



Original research article

Nasal nitric oxide in upper airways in children with asthma and allergic rhinitis

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ABSTRACT

Purpose: The aim of this study is to compare levels of nasal nitric oxide (nNO) in pediatric patients with respiratory diseases.

Materials and methods: nNO was measured by an electrochemical analyzer in 179 patients aged 7–15 with asthma, allergic rhinitis or with asthma and allergic rhinitis and in healthy children recruited from a local allergology clinic. Correlations between nNO levels and patient clinical parameters were assessed.

Results: nNO was significantly higher in patients with allergic rhinitis (2316.3 ± 442.33 ppb, $p < 0.001$) as well as with asthma and allergic rhinitis (2399.9 ± 446.73 ppb, $p < 0.001$) compared to asthmatic and healthy children (1066.4 ± 416.75 ; 836.2 ± 333.47 ppb, respectively). A receiver operating characteristic curve analysis revealed that a cut-off value of 1545 ppb nNO and 1459 ppb nNO has sensitivity of 100% and specificity of 100% in distinguishing allergic rhinitis and combined asthma and allergic rhinitis from healthy subjects. A positive correlation between nNO and age and height was determined only in groups of healthy controls. We found no association between nNO level and clinical parameters including percent of eosinophils and total IgE.

Conclusion: Levels of nNO are currently measured by different analyzers and with different methods, so assessment of nNO is in need of standardization improvement to become a more reliable tool. However, because it is cheap, painless and fast, it may be helpful in combination with recognition of clinical symptoms and typical diagnostic methods, especially in estimation of inflammation.

1. Introduction

Nasal nitric oxide (nNO) refers to NO measured in air aspirated from the nasal cavity and sinuses. nNO is synthesized from L-arginine by NO synthases (NOS) by epithelial cells of the paranasal sinus [1]. Nitric oxide synthases exist in three distinct isoforms - neural (nNOS), endothelial (eNOS) and inducible (iNOS). While the first two enzymes are active mainly under physiological conditions and release small amounts of NO, iNOS may release large amounts of NO in the respiratory tract, especially after upregulation of its expression by pro-inflammatory cytokines [2]. The NO molecule is involved in several physiological processes such as modulation of cilia motility, improvement of oxygen uptake and reduction of pulmonary vascular resistance which generally maintains adequate ventilation perfusion in the respiratory tract [3]. In the sinuses, NO is important for maintenance of local host defense mechanisms against bacteria, fungi, viruses and parasites [4]. Currently, measurement of nNO is used as indicator of local inflammation and responsiveness to treatment with corticosteroids [5]. Nasal NO in

the upper airways can be determined by direct or indirect methods. The direct method known as the gold standard is based on use of a chemiluminescence analyzer for photochemical reactions between NO and ozone. Currently, sensitive electrochemical analyzers are also available and are commonly used. Indirect determinations are analyses of the products of NO metabolism and NOS expression [6].

Currently, nNO has found application in screening for primary ciliary dyskinesia [7] and cystic fibrosis [8] as patients have statistically significantly lower ($p < 0.005$) nNO levels than healthy controls. In children with cystic fibrosis, the presence of nasal polyps as well as *Streptococcus aureus* colonization is associated with statistically significantly lower ($p = 0.001$) nNO levels [9]. nNO levels measured in exhaled air from upper airways are generally elevated in chronic inflammatory lung diseases such as asthma with poor control and allergic rhinitis [10–12]. Inflammation leads to lung tissue damage followed by the release of cytokines and the stimulation of iNOS causing an increase in the level of nNO.

The primary aim of this study was to find out the differences

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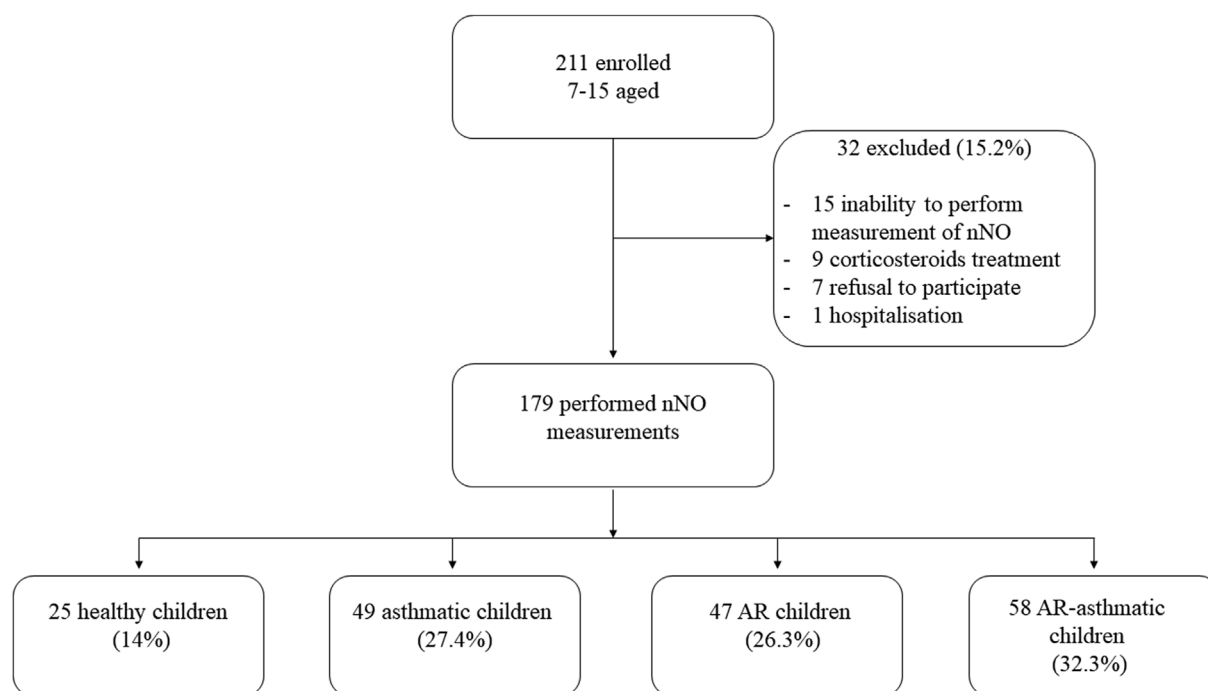


Fig. 1. Flowchart of the study recruitment process.

between the levels of nNO in pediatric patients aged 7–15 with asthma, allergic rhinitis (AR) as well as in patients with both asthma and allergic rhinitis (AR-asthma) in comparison to healthy children. Additionally, we compared nNO levels with patient gender and place of residence. Moreover, we determined the nNO level cut-off point by constructing a receiver operating characteristic (ROC) curve for each disease state.

2. Materials and methods

2.1. Study group

We invited children aged 7–15, through their family doctors, to participate in the study. We received replies from 211 potential participants from both rural and urban regions. We excluded 32 children from participation in the study. A flow chart outlining the recruitment process is shown in Fig. 1.

Ultimately, this study was carried out in a sample of 179 pediatric patients without glucocorticoid treatment between 7 and 15 years of age divided into 4 groups according to diagnosis based on the medical criteria of asthma, AR, AR-asthma, as well as healthy controls.

The diagnosis of asthma was made on the basis of The Global Initiative for Asthma (GINA) criteria. Spirometry was used to confirm the reversibility of airway obstruction [13]. AR patients were diagnosed when they had one or more symptoms (nasal congestion, nose running, nasal itching, or sneezing) longer than 4 days per week and occurring after exposure to allergens [14]. The most common AR related symptoms among our patients included rhinorrhea, nasal blockage, itching and sneezing.

All subjects were recruited from the Allergology Outpatient Department, Provincial Hospital No 2, Rzeszow (Poland) between November 2018 and June 2019. Patient characteristics are listed in Table 1.

Patients were excluded if they had asthma exacerbations, acute respiratory infections, associated diseases, received glucocorticoid, anti-inflammatory or anti-histaminic treatment or if children were not able to take the test or refused to participate. Exclusion criteria were also as follows: forced expiratory volume in the first second (FEV1) lower than 70% of predicted value and hospitalization 30 days prior to

nNO measurement. Patients did not use any medication for 3 months except for topical steroid emollients in case of atopic dermatitis.

Healthy controls were recruited simultaneously in the clinic. The control group consisted of sex-matched children aged 7–15 without asthma, AR allergies, allergic dermatitis in their clinical history and physical examination. In all patients with asthma, AR and AR-asthma as well as healthy subjects, FEV1 using a standard spirometry device (Lungtest 10000 MES SJ, Poland) was performed according to recommendations [15]. Results of blood counts were obtained by using hematology analyzer ADVIA2120i (Siemens Healthineers, Germany). Total IgE were assayed using enzyme immunoassay (VIDAS bioMérieux, S.A, France) according to the manufacturer's instructions. Also, pediatric patients had allergy tests with inhaled allergens (Skin prick tests - BASIC SET inhaled Allergopharma, Germany).

2.2. Nasal nitric oxide measurements

The concentration of nNO in exhaled air was measured using the Hyp'Air FeNO electrochemical analyzer (MediSoft, Belgium) with a measuring range of 0–6000 ppb in the case of nasal measurement. NO measurements were performed three times for each patient according to the recommendations of the American Thoracic Society (ATS) [16]. Three subsequent correctly made measurements were averaged for each patient. The patients exhaled through disposable nosepieces at a constant flow of 350 mL/s for 60 s. The children had not eaten, drank or had physical exercise before nNO measurements. Assessment of nNO was performed prior to the spirometry test in the morning.

2.3. Statistical analysis

Data are given in the form of arithmetic mean values and standard deviations. The statistical significance of differences was evaluated using the Kruskal-Wallis test or Mann-Whitney *U* test. ROC curves were used to analyze results for the determination of cut-off point in levels of nNO which may be a prognostic indicator of asthma, AR and AR-asthma. Spearman's rank correlation coefficient analysis was employed to estimate the relationships between nNO and patient age, height, weight, BMI, spirometry result and eosinophils number, assuming

Table 1Anthropometric, demographic, clinical and functional characteristics of the study participants^a.

	Healthy control	Asthma	AR	AR-asthma
n	25	49	47	58
Sex (F/M)	11/14	25/24	21/26	29/29
Place of residence (urban/rural)	12/13	27/22	24/23	30/28
Age (years)	10.08 ± 2.64	10.63 ± 2.24	10.98 ± 2.55	10.85 ± 2.37
Height (cm)	143.64 ± 10.58	144.78 ± 11.41	144.09 ± 12	145.29 ± 10.96
Weight (kg)	39.12 ± 8.17	39.59 ± 8.43	39.66 ± 10.71	40.96 ± 8.40
BMI	18.82 ± 2.42	18.79 ± 2.75	18.86 ± 3.53	19.22 ± 2.03
FEV1% predicted	87.49 ± 6.10	80.92 ± 12.06	87.39 ± 7.3	81.57 ± 10.34
Eosinophil in peripheral blood (%)	3.02 ± 1.33	4.06 ± 3.26	4.30 ± 2.13	5.77 ± 2.25
Total IgE (kU/l)	18.25 ± 9.33	169.39 ± 116.94	329.17 ± 174.95	632.46 ± 440.15
Atopic dermatitis, confirmed (%)	–	22.4	40.4	48.3

^a Data are presented as mean ± SD.

linear dependence. Statistical analysis included a comparison of the nNO levels of various disease entities, as well as a comparison of nNO level depending on the place of residence (urban/rural) and gender (boys/girls).

Statistical analysis of the data was performed using STATISTICA software package (version 13.1, StatSoft Inc. 2016, Tulsa, OK, USA, www.statsoft.com) and MedCalc® (version 19.0.4, MedCalc Software, Ostend, Belgium, <https://www.medcalc.org/index.php>) for ROC curve construction and calculation of the Youden's index (J).

2.4. Ethical issues

The study was approved by the Bioethical Committee of Rzeszów University (Poland) (7/10/2018). All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The pediatric patients and parents or legal guardians were informed about the conditions of participation, and those that demonstrated their willingness to participate in the study signed a consent form.

3. Results

Differences between healthy subjects and groups with uncontrolled asthma, AR as well as combined asthma and AR patients are presented in Table 1. Age, height, weight, distribution of gender and place of residence, and BMI were similar between the four groups. There was a statistically significant difference between the spirometry results in AR and AR-asthma patients ($p < 0.05$). Patients with AR-asthma had a statistically significantly higher level of eosinophils in peripheral blood than the healthy subjects and patients with asthma ($p < 0.001$), as well as AR patients ($p < 0.01$).

Healthy children had statistically significantly lower levels of total IgE than the other patients studied ($p < 0.001$), while AR-asthmatic children had statistically significantly elevated levels of total IgE compared to asthmatic ($p < 0.001$) and AR children ($p < 0.01$). Similarly, patients with AR had an increased total IgE when compared with asthmatic children ($p < 0.01$).

It was found that nNO level was statistically significantly increased in patients with AR (2322.3 ± 447.24 ppb) as well as with AR-asthma (2397.3 ± 423.25 ppb) than in children with asthma and in the control group (1017.4 ± 396.85 and 836.2 ± 333.47 ppb, respectively). Levels of nNO were similar in both asthmatic and healthy subjects. There were no statistically significant differences in nNO levels between AR and AR-asthma patients (Fig. 2). Table 2 shows the number of patients in the studied groups who are allergic to the most common allergens. In our case, the most common allergies were to dust mite.

Table 3 presents a statistical analysis of the differences in patient

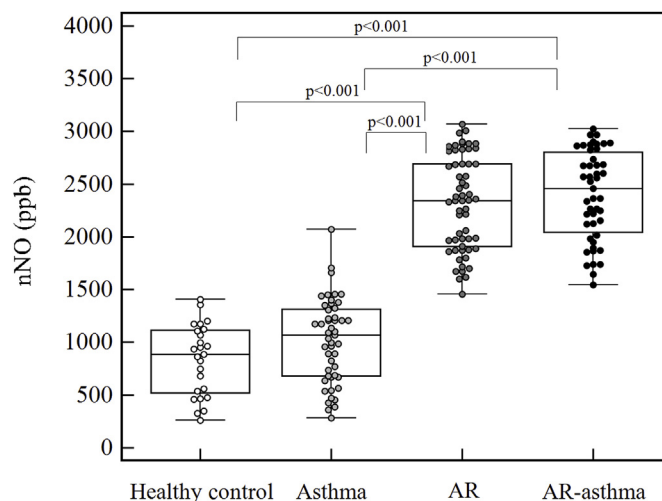


Fig. 2. Nasal nitric oxide (nNO) in control subjects, asthma, allergic rhinitis (AR) and combined asthma and allergic rhinitis (AR-asthma). Data are presented as mean ± SD. Differences between means were analyzed using Kruskal-Wallis test using Statistica software (version 13.1, StatSoft Inc. 2016, Tulsa, OK, USA, www.statsoft.com).

nNO levels with regard to sex and place of residence. There was no statistically significant difference between nNO levels of patients living in urban and rural areas in each studied group. Healthy children living in the city had increased, but not statistically significant, levels of nNO in comparison to children from rural areas (913.76 ± 267.40 vs 764.62 ± 381.18 ppb). On the other hand, children suffering from AR-asthma living in the city had decreased levels of nNO compared to those living in the village (2313.24 ± 399.12 vs 2485.03 ± 438.48 ppb). Similar levels of nNO were measured among asthmatic and AR patients regardless of their place of residence.

In this study, a statistically significantly higher nNO level in males than in females was observed only in the case of AR patients (2207.22 ± 451.13 vs 2437.38 ± 419.79 ppb, $p = 0.029$); elevated but not statistically significant nNO was also noted in healthy males when compared to female subjects (946.78 ± 277.06 ppb vs 695.48 ± 358.05 , $p = 0.101$). In other cases – asthma and AR-asthma, showed no statistically significant differences and associations between nNO and sex.

We attempted to find a dependence between nNO level and age, height, weight, BMI, spirometry results, as well as percent of eosinophils in peripheral blood by using Spearman correlation. A positive significant correlation between nNO and patient age ($R = 0.46$, $p = 0.021$) as well as height ($R = 0.495$, $p = 0.012$) was found only in the control group. There was, however, no association between nNO and other characteristics of patients including percent of eosinophils in

Table 2
Most common allergens in the studied groups.

	Healthy control	Asthma		AR		AR-asthma	
		Sex female/ male	Place of residence urban/rural	Sex female/ male	Place of residence urban/rural	Sex female/ male	Place of residence urban/rural
<i>Dermatophagoides pteronyssinus</i> , <i>Dermatophagoides farinae</i>	0	5/6	7/4	12/16	13/15	23/19	18/24
grass and cereals pollen	0	4/6	5/5	8/13	9/12	15/22	18/19
trees pollen	0	4/3	5/2	7/9	10/6	9/6	11/4
animal danders	0	3/4	2/5	4/6	5/5	9/7	6/10
<i>Artemisia vulgaris</i>	0	2/1	3/0	4/7	5/6	8/4	5/7

the blood and total IgE (Table 4).

We used a ROC curve analysis to determine a cut-off value. It was found that the optimal cut-off of 1545 ppb nNO to predict AR obtained 100% sensitivity and 100% specificity. In this case, the area under the ROC curve (AUC) was 1.0 while J was equal to 1.0. (Fig. 3a). Similarly, the cut-off of 1459 ppb nNO to predict AR in asthmatic patients also obtained a value of 100% in both sensitivity and specificity (AUC = 1.0, J = 1.0, Fig. 3b).

4. Discussion

The results of our study showed that 1) the level of nNO in children with AR and AR-asthma was statistically significantly increased compared to control and asthmatic subjects, 2) based on ROC curve analysis, the cut-offs for nNO in diagnosis of AR in pediatric patients with and without asthma were 1459 and 1545 ppb, respectively, 3) there are no differences between the cut-off of nNO for diagnosis of AR in pediatric patients with and without asthma.

Assessment of nNO is a reliable and noninvasive method used to estimate inflammation in human respiratory tract. In the airways, there are two main sites producing NO; the epithelium of nasal region produces about 90% of the NO, with the remainder being released by epithelial cells of the paranasal sinuses [17].

Elevated nNO is observed in AR, while reduced level of nNO is associated with primary ciliary dyskinesia [7], panbronchiolitis [18], nasal polyposis [19] as well as with cystic fibrosis [8,20]. Assessment of nNO may be a useful tool for the diagnosis of prolonged cough associated with sinusitis [21].

In this study, by using an electrochemical analyzer of NO, elevated nNO was found in uncontrolled pediatric patients with AR as well as in patients with combined asthma and AR as compared to the control group of healthy children (2316 ± 442 and 2399 ± 446 ppb vs 836 ± 333 ppb, respectively). Wang et al. [11] also observed that children aged 3–14 with mild and moderate AR had statistically significantly increased level of nNO measured with a nanocoulomb breathalyzer. Similarly, Nesic et al. [12] showed that AR had higher average oral and nNO levels in adult patients; a cut-off point of 564.5 ppb nNO gave the best combination of sensitivity and specificity. Elevated levels of nNO in AR patients was also measured among

Japanese adults [22] and young Indian patients [23]. In contrast, a study by Alexanderson et al. [24] revealed that there was no difference between nNO in AR and healthy subjects. Similarly, the same level of nNO was observed among Scottish patients with AR and healthy volunteers (853 vs 878 ppb) [25].

In AR patients, nNO correlates with exhaled NO from lower airways as well as opacification score [26]. nNO may reflect the severity of nasal inflammation in AR patients with mild-to-moderate nasal obstruction in which nNO is increased, while in severe obstruction AR, patient nNO level was decreased when compared to controls [27].

It is widely known that asthma and AR often coexist in the same subjects [28]. About 80% of patients with asthma are affected by AR and 10–40% of AR subjects have asthma as well [29]. A study using a Hyp'Air FeNO Device on Vietnamese children aged 5–18 revealed that nNO level was elevated in children with AR as well as AR-asthma when compared to healthy subjects (1614 ± 629 and 1686 ± 614 ppb vs 582 ± 161 ppb, respectively). A cut-off of 775 ppb and 1458 ppb nNO were determined for AR and AR-asthma. Similar to our research, they found that there was no statistical difference between AUC as well as average nNO between patients with both diseases [30]. Higher nNO was also noted in the study by Gupta et al. [23] on group of adult patients with bronchial asthma and AR as compared to controls. They also found that nNO in AR-asthma patients was increased when compared to AR patients, however, the difference was not statistically significant. On the other hand, a statistically significant difference in nNO level measured by using handheld electrochemical analyzer was observed between adult patients with AR and AR-asthma (76.9 vs 102.7 ppb, $p < 0.05$) [31].

We found that asthmatic patients had increased nNO, however the difference was not statistically significant as compared to healthy controls (1066.38 vs 836.21 ppb). In contrast to our study, the use of a chemiluminescence NO analyzer in 142 adult asthmatic and healthy subjects showed that patients with asthma had statistically significantly lower level of nNO as compared to controls. Moreover, patients with controlled asthma had higher nNO than uncontrolled asthmatic patients [32]. The inverse relation between nNO and asthma is related to high prevalence of acute or chronic rhinosinusitis, specifically eosinophilic, in asthmatic patients [32–34]. A similar association between poor asthma control and low level nNO was also found by Krantz et al. [10]

Table 3
Differences in nNO level depending on sex and place of residence of patients^a.

	Sex			Place of residence		
	female	male	p	urban	rural	p
Healthy control	695.48 ± 358.05	946.78 ± 277.06	0.101	913.76 ± 267.40	764.62 ± 381.18	0.341
Asthma	1041.18 ± 423.29	1020.41 ± 378.47	0.849	1020.88 ± 428.08	1013.03 ± 364.75	0.991
AR	2207.22 ± 451.13	2437.38 ± 419.79	0.029	2310.44 ± 452.96	2335.01 ± 448.96	0.785
AR-asthma	2404.11 ± 401.89	2391.82 ± 440.69	0.966	2313.24 ± 399.12	2485.03 ± 438.48	0.142

^a Data are presented as mean ± SD, differences between means were analyzed using Mann–Whitney U test using Statistica software (version 13.1, StatSoft Inc. 2016, Tulsa, OK, USA, www.statsoft.com).

Table 4
Correlation coefficients between nNO level and clinical features of studied patients^a.

	Healthy control		Asthma		AR		AR-asthma	
	R	p	R	p	R	p	R	p
Age (years)	0.460	0.021	0.090	0.540	−0.004	0.974	−0.113	0.450
Height (cm)	0.495	0.012	0.193	0.184	−0.150	0.262	−0.048	0.749
Weight (kg)	0.307	0.136	0.214	0.140	−0.047	0.728	−0.041	0.784
BMI	0.140	0.506	0.143	0.326	−0.004	0.978	0.096	0.521
FEV1% predicted	−0.006	0.977	0.177	0.223	−0.060	0.653	0.093	0.536
Eosinophil in peripheral blood (%)	−0.294	0.154	−0.141	0.334	0.088	0.513	−0.226	0.126
Total IgE (kU/l)	−0.009	0.674	0.027	0.854	−0.093	0.485	−0.057	0.703

^a Spearman's rank correlation coefficients were estimated using Statistica software (version 13.1, StatSoft Inc. 2016, Tulsa, OK, USA, www.statsoft.com).

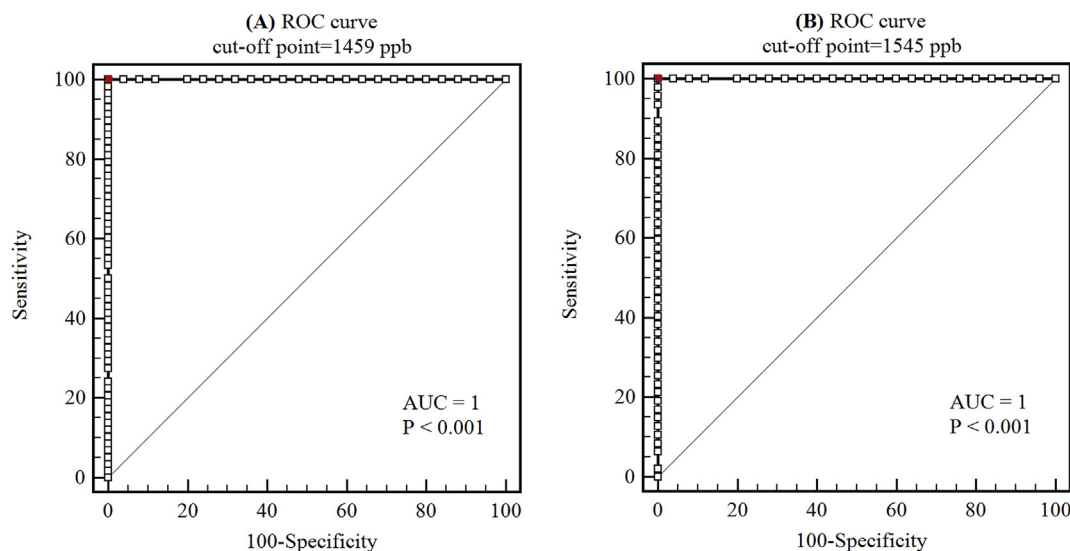


Fig. 3. Receiver operating curves (ROC) were employed to assess the area under the curve (AUC) and cut-off value of nNO in children with a) allergic rhinitis (AR), b) asthma and allergic rhinitis (AR-asthma) as compared to healthy children.

as well as by Williamson et al. [25].

Indian bronchial asthmatic patients had similar levels of nNO when compared to healthy controls [23]. The same level of nNO in asthmatic and healthy subjects measured by using a chemiluminescent NO analyzer was also described by Walker et al. [35] who determined that maximum levels of nNO were higher in asthmatic patients when compared to controls (1124 vs 886 ppb).

Results reporting nNO values vary depending on the country of origin, ethnicity, as well as the technique used to conduct measurements. Data on the physiological factors affecting the level of nitric oxide are inconsistent. There are reports describing that there is no statistically significant correlation between nNO and sex, age or height in healthy children, teens and young people [36,37]. In healthy Chinese subjects aged 9–22 years, only a correlation between nNO values and exhaled NO from lower airways was found while it was independent of age, sex, height, weight, BMI [37]. Nevertheless, it was shown that in healthy children 6–12 years of age, levels of nNO are positively correlated with patient age, but in older children there was no such dependence. The association between nNO and age in children younger than 12 years of age was approximately three times stronger as compared with older children [38]. Similarly, a positive correlation between age and BMI ($R = 0.4$, $p < 0.001$) of healthy adult volunteers and nNO was found [39]. In that study, a fairly positive correlation between nNO level and age as well as height was determined only in healthy children. Likewise, nNO was dependent on age and weight in pre-school children [40] as well as positively correlated with age and gender in a study on 80 healthy Chinese adults [41]. This can be explained by the anatomical development of the volume of the paranasal sinus,

nasopharyngeal airway and the surface of the airway epithelium, which is the main source of nNO. Facial sinuses reach their final size in the 12th year of life, hence physicians interpreting the results need to be aware of the age impact on the level of nNO. We found no statistically significant association between nNO and sex distribution among studied groups, with the exception of AR patients, which is consistent with available data and suggests that the sex of patients has no influence on nNO levels. Statistically significant differences between girls and boys with AR might be explained by the fact that more male AR patients had atopy (boys – 12, girls – 7) and allergies than female subjects. According to study by Kumar and Gupta [42], atopic AR patients had higher nNO compared with non-atopic patients (292.13 ± 154.1 vs. 213.25 ± 42.3 ppb).

Similar results showing that nNO is independent of sex among healthy and adults suffering from respiratory diseases were obtained by Alexanderson et al. [24] ($p = 0.9$), Suojalehto et al. [26] ($p = 0.075$) as well as You et al. [37] ($p = 0.307$).

We wanted to determine the association between the measurement of NO – as a non-invasive biomarker, and eosinophilic airway inflammation. Moreover, we wanted to estimate whether the percentage of eosinophils in the blood is more important than the nNO level, however, this study showed that nNO was independent of percent eosinophils in peripheral blood as well as total IgE in each group of the studied patients. A positive association between nNO and absolute eosinophil count ($p < 0.01$) was found in the group of patients with bronchial asthma, AR, bronchial asthma and AR and healthy subjects [23]. Suojalehto et al. [26] observed that nNO correlated with nasal eosinophil count in AR patients without a marked sinus ostial

obstruction. Moreover, nNO was negatively correlated with eosinophil levels in patients with eosinophilic chronic rhinosinusitis [34]. It is worth mentioning that nNO level was not statistically significantly correlated with the number of positive responses to skin prick testing against 58 common aeroallergens, spirometry results and, similarly to our results, with total IgE levels [23].

Our study also suggests that the place of patient residence had no impact on the levels of nNO, although it might seem that children living in rural areas would have lower nNO levels. To our knowledge, this is the first study reporting that there is no difference in the level of nNO in a group of healthy children and those suffering from asthma and AR depending on the place of residence. Probably, as in the case of exhaled NO (from lower airways), this level may be influenced by air pollution in Poland, especially PM_{2.5} related to smog, leading to airway inflammation, however, there are no studies on this topic yet [43]. Moreover, the lack of differences might be explained by the fact that a similar number of studied patients suffer from allergies regardless of the place of residence.

Measuring nNO is a technique which has several limitations. First of all, the level of nNO might change with circadian rhythm – lower morning nNO levels than afternoon levels during the same day are noted. Moreover, the patient's cooperation with the device might influence the final results. Low sampling flow rate is associated with increased nNO, while high sampling flow rate is related with decreased nNO [44]. Reports show that measurement of nNO negatively correlated with peak expiratory flow and peak inspiratory flow rate in adults with AR and AR-asthma [32]. It seems that nNO measurement is more precise and easier to perform than peak expiratory flow technique. Afterwards, nNO assessment does not require patient involvement, the measurement is passive in contrary to assessment of peak expiratory flow which is a demanding technique.

4.1. Limitation of the study

Interesting findings were pointed out in this report, however several limitations of the study have to be mentioned. Firstly, this study analyzed a small sample size. Moreover, there was a lack of correlation between nNO measurement and the exposure to allergen. The role of nNO assessment in treatment of inflammation in AR patients was not shown.

However, this study also has strengths in that the population was homogenous and the distribution of patients in the studied groups were equal and statistically significant changes of nNO in children with AR were determined. Assessment of nNO might be helpful in clinical practice to easily diagnose and differentiate AR in children with or without asthma, without painful, expensive and long-lasting laboratory tests. Moreover, in additional studies, these findings might be useful in evaluating the severity of AR.

5. Conclusions

Generally, there are many reports describing the measurements of nNO in patients with respiratory diseases but they are quite difficult to compare due to the use of different methods of measurements or analyzer [11,12,32,35]. However, it seems that measurements of nNO provide additional information about ongoing inflammation, especially valuable due to the speed, low cost and painlessness.

In summary, assessment of nNO still needs improvements in methodology and standardization to become a more reliable tool for screening, diagnosis and monitoring inflammation in the respiratory tract, especially in the upper airways.

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The author contribution

Study Design: Marta Rachel.

Data Collection: Sabina Galiniak, Marta Rachel.

Statistical Analysis: Marek Biesiadecki.

Data Interpretation: Sabina Galiniak, Marta Rachel.

Manuscript Preparation: Sabina Galiniak, Marek Biesiadecki, David Aebisher, Marta Rachel.

Literature Search: Sabina Galiniak.

Funds collection: n/a.

Declaration of competing interests

The authors declare no conflict of interest.

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