FeNO and nNO to ascertain the reliability of nNO detection in management of seasonal AR.

Methods

Study population

The study population consisted of 100 participants. All participants recruited to the control group (n=50) have met the inclusion criteria, they were older than 18 years, have no chronic respiratory disease, no lower airway symptoms (cough, breathlessness, chest tightness etc.), no acute respiratory infection within 3 weeks prior the test, non-smokers with the willingness to cooperate.

All participants with allergic rhinitis recruited to the “rhinitis” group (n=50) have met the inclusion criteria, they were older than 18 years, non-smokers, with positive skin prick tests to common seasonal allergens, seasonal presence of the upper airway/eye symptoms, pharmacotherapy with antihistamines and/or local corticosteroids with willingness to cooperate. Characteristics of the study population are summarized in Table 1.

Measurement

The study was approved by the Ethical

Committee at Jessenius Faculty of Medicine and Martin University Hospital and informed consent was obtained from all participants after the purpose of the study had been explained.

Measurements of FeNO and nNO were performed by analyser NIOX MINO® (Aerocrine, Sweden), specific sensors and filters were used for FeNO and nNO measurements. Procedures were performed according to ATS & ERS guidelines. Subjects were educated about the methods and practical performance of the test, which was carried out in a sitting position after 15 min of rest in the laboratory. In case of FeNO, subjects inhaled air without NO (NO<5 ppb) via mouthpiece with filter until they reached total lung capacity (TLC) and this inhalation was followed by exhalation via mouthpiece lasting up to 10 s with at least 6 s plateau of NO values detected automatically by the device. Exhalation rate was maintained at the flow of 50 ml/s. Values of FeNO were expressed in ppb (parts per billion) (ATS/ERS 2005).

Detection of nNO was performed using the research application of NIOX MINO. nNO was measured in each nostril (RnNO – right nostril, LnNO – left nostril) during passive aspiration of air via special ergonomic olive (filter) at the flow 5 ml/s, with tidal breathing technique with velum closure. Values of nNO from right and left nostril were averaged and expressed in ppb.

Patients with allergic rhinitis were examined out of pollen season, during the pollen season (March – June) without treatment (untreated), during the pollen season after at least 3 weeks of treatment with oral antihistamines and/or nasal corticosteroids. Data from healthy controls were taken irrespective to pollen season. All participants were instructed to avoid factors affecting FeNO and nNO a day prior to the measurement. All participants were examined after 10 minutes of rest, at least 1 hour after the food intake and in the same time of the day respecting diurnal variations of NO production - all patients were examined about 10 a.m.

Table 1. Characteristics of the study population

Participants	n	Age (years)	Weight (kg)	Height (cm)
<i>control – women</i>	30	21.06 ± 3.72	58.7 ± 7.9	168.10 ± 6.4
<i>control – men</i>	20	21.30 ± 1.75	78.9 ± 11.5	182.7 ± 6.3
<i>rhinitis – women</i>	35	39.00 ± 10.92	64.3 ± 10.2	165.2 ± 5.6
<i>rhinitis – men</i>	15	42.50 ± 15.36	87.12 ± 4.92	182.4 ± 4.5

Statistical analysis

Comparison of the average FeNO and nNO values between controls and seasonal AR group and also FeNO and nNO values measured out of the pollen season, then after allergen exposure and after treatment was performed by the t-test and one way-ANOVA. Values of $p < 0.05$ were considered as statistically significant. Data were processed by the SPSS software and Microsoft Excel.

Results

The effect of allergic airway inflammation and medication on FeNO and nNO levels

The value of FeNO in the AR group measured out of the pollen season did not differ from the values of the control group. During the pollen season, after the exposure to aeroallergens and the onset of nasal symptoms the data for FeNO increased significantly to 20.5 ppb, ($p = 0.002$) even the participants did not have any lower airways symptoms (Table 2 and 3).

Similarly, nNO levels were not different

between healthy controls and allergic subjects out of the pollen season. Measurement was performed in both nostrils (right – RnNO and left LnNO) concerning the nasal cycle and then averaged. There were small, however not significant differences between the left and right nasal passages both in control and allergic rhinitis groups.

Values of nNO in subjects with allergic rhinitis were significantly higher after the allergen exposure during the pollen season ($p < 0.001$), for a summary, see Table 2.

All participants with allergic rhinitis were treated with anti-allergic drugs ($n = 50$, 35F, 15M). 24 participants (17F, 7M) were treated by H₁-antihistamines (desloratadine, levocetirizine and fexofenadine), and 26 patients (18F, 8M) with a combination of H₁-antihistamines and local nasal corticoids treatment (beclomethasone, fluticasone and mometasone). Pooled data in the AR group failed to show any significant differences in FeNO and nNO after three weeks of treatment (Table 3).

Table 2. The effect of allergic airway inflammation on FeNO and nNO levels

	Healthy controls (average values)	Allergic rhinitis pooled data (average values)
FeNO (ppb)		
out of the season	16.95 (6.00-38.00)	17.00 (7-70)
allergen exposure	(n.s.)	22.50 (7-72) *
3 wks of treatment	(n.s.)	17.00 (6-65) (n.s.)
nNO (ppb)		
out of the season	393 (150-963)	620 (402-1320)*
allergen exposure	(n.s.)	824 (443 -2003)**
3 wks of treatment	(n.s.)	834 (473 – 1131) (n.s.)

* ($p < 0.05$) vs controls, ** ($p < 0.01$) vs controls, (n.s.) without significant difference

Table 3. The effect of anti-allergic therapy on FeNO and nNO in allergic rhinitis subjects

	n	FeNO (ppb)	FeNO (ppb)	nNO (ppb)	nNO (ppb)
		Allergen exposure	3-week treatment	Allergen exposure	3-week treatment
AR Pooled data	50	21 (7-72) *	17 (6-65) (n.s.)	824 (443-2003) (n.s.)	834 (473-1131) (n.s.)
AR AH treatment	24	22 (7-68) *	18 (7-54) ##	737 (433-1031) (n.s.)	722 (421-1075) (n.s.)
AR AH+CS treatment	26	19 (10-72) *	15 (6-65) ##	875 (489-2003) (n.s.)	813 (315 -1 705) ##

* ($p < 0.05$) vs controls, ## ($p < 0.05$) vs before treatment, (n.s.) without significant difference, AR pooled data – data of all subjects regardless the treatment, 3wks AH – 3 weeks on antihistamines, 3wks AH+CS – 3 weeks on oral antihistamines in combination with nasal corticosteroids

Further analysis of results for the effect of H₁ – antihistamines proved a significant decrease of FeNO as a response to three weeks' treatment. Antihistamines surprisingly did not affect the level of nNO even after separate analysis for antihistamines and corticoids (Table 3). Combination of H₁-antihistamines and nasal corticoids significantly reduced FeNO and nNO values (Table 3) pointing towards the better therapeutic effect of combined therapy for both upper and lower airways.

The effect of gender on FeNO and nNO values

Gender differences in FeNO levels were also detected during data analysis in both control and rhinitis groups with women having a higher concentration of FeNO 19.5 (9-38) ppb vs 15.2 (6-34) ppb, (p<0.05). This pattern continues throughout all measured points in both groups and women have always higher FeNO than men with the highest significance obtained after the treatment (p<0.01) indicating that women with AR have a better response to the treatment than men. No gender differences in nNO were observed neither for control nor allergic rhinitis groups (data not shown).

Discussion

Diagnosis and therapeutic management of allergic airways disease require as precise monitoring of inflammation as possible, therefore, we tested whether nNO could be a reliable marker of AR. Instead of well-established reliability of FeNO measurement in asthma, measurement of nNO is under discussion (Kharitonov *et al.* 1997, Henriksen *et al.* 1999). The idea of nNO measurement is based on “one airway - one disease” concept. Even though asthma and allergic rhinitis vary with the clinical phenotype, Th1/Th2 signalling, main cellular and biochemical profile, they share the main pathogenetic features (Bachert *et al.* 2002). One of them is eosinophilic inflammation that increases the expression of iNOS, leading to increased production of NO (Williamson *et al.* 2010).

Studies about nNO as a marker of allergic rhinitis share conflicting evidence and measurement of nNO is still not validated for routine clinical use (Lee *et al.* 2012). Low reliability of nNO measurement is caused mainly by extremely high variability of nNO values which range from 200 to 2000 ppb (Serrano *et al.* 2004).

The aim of our study was to analyse levels of nNO and FeNO in subjects with AR and to observe the effect of medication during the pollen season on those

levels. Our study showed that FeNO levels did not differ between control and allergic subjects out of the pollen season, but are significantly elevated after the allergen exposure during the season even allergic subjects did not have any symptoms from the lower airways. This finding indicates the presence of inflammation in the lower airways at the sub-clinical level (Corren, 1998, Polosa *et al.* 2000, Bachert *et al.* 2002). Increased levels of FeNO in adults with AR were reported by Downie *et al.* (2004), and other authors (Gratziau *et al.* 2001, Linhares *et al.* 2011). Control of inflammation in the lower airways in allergic subjects is important to prevent the onset of complication in the lower airways. nNO values differed significantly between healthy control subjects and allergic subjects also out of the season, with significant elevation of nNO production after the allergen exposure.

The increase of FeNO and nNO with the start of the pollen season is highly indicative of the increased activity of iNOS, as its expression and activity increases due to allergic inflammation in the airways (Arnal *et al.* 1997). Significant increase of FeNO (p<0.001) and nNO (p<0.001) indicates the presence of inflammation in both compartments – upper and lower airways in subjects with allergic rhinitis.

Our data showed that nNO levels are significantly higher in allergic subjects also out of the pollen season, which is in conflict with other studies which failed to detect elevated levels of nNO in allergic subjects out of the season (Jilma *et al.* 1996, Henriksen *et al.* 1999), however, these studies did not consider the presence of perennially sensitized subjects, which may contribute to such findings.

Gender-related differences were found in the FeNO, but not in the nNO levels. Our data are in agreement with previously published results for both FeNO and nNO (Palm *et al.* 2003). These gender differences in the FeNO were for the first time noticed by Taylor *et al.* (Taylor *et al.* 2006), in a sample consisting of nearly 900 participants, suggesting gender being an important determining factor of FeNO values. Based on the literature data, nNO does not show gender differences (Lee *et al.* 2012) and our data are in agreement with these findings. The difference can be a consequence of different sensitivity of NO synthase isoforms to oestrogen. While the FeNO reflects mainly the activity of iNOS, nasal NO is a product of more isoforms (Yuksel *et al.* 2008). Gender-specific findings in our allergic subjects must be interpreted with caveats, because of the composition of allergic groups where majority of subjects

are women. A higher proportion of men would perhaps bring more clarity to these results.

nNO was measured in both nostrils and then averaged. It is important to notice that there were no differences in nNO levels measured in the right versus left nostril in our subjects. The side-related differences may be a consequence of e.g. impaired communication of the nasal cavity with sinuses at one side due to mucosal swelling or some other types of obstruction in osteomeatal complex, like hyperplastic mucosa, septal deviation, concha bullosa etc. The role of the nasal cycle is important because it can influence the detection process.

The main objective of our work was to assess the response of FeNO and nNO to medication. The guidelines recommend using two main types of medication – antihistamines and nasal corticosteroids. Antihistamines act as inverse agonists of histamine receptors, reducing histamine-induced signalling and the majority of the symptoms (Wang 2002). Corticosteroids reduce eosinophilic inflammation by rather a complex effect (Basyigit *et al.* 2004). Subjects of the rhinitis group were divided into two groups. First one was treated by oral H₁-antihistamines only, while the second group was treated by a combination of oral H₁-antihistamines and nasal corticosteroids. Our subjects were not stratified according to the symptoms severity, because it is known that magnitude of symptoms does not correlate with detected nNO (Lee *et al.* 2012), e.g. patients with massive mucosal oedema and nasal discharge, or eventually patients with occlusion of sinuses have low levels of nNO despite the high intensity of inflammation in the upper airways.

The results showed that monotherapy by H₁-antihistamines reduced significantly the levels of FeNO, but it did not have any effect on nNO. The effect of H₁-antihistamines on FeNO, but not on nNO was gender-specific. Studies showed that antihistamines directly downregulate the expression of iNOS protein and modulate its activity (Yamada *et al.* 2012). Poor effect of H₁-antihistamines on nNO may indicate either ineffective treatment of upper airway inflammation or poor relevance of nNO detection. We speculate that even though the medication caused symptom relief, it was not effective enough to fully suppress eosinophilic inflammation in the nasal cavity and sinuses. Duration of the treatment period was also questionable, but according to the guidelines for clinical trials in allergic rhinitis, the optimal duration of studies assessing treatment efficacy is 2 weeks, and

longer study periods are not likely to add meaningfully to the assessment of drug efficacy (Krouse *et al.* 2005).

Physicians prefer combined treatment with oral antihistamines and local corticosteroids regardless of the magnitude of AR (Navarro *et al.* 2011, Yamada *et al.* 2012). Treatment by the combination of antihistamines and nasal corticosteroids led to the significant decrease of FeNO and nNO ($p < 0.05$) and this effect was more significant for women ($p < 0.001$). These results confirm previous findings that treatment of inflammation in the upper airways leads also to the suppression of inflammation in the lower airways. However, there are studies which failed to show the effect of nasal corticosteroid treatment on nNO levels (Lundberg *et al.* 1997, Maniscalco *et al.* 2001). This conflicting result may not be related strictly to the nNO production, but they are very likely influenced by other factors, such as diffusion impairment, extensive mucus production, mucosal oedema, impaired communication with sinuses, or occlusion of the nostril and application of decongestants (Olin *et al.* 1998). In the nose, nNO is produced by constitutive NO synthase along with the iNOS, which is inhibited by corticosteroids. Therefore, high levels of nNO after corticosteroid treatment could be also explained by the involvement of other isoforms of NO synthase (Olthoff *et al.* 2002, Struben *et al.* 2006).

Inflammation itself could be the factor increasing elimination of nNO by increased mucosal blood flow and vascular permeability in the acute phase of an allergic reaction (Henriksen *et al.* 1999). There are also studies documenting the elevation of nNO levels after corticosteroid treatment in participants with chronic inflammation and nasal polyps. Reduction of inflammation and mucosal swelling led to the opening of the osteomeatal complex, with increased contribution of NO produced in sinuses to total nNO values (Wilson *et al.* 2000).

While the measurement of FeNO is quick, easy-to-perform, safe and non-invasive technique for the monitoring of the lower airway inflammation, detection of nNO does not seem to be the optimal method for monitoring of eosinophilic inflammation in the nose and sinuses and the reasons are many. The most important is a finding that the severity of nasal mucosal inflammation does not correlate with levels of detected nNO. Even though nNO levels are increased in allergic subjects during the pollen season, the values are characterized by high variability and do not respond to antihistamine treatment. Even they do respond to combined therapy,

there are still many factors related to inflammation (mucosal blood flow, mucus layer, diffusion problems, communication with sinuses, other than iNOS sources of nitric oxide in the upper airways) (Lundberg *et al.* 1997, Olin *et al.* 1998, Wilson *et al.* 2000, Maniscalco *et al.* 2001) along with high range of reference values and inter-individual variability, which make the nNO detection method unreliable in management of allergic rhinitis.

Conflict of Interest

There is no conflict of interest.

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