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Measurement of nasal and fractional exhaled nitric oxide in children with upper airway inflammatory disease: Preliminary results

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ABSTRACT

Objectives: To assess the clinical significance of nasal nitric oxide (nNO) and fractional exhaled nitric oxide (FeNO) concentrations in children with upper airway inflammatory disease.
Methods: Fifteen healthy children, 30 with allergic rhinitis (AR), 10 with non-allergic rhinitis (NAR), and 30 with sleep disordered breathing (SDB) were enrolled. The FeNO and nNO concentrations were measured non-invasively using a NIOX MINO system.
Results: Both nNO and FeNO were significantly higher in children with AR than in healthy children ($P = 0.000$ and $P = 0.000$, respectively). Compared to healthy children, nNO was also significant higher in children with NAR ($P = 0.011$) or SDB ($P = 0.027$). In contrast, FeNO did not differ from controls in children with NAR or SDB.
Conclusions: Our data suggest that nNO has potential value for diagnosing upper airway inflammation. Moreover, elevated FeNO distinguishes allergic from non-allergic rhinitis.

1. Introduction

The concentration of exhaled nitric oxide (eNO) is correlated with airway inflammation [1]. Orally exhaled gases contain NO derived from both lower and upper airways, while the NO in nasal exhalant (nasal NO, nNO) is produced mainly in the upper respiratory tract, predominantly from the sinuses and to a lesser the nasal mucosa [1]. Thus, measurement of eNO and nNO concentrations may provide information on the primary location and extent of airway inflammation to help guide the management of respiratory tract diseases [1]. The 2011 American Thoracic Society (ATS) guidelines [2] provide for the use of fractional exhaled NO (FeNO) in clinical practice. Elevated FeNO is a marker of eosinophilic airway inflammation, and can be used in the diagnosis and treatment evaluation of asthma.

While a long-term (>10 year) international clinical study focused on the association between FeNO and lower airway inflammation [2], there is limited research on FeNO or nNO in upper airway inflammation. The current study was designed to compare FeNO and nNO concentrations between healthy children and children with upper airway inflammatory diseases in order to assess the clinical significance of upper airway NO release.

2. Materials and methods

2.1. Patient recruitment

Seventy-nine consecutive children (60 males and 19 females, 60–168 months of age) treated in our department between January 2014 and September 2014 were initially selected for this study. We excluded patients < 60 months of age because they were too young to cooperate during the examination. Nine children were excluded because their parents would not give permission for participation. All 70 remaining patients underwent physical examination, video laryngoscopy (Olympus, Japan), polysomnography (PSG; Compumedics E-Series; USA) with continuous sleep monitoring for >7 h at night, and allergy testing using skin prick tests (SPTs) and/or serum-specific IgE screening. A mite allergen skin prick reagent kit (Recordati S.P.A., Italy) was used for skin prick testing (≥++ considered positive) and a special serum protein analysis kit (Beckman Coulter, USA) for serum-specific IgE screening (≥3 considered positive).

Based on symptoms, physical examination, video laryngoscopy, PSG findings, and skin prick test and/or specific allergen screening (serum-specific IgE) results, the 70 patients were divided into 3 groups (Table 1), 30 with allergic rhinitis (AR), 10 with non-allergic rhinitis (NAR), and 30 with sleep disordered breathing (SDB). In the current study, the diagnostic criteria for AR and NAR met the 2008 updated Allergic Rhinitis and its Impact on Asthma (ARIA)

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Table 1
Clinical condition of enrolled subjects.

	AR	NAR	SDB	Healthy Children
Symptoms	Typical of AR [3]	Typical of NAR [3]	Typical of SDB [4] and absence of nasal inflammatory diseases	No clinical symptoms of disease
Physical examination	Met diagnostic criteria for AR [3]	Met diagnostic criteria for NAR [3]	Met diagnostic criteria for SDB [4] (for example, tonsil hypertrophy)	Normal
(1) Skin prick test (≥++[positive]) (2) Serum specific IgE (≥3[positive])	(1) and/or (2) was positive	Neither (1) nor (2) was positive	Neither (1) nor (2) was positive	Neither (1) nor (2) was positive
Video laryngoscopy	Met diagnostic criteria for AR [3]	Met diagnostic criteria for NAR [3]	Met diagnostic criteria for SDB [4] (e.g., adenoidal hypertrophy)	Normal
PSG parameters	AHI < 1/h and OAI < 1/h	AHI < 1/h and OAI < 1/h	AHI ≥ 1/h	AHI < 1/h and OAI < 1/h

AR: allergic rhinitis, NAR: non-allergic rhinitis, SDB: sleep disordered breathing, AHI: apnea-hypopnea index, OAI: obstructive apnea index.

guidelines [3]. Non-allergic rhinitis is characterized by nasal symptoms, including anterior or posterior rhinorrhoea, sneezing, nasal blockage, and/or itching of the nose, but video laryngoscopy findings have shown that there is no mucopurulent discharge from the middle meatus and/or edema/mucosal obstruction in the middle meatus. The skin prick test and/or specific allergen screening results are also negative in NAR [3]. Children with AR and NAR have normal PSG findings (Apnea-Hypopnea Index (AHI) < 1/h, and Obstructive Apnea Index (OAI) < 1/h). Sleep disordered breathing was diagnosed based on an AHI ≥ 1/h in the absence of nasal inflammatory diseases [4]. Neither the skin prick test nor the serum-specific IgE screening results are positive in children with NAR or SDB.

Fifteen healthy children matched for age and sex ratio (11 boys and 4 girls, 62–163 months of age) were recruited from the children of hospital staff during the same period as a control group. These healthy children had no clinical symptoms of disease, and the physical examination, video laryngoscopy, and skin prick test and/or specific allergen screening results were normal. PSG findings indicated an AHI < 1/h total sleep time (TST) and OAI < 1/h (Table 1). The exclusion criteria included chronic lung disease, central hypoventilation syndrome, immune deficiency disease, diabetes, tuberculosis, asthma, systemic metabolic storage diseases, morbid obesity, history of upper and/or lower airway surgery, systemic infection, and use of topical or systemic drugs in the previous 15 days. None of the children smoked tobacco actively or were exposed to secondhand smoke (passive smoking).

The study was approved by the Medical Ethics Committee of Guangzhou Women and Children Medical Centre. All parents or guardians provided informed consent.

2.2. Nitric oxide measurements

The nNO and FeNO concentrations were measured non-invasively using a NIOX MINO system (Aerocrine AB, Solna, Sweden) and are expressed as parts per billion (ppb 1ppb = 10^{-9}). All measurements were conducted between 2:00 pm and 9:00 pm in a room maintained at 20–30 °C with relative humidity of 20–60%. The environment was clean and measurements were obtained away from windows (sources of dust and pollen) and volatile gases. Interruptions from mobile phones and other strong electromagnetic signals within 2 m were avoided. Subjects were instructed not to drink or eat anything during the 2 h prior to NO testing, and not to drink liquids containing caffeine for 24 h. before testing. Subjects were also instructed not to eat foods rich in nitrogen, such as sausage, organ meats, lettuce, and spinach, for 24 h before test. The children abstained from intensive physical activities on the day of the measurements.

2.2.1. Fractional exhaled NO

Exhaled NO was measured using the on-line standardized single-breath technique. In the sitting position, the children were asked to grasp the handle and mouthparts tightly and inhale deeply after a heavy exhalation. Then, the children were instructed to slowly exhale at a constant flow of 50 ml/s for 6 s. The instrument automatically determined FeNO values.

2.2.2. Nasal NO

After resting for approximately 15 min, children were seated with their mouths closed. An olivary probe was placed on the right nostril, and children continued to breathe normally. The instrument continuously pumped nasal gas into the sampling tube at 2 ml/s for 2 min and measured nNO automatically in the total sample.

2.3. Statistics

Statistical analyses were performed using SPSS software (IBM SPSS statistics 20.0). Dataset distributions were assessed by the one-sample Kolmogorov–Smirnov test. Normally distributed data are expressed as the mean ± standard deviation (SD) and non-normally distributed data by the median (25th and 75th percentiles). Continuous variables were compared by the independent samples Student's *t*-test or Mann–Whitney test depending on distribution. Categorical variables were compared by the Kruskal–Wallis test. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Elevated nNO and/or FeNO levels in children with allergic rhinitis, non-allergic rhinitis, or sleep disordered breathing

Both FeNO and nNO concentrations were significantly higher in children with AR compared to healthy children (Table 2), while the two groups were well matched for age, sex ratio, and body mass index (all $P > 0.05$). Children with NAR also exhibited a significantly higher nNO concentration than healthy children (Table 3), but unlike AR patients, FeNO concentration did not differ significantly from controls. Again, NAR patients and healthy controls were well matched for age, sex ratio, and body mass index (all $P > 0.05$). Similar to children with NAR, children with SDB exhibited a higher nNO concentration than controls, while the FeNO concentration did not differ significantly (Table 4). As with the other intergroup comparisons, SDB patients and healthy controls were well matched for age, sex ratio, and body mass index (all $P > 0.05$). Thus, children with non-allergic upper airway inflammatory diseases exhibited elevated nNO, while children with AR also exhibited elevated FeNO.