



Comparison of exhaled nitric oxide levels in pediatric patients with allergic rhinitis



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ABSTRACT

Objective: To determine whether the measurement of exhaled nitric oxide (eNO) can help distinguish children with allergic rhinitis (AR) from healthy controls and whether eNO in children with AR correlates with disease severity.

Methods: From August 2015 to 2016, children aged 5–15 years of age grouped into those with allergic rhinitis (n = 40) and those classified as healthy control subjects (n = 40) had exhaled nitric oxide (eNO) levels measured. The eNO level was additionally compared to the patient's clinical disease severity according to the ARIA (Allergic Rhinitis and its Impact on Asthma) classification.

Results: Mean eNO in children with AR (12.64 ± 14.67 ppb) was significantly higher than that in the healthy control group (7.00 ± 6.33 ppb) (*p*-value = 0.046). In the persistent AR group (17.11 ± 18.40 ppb), eNO level was significantly higher than individuals in the intermittent AR group (8.59 ± 8.88 ppb, *p*-value = 0.024) and the healthy control group (7.00 ± 6.33 ppb, *p*-value = 0.008). Among children with AR, eNO was not significantly different with relationship to gender, age, weight and passive smoking exposure.

Conclusions: Exhaled nitric oxide may be elevated in children with AR that do not have concomitant asthma. This suggests exhaled nitric oxide may show utility as a parameter to monitor the severity of allergic rhinitis and to monitor the efficacy of the treatment. Physicians should consider comorbid AR when utilizing exhaled nitric oxide as a monitoring parameter in the treatment of asthma.

1. Introduction

Allergic rhinitis (AR) continues to have a global impact with a prevalence of 10%–20% of the population worldwide. The prevalence in Thailand alone has increased nearly 3-fold (from 17.9% to 44.2%) during the last few decades [1] and has impacted individuals and countrywide health and healthcare significantly [2]. Recent studies have shown that patients with AR have reduced performance, work productivity, and quality of life [3]. In line with the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline, AR is classified as intermittent or persistent according to the duration of symptoms and as mild or moderate-severe depending on its severity. The severity of AR depends on its affect on quality of life, and this effect is classified as moderate to severe persistence if the patient has one or more items of sleep disturbance, impairment of daily activity/sport/leisure,

impairment of school or work, or troublesome symptoms. Given that the classification remains a subjective measure, we hypothesize that exhaled nitric oxide (eNO), a non-invasive marker of airway inflammation, might correlate with AR symptom severity.

Allergic rhinitis as we are aware of, involves IgE-mediated cytokine release due to exposure of the nasal mucous membranes to offending allergens [4]. This specifically has been correlated with eosinophilic airway inflammation. Airway inflammation in asthma and AR involves the release of inflammatory biomarkers including nitric oxide. Exhaled nitric oxide (eNO) is NO in the lower airway measured by oral exhalation. Nasal nitric oxide (nNO) is measured in air aspirated from the nasal cavity and is produced constitutively in the paranasal sinuses without inflammatory stimuli. Previous studies have shown that nNO and eNO are correlated with the classification of AR in adults, revealing significantly higher levels when compared to normal controls [5].

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There is, however, few data on eNO in pediatric patients with AR and therefore no comparative studies at this time.

2. Material and methods

2.1. Population

A cross sectional study was performed between August 2015 and August 2016 at Thammasat University Hospital in Pathum Thani, Thailand. The ethical board of Thammasat University Chlaremprakiat Hospital approved this study and informed consent was obtained from all parents and children enrolled in this study. Enrollment included those aged 5–15 years of age with a diagnosis of AR who could reliably exhale through a mouthpiece for a total of six seconds. A total of 40 children with AR and 40 healthy subjects were enrolled from the pediatric outpatient department at Thammasat University Hospital, Pathumtani, Thailand. Allergic rhinitis was diagnosed by documenting the presence of the following symptoms: sneezing, runny nose, congestion, and nasal itching. Additionally clinical assessment and positive skin prick test was used for confirmation. Skin prick testing performed utilized five common aeroallergens (*D. pteronyssinus*, mixed grass, mixed cockroach, cat epithelium, and dog epithelium). Glycerin and histamine were used as negative and positive controls, respectively. A positive result was noted when wheal size was 3 mm greater than the negative control [6].

Patients were excluded from the study if any of the following were noted: active respiratory tract infection, comorbid asthma, nasal polyposis, previous adenotonsillectomy within the last 3 months, smokers, patients utilizing intranasal steroids or antileukotrienes within 3 weeks, and those AR patients who had previously been treated with immunotherapy. A total of 80 children completed the study.

2.2. eNO measurement

In this study, we exhaled NO in children was measured in both subject groups. Patients were instructed to exhale through a mouthpiece slowly over 10 seconds (exhalation time dependent upon the response time of the analyzer) via NObreath® (Bedfont Scientific Ltd., Kent, UK) with constant flow (the ball in the flow indicator was suspended in the middle of the band, providing accuracy of ± 5 ppb of the measured value under ≤ 50 ppb). Patients repeated this test 3 times and the mean value was obtained.

2.3. Data collection and statistical analysis

Descriptive data collection was collected from both the AR and control group. Duration and severity of AR was recorded via patient responses. Statistical analysis was completed with SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA). Mean differences between the groups were analyzed using Student's *t*-test, the chi-square test, the Mann-Whitney *U* test, and the Kruskal-Wallis test. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographics

A total of eighty patients were enrolled at Thammasat University Hospital and all completed the assigned questionnaires. Sixty-one percent (61%) were females. Ages ranged from 5 to 15 years, with a mean standard deviation (SD) of 2.6 years. Among the AR group, weight and BMI was significantly higher than the control group but age, height, and smoke exposure was no different. The characteristics of the subjects with AR and the control group are shown in Table 1.

Table 1
Patient characteristics.

	AR (n = 40)	Control (n = 40)	P value
Gender male, n (%)	24 (60.00)	15(37.5)	0.044
Age (years)			0.429
- median and range	10.00 (5.0–15.0)	8.50 (5.0–15.0)	
- mean $\pm$ SD	9.25 $\pm$ 2.59	8.85 $\pm$ 2.98	
Weight(kg)			0.038
- median and range	31.80 (19.00–85.00)	26.00 (14.00–108.00)	
- mean $\pm$ SD	36.00 $\pm$ 14.80	33.38 $\pm$ 20.82	
Height (cm)			0.118
- mean $\pm$ SD	137.78 $\pm$ 16.24	131.25 $\pm$ 20.48	
- median and range	136.50 (105–170)	130.00 (74–174)	
BMI (kg/m ²)			0.036
- median and range	17.25 (13.40–33.80)	14.81 (9.80–37.30)	
- mean $\pm$ SD	18.56 $\pm$ 4.62	17.36 $\pm$ 5.72	
Contact smoking, n (%)	9 (22.5)	16 (40.0)	0.091
Exhaled nitric oxide (ppb)			0.046
- median and range	8.50 (0.00–75.70)	6.00 (1.00–24.00)	
- mean $\pm$ SD	12.64 $\pm$ 15.04	7.00 $\pm$ 6.33	
Polysensitized, n (%)	26 (72.22)	-	
DP/DF positive, n (%)	21 (58.33)	-	

3.2. Exhaled nitric oxide

Mean eNO in children with AR (AR) (12.64 $\pm$ 14.67 ppb) was significantly higher than in the healthy control (7.00 $\pm$ 6.33 ppb) (p -value = 0.046). Among the children with AR, eNo was not significantly different in terms of gender, age, weight, passive smoke exposure, or severity of disease. Differences between eNO relating to symptom severity and duration of symptoms amongst the AR group is shown in Table 2. With regards to duration of symptoms, the persistent AR group eNO level (17.11 $\pm$ 18.40 ppb) was significantly higher than individuals in both the intermittent AR group (8.59 $\pm$ 8.88 ppb, p -value = 0.024) and healthy control group (7.00 $\pm$ 6.33 ppb, p -value = 0.008) as shown in Fig. 1. When comparing groups based upon the severity of symptoms, eNO was not statistically different between mild, and moderate to severe symptoms.

4. Discussion

Previous studies have related eNO to AR in adults, we have found similar evidence in children. Although previous studies have compared eNO in asthma patients, there has yet been a study to evaluate eNO

Table 2
Difference between eNO according to symptom severity and duration in the allergic rhinitis (AR) group.

	eNO (ppb)	
	Mean	Median
Allergic rhinitis duration		
Intermittent (< 4 days/week or < 4 weeks) (n = 21)	8.59 $\pm$ 8.88	5.50 (0.0–38.00)
Persistent (> 4 days/week and > 4 weeks) (n = 19)	17.11 $\pm$ 18.40	12.00 (1.00–75.70)
P-value	0.024	
Allergic rhinitis severity		
Mild (n = 4)	9.68 $\pm$ 6.86	9.00 (2.0–18.70)
Moderate-severe (n = 36)	12.96 $\pm$ 15.32	8.00 (0.0–75.70)
P-value	0.865	
Allergic rhinitis and its impact on asthma (ARIA)		
Intermittent mild (n = 2)		
Intermittent moderate-severe (n = 19)	8.54 $\pm$ 9.36	5.30 (0–38)
Persistent mild (n = 2)	10.35 $\pm$ 11.80	10.35 (2–18.7)
Persistent moderate-severe (n = 17)	17.90 $\pm$ 19.12	12 (1–75.7)

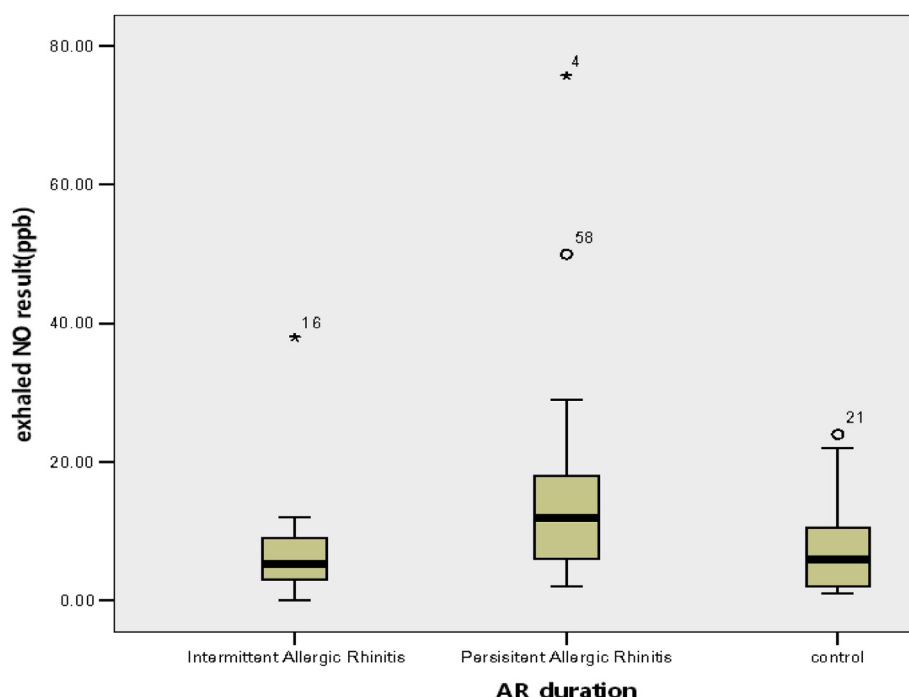


Fig. 1. Comparison eNO and AR duration.

- Comparison between persistent AR and control *p*-Value 0.009.

- Comparison between intermittent AR and control *p*-Value 0.965.

correlated with AR in the pediatric population.

According to the ARIA classification, 52% of patients had intermittent symptoms and 48% had persistent symptoms in our represented population. With regards to severity, 10% had mild symptoms and 90% had moderate to severe symptoms. Consistent with the previous study in Thai children, the mild and moderate/severe persistent symptoms were 17.5% and 82.55% respectively [7]. The increase in the severity of AR in our study could be secondary to parental concern expressed by the caregivers with regards to AR treatment.

House-dust mite is the most common causative allergens (58.33%) which is similar to previous reports amongst Thai children [7,8]. There was no statistical difference when comparing eNO in house dust mite positive and the house dust mite negative group. We found that the patients classified as overweight was significantly higher in the AR group. This is similar to previous findings in a study looking at obesity and AR [9].

The mean eNO in healthy control children was 7.00 ± 6.33 ppb. In 1999, Baraldi E et al. [10], established reference values for exhaled NO concentrations in a large number of healthy children aged 6–15 years. The mean level of eNO in their study was 8.7 ppb and there was no difference found between sex, age and height. Our results revealed similar results and therefore we feel may allow one to utilize it as a barometer of efficacy of AR treatment, but not as a diagnostic tool of AR alone. In 2012 Keon Jung Lee et al. compared mean eNO concentration between AR and healthy adults, reporting a significantly higher level of eNO in AR than that of the normal control group and higher level of eNO in persistent AR [11]. However, eNO was similar amongst the four classifications of ARIA guidelines. Our study found similar results in the pediatric population.

Most of the literature regarding eNO in children has been in relationship to asthma. Cindy MA de Bot et al. [12] compared children with only AR and combined AR and asthma. Both groups revealed elevated levels. The median eNO reported was 34 (16–55) in the AR group in contrast to eNO 8.50 (0.00–75.70) in our study.

There are, however, several limitations to our study's results. Our study size was relatively small. Additionally, as with any study

incorporating subjective data, there is a chance for bias from participants that can alter severity results. The correlation between AR and asthma is well supported with the united airway disease hypothesis [13]. Compalati et al. found a strong correlation between AR and asthma with up to 38% of AR patients having comorbid asthma and up to 80% of asthma patients with comorbid AR [14]. The AR and asthma connection was also clearly observed by Trakultivakorn M et al. [8], who found that 13.9–25% of children with rhinitis had asthma as well, therefore the elevation of eNO could have been secondary to the patient's comorbid asthma and not AR.

5. Conclusion

eNO measurements may be used to evaluate improvement in AR symptoms among children undergoing therapy. Further studies of eNO in children are necessary to confirm the utility of eNO in measurement in AR disease.

Conflicts of interest

The authors have no conflict of interest in relation to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijporl.2019.109603>.

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