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Review

Nasal Nitric Oxide in Children: A Review of Current Outreach in Pediatric Respiratory Medicine

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Abstract: Nasal nitric oxide (nNO) is a gas synthesized by the inducible and constitutive NO synthase enzyme in the airway cells of the nasal mucosa. Like lung nitric oxide, it is thought to be associated with airway inflammation in various respiratory diseases in children. The aim of our review was to investigate the current state of use of nasal nitric oxide measurement in children. A comprehensive search was conducted using the Web of Science and PubMed databases specifically targeting publications in the English language, with the following keywords: nasal NO, children, allergic rhinitis, chronic rhinosinusitis, acute rhinosinusitis, primary ciliary dyskinesia (PCD) and cystic fibrosis (CF). We describe the use of nNO in pediatric allergic rhinitis, chronic rhinosinusitis, acute rhinosinusitis, primary ciliary dyskinesia (PCD), and cystic fibrosis (CF) based on the latest literature. CONCLUSION: nNO is a noninvasive, clinically applicable test for use in pediatric allergic rhinitis, chronic rhinosinusitis, acute rhinosinusitis, PCD and CF. It can be used as a complementary method in the diagnosis of these respiratory diseases and as a monitoring method for the treatment of allergic rhinitis, acute and chronic rhinosinusitis.

Keywords: nasal nitric oxide; children; allergic rhinitis; chronic rhinosinusitis; primary ciliary dyskinesia; cystic fibrosis

INTRODUCTION

Nitric oxide is a gas that can be synthesized by numerous cells of the upper and lower respiratory tract, including endothelial and epithelial cells, neutrophils, and alveolar macrophages. It plays a role in stimulating ciliary motility, as a mediator in inflammatory responses, has bacteriostatic and antiviral effects, and regulates bronchial muscle tone and pulmonary vascular tone (1).

Nasal nitric oxide is a gas synthesized by the inducible and constitutive enzyme NO synthase in the airway cells of the nasal mucosa and paranasal sinuses (2, 3). Like pulmonary nitric oxide, it has been implicated in airway inflammation in various respiratory diseases in children (4). Measurement of nNO is a completely noninvasive procedure that can be performed in children without much effort. The preferred method for measuring NO is chemiluminescence with a standardized procedure suitable for children 4 years of age and older and adults who can cooperate in sampling to ensure closure of the velum (5). In preschool-aged children, electrochemical analyzers are often used instead of chemiluminescent devices. As of 2023, there is a technical standard published by the European Respiratory Society for nNO sampling in children with primary ciliary dyskinesia (6).

Current approaches to measuring nNO include sampling nasal air either directly from a nostril (aspiration method) or during a nasal single breath exhalation using a nasal mask (exhalation method) (7).

Because all methods are noninvasive, nasal NO in children has become a research subject for diagnosis, monitoring, and evaluation of therapy for various respiratory diseases (8).

The objective of our review was to investigate the utility of nasal nitric oxide (NO) measurement in children diagnosed with various respiratory diseases. A comprehensive search was conducted using the Web of Science and PubMed databases specifically targeting publications in the English

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language, with the following keywords: nasal NO, children, allergic rhinitis, chronic rhinosinusitis, acute rhinosinusitis, primary ciliary dyskinesia (PCD) and cystic fibrosis (CF).

nNO IN ALLERGIC RHINITIS

Allergic rhinitis is an atopic disease characterized by a Th-2 inflammatory response. Because it is the most common allergic upper respiratory disease in children and adults, an immediate attempt was made to establish a relationship between nNO levels and allergic inflammation in these patients (9). The data by the year 2000 were controversial in that, that several studies claimed that nasal NO could be used to predict allergic rhinitis (10, 11, 12), whereas others, in contradiction, claimed that nNO levels in allergic rhinitis were not significantly different from those in healthy subjects (13, 14). The controversial nature of these results may be attributed to several factors, including swelling of the nasal mucosa and the blockage of sinus ostia, which can impede the distribution of nasal nitric oxide (nNO) into the nasal cavity. Furthermore, the administration of therapeutic interventions aimed at symptom control, the timing of measurements in relation to allergen exposure, and the techniques employed for nNO measurement can all contribute to the observed discrepancies (15). It has been demonstrated that the choice of measurement technique and the type of analyzer employed can significantly influence nNO values. Both the type of analyzer (chemiluminescence vs. electrochemical) and the aspiration rate during sampling, as well as the specific sampling technique used, can impact nNO levels. Chemiluminescence analyzers utilize exhalation against resistance and the breath-holding technique, whereas electrochemical analyzers employ the tidal breathing technique. These different approaches have been found to have varying degrees of reproducibility in measuring nNO values, with electrochemical analysis being less extensively studied and exhibiting lower reproducibility (6).

In 2021, Wang et al. conducted a systematic review with meta-analysis of nNO levels and their clinical use in children with allergic rhinitis, which found significantly elevated nNO levels compared with healthy controls (15). Cutoff values to distinguish between AR and healthy controls were 169.4 and 161.4 nl/min, in two different studies by Nesic et al. and Wen et al., respectively, with sensitivity of 83% and 100% and specificity of 80 and 94.4% (11, 16).

Wang et al. also compared the influence of different types of NO analyzers, NO sampling methods, and sampling flow rates and found no evidence of differences between subgroups. There were also no differences between subgroups with symptoms of asthma and allergic rhinitis. Results were expressed as standard mean difference (SMD) between subgroups. For the stationary analyzer group, the SMD was 0.554; 95% CI: 0.260, 0.849; p = .010; I2 = 46.3%, p = .114; for the portable analyzer group, the SMD was 1.526; 95% CI: 0.361, 2.691; p = .010; I2 = 95.6%, p = .000. For breath-holding technique, the SMD was 1.717; 95% CI: 0.029, 3.404; p = .046; I2 = 97.0%, p = .000, while for exhalation against resistance, the SMD was 0.638; 95% CI: 0.337, 0.938; p = .000; I2 = 57.3%, p = .039. Sampling flow rate was compared between 3 l/min and 0.3 l/min, where the SMD was 0.374; 95% CI: 0.092, 0.656; p = .009; I2 = 0.0%, p = .369 and 1.316; 95% CI: 0.368, 2.264; p = .007; I2 = 95.3%, p = .000, respectively. Studies in patients with allergic rhinitis only and in patients with allergic rhinitis and concomitant asthma showed an SMD of 0.987; 95% CI: 0.310, 1.665; p = .004; I2 = 93.6%, p = .000 and an SMD of 1.011; 95% CI: 0.593, 1.428; p = .000; I2 not applicable p. Studies of patients with rhinitis symptoms and patients without rhinitis symptoms showed SMD 0.404; 95% CI: 0.169, 0.638; p = .001; I2 = 0.0%, p = .545 and SMD 1.438; 95% CI: 0.529, 2.346; p = .002; I2 = 94.5%, p = .000.

Smoking also did not affect the discrimination of AR based on nNO values. SMD values in patients who excluded smoking were 0.723; 95% CI: 0.174, 1.272; p = .010; I2 = 67.2%, p = .027 and in those who did not exclude smoking 1.157; 95% CI: 0.264, 2.049; p = .011; I2 = 95.8%, p = .000.

The three entities that undermine the differentiation of children with allergic rhinitis based on nNO values are nasal polyps (SMD−0.215; 95% CI: −0.905, 0.476; p = .543; I2 not applicable, p not applicable), sinusitis (SMD: 0.972; 95% CI: −3.627, 5.571; p = .679; I2 = 99.3%, p = .000), and marked ostial obstruction (SMD: −0.668; 95% CI: −1.498, 0.161; p = .114; I2 = 72.5%, p = .057). (15)

Hong et al. and Parisi et al. have shown that nNO levels can also be used as a noninvasive test of clinical efficacy in the treatment of allergic rhinitis in children. They demonstrated a significant

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reduction in symptoms and nNO values of allergic rhinitis after treatment according to the guidelines of ARIA (nNO (91.4±56.7 vs 72.9±52.4; p <0.05)) and after treatment with sublingual allergen-specific immunotherapy (nNO (1035.2 ± 956.08 vs. 139.2 ± 59.01; p < .05)) (17, 18). In the study by Antosova et al, the data for treatment with H1 antihistamines alone were not reviewed. Only the combination treatment of antihistamines and nasal corticosteroids significantly decreased nNO levels in patients with allergic rhinitis (19).

In allergic rhinitis triggered by house dust mites, Sutiratanachai et al. found that nNO can distinguish the severity of allergic rhinitis. Children with severe allergic rhinitis had significantly higher nNO levels than children with moderate rhinitis (1652.05 vs. 941.30 ppb, P = .002). The cut-off value for nNO was 1350 ppb (AUC 0.764, 95% CI: 0.616-0.911, P = .002) for the detection of severe HDM-induced allergic rhinitis, with a sensitivity of 78% and a specificity of 71%. FeNO levels were not changed as a function of severity of allergic rhinitis (20).

In seasonal allergic rhinitis, nNO levels are significantly elevated during and after pollen exposure, suggesting increased activity of iNOS during pollen exposure. The nNO levels in allergy patients were also higher during the year than in the control group (20). In contrast to the study conducted by Sutiratanachai et al., Antosova et al. did not categorize patients based on the severity of their condition. This omission implies that individuals experiencing significant mucosal swelling and nasal discharge may exhibit lower levels of nasal nitric oxide (nNO), despite the presence of intense inflammation (19).

When examining clusters of seasonal allergic rhinitis in children, Malizia et al. found significantly different nNO values between the different clusters. Cluster I had intermediate nNO values, a lower percentage of neutrophils, low IL-5 and IL-17, high IL-23, and IFN-y responses. Cluster 2 had high nNO levels, higher ocular symptom score, and high IL-5 response. Cluster 3 had a neutrophil response, predominantly Th1/Th17 with significantly higher levels of IL-17, IL-23, and IFN-y than in other clusters with lower nNO levels. This makes nNO a potential biomarker for endotyping allergic rhinitis (21).

nNO IN CHRONIC RHINOSINUSITIS

Because the upper respiratory tract is the main source of nNO and the paranasal sinuses are the main site of nNO production (2,3), it has also been the subject of numerous studies in chronic rhinosinusitis. Chronic rhinosinusitis in children is a condition defined by a duration of at least 90 days with two or more symptoms of purulent rhinitis, nasal obstruction, facial pressure/pain, and either endoscopic evidence of mucosal edema, purulent discharge, or nasal polyposis and/or CT imaging mucosal changes in the ostiomeatal complex and/or sinuses. It is divided into two distinct entities: chronic rhinosinusitis with and without nasal polyposis (22).

Studies of nNO in chronic rhinosinusitis are mostly performed in adults (23, 24, 25), although there are studies in children (26).

In all studies, nNO levels were consistently decreased in chronic rhinosinusitis, especially in cases with nasal polyps (27). Patients with chronic rhinosinusitis and nasal polyposis have significantly lower nNO levels compared to patients with chronic rhinosinusitis without nasal polyposis and with healthy subjects (28).

The conclusion from the various studies is that inflammation of the nasal mucosa, especially in association with polyps, prevents the flow of nNO from the sinuses into the nasal cavities, resulting in a decrease in nNO levels (23, 24, 25, 27). Another possible explanation for the decreased nNO levels in patients with chronic rhinosinusitis could be an impairment of NOS-2 synthase expression in the ciliary epithelial cells of the paranasal sinus mucosa (29, 30).

Since nNO plays a role in airway defense, this may lead to an additional increase in the risk for recurrent infections (31).

Response to treatment of chronic rhinosinusitis is also difficult to assess. Symptom scores, endoscopic findings, and parallel measures such as saccharin clearance are methods that can be used to assess response to therapy, as computed tomographic examinations are not suitable for repeated use. nNO has also been shown to be a useful tool to monitor chronic rhinosinusitis response to

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therapy. The study by Ragab et al. showed that initial absolute nNO values correlate inversely with changes in CT scans (Kendall's tau-b correlation coefficient -0.483, p<0.001), whereas the percentage increase in nNO after both drug and surgical treatment correlates with changes in symptom scores (Kendal's tau-b correlation coefficient -0.298, p<0.001), saccharin clearance time (Kendal's tau-b correlation coefficient -0.676, p<0.001), endoscopic changes (Kendal's tau-b correlation coefficient -0.368, p<0.001), polyp grades ((Kendal's tau-b correlation coefficient -0.209, p<0.05, and surgical scores (Kendal's tau-b correlation coefficient 0.291, p<0.01). (32). Absolute nNO values changed according to groups: in medically treated group the absolute nNO values increased from 724 ± 486 ppb to 1137 ±547ppb (p<0.001) as well as in the surgically treated group from 773 ± 426ppb to1129 ± 496ppb (p<0.001) at sixth months follow up (32).

nNO IN ACUTE RHINOSINUSITIS IN CHILDREN

Acute rhinosinusitis occurs as a complication of an upper respiratory tract infection. It is accompanied by inflammation of the mucous membrane of the paranasal sinuses and swelling of the mucous membrane, resulting in mechanical obstruction of the openings of the paranasal sinuses (33).

Hard-to-control cases of allergic rhinitis with persistent nasal symptoms and chronic cough are often predisposed by acute rhinosinusitis. However, there are few studies investigating the utility of nNO levels in the diagnosis of acute bacterial rhinosinusitis in children. One of them is a previously mentioned study by Wen et al. They compared the nNO values of children with unilateral maxillary sinusitis in children with allergic rhinitis with healthy controls. The nNO values of the healthy children were 389.9 +/- 97.2 ppb. The nNO values of children with allergic rhinitis were significantly higher (765.4+/-152.1 ppb, p<0.05). In patients with acute maxillary sinusitis, nNO values on the lesion side were significantly lower (151.2 ± 87.5 ppb, p<0.05) than in patients with allergic rhinitis and healthy subjects. The nNO values on the unaffected side were not significantly lower than in persistent allergic rhinitis and healthy subjects (748.1 ± 130.9 ppb). After antibiotic therapy, the nNO of the lesion side increased to the level of the unaffected side compared to unaffected lesion side (161.4 ± 164.6 ppb vs 9.6 ± 64.2 ppb; p < 0.05) (16).

Significant changes in biomarker levels and reciprocal correlations suggest that acute rhinosinusitis (ARS) elicits both local and systemic inflammatory responses, with the most severe response occurring after 2 to 3 days. Of the biomarkers examined in the study by Autio et al, high-sensitivity CRP and nNO most accurately reflect this inflammatory response, with CRP levels increasing and nNO levels decreasing in parallel with the increase of inflammation level (34).

nNO IN PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive inherited disorder characterized by the absence of ciliary structure or a deficiency in its function. It affects approximately 1 in 7500 individuals worldwide (35). Because the disorder impairs ciliary function, abnormal mucus excretion from the upper and lower airways occurs, resulting in respiratory distress in neonates of unknown etiology, productive wet cough in infancy, perennial rhinosinusitis, chronic bronchitis, and bronchiectasis. Low nNO levels in PCD were reported more than 20 years ago. When nNO levels are observed in children with PCD, they are extreme, even less than 10 times lower than normal levels in healthy patients. (36) Although nNO levels are quite low in PCD, similar nNO levels are reported in cystic fibrosis (37), diffuse panbronchiolitis (38), and acute viral respiratory infection (39). For a correct differential diagnosis, it is important to know that patients with allergic rhinitis and asthma, chronic obstructive pulmonary disease, primary immunodeficiency, non-CF-bronchiectasis, and chronic rhinosinusitis without nasal polyposis have higher nNO levels than patients with PCD (Table 1) (40). The situation is somewhat different in infants and young children, where nNO levels can often overlap with those of healthy infants. These levels in infants may be influenced by external factors, such as high concentrations of the environment NO.(41, 42). Even in children 2 to 5 years of age, nNO cannot always distinguish between healthy individuals and PCD patients. nNO levels increase rapidly during the first 18 months and then gradually approach adult levels at 12 years of age (42) (Table 2). Because there are few standards for nNO in neonates, healthy infants, and young children,

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measurement of nNO in these age groups is limited to research centers or, for ages older than 12 months, to experienced technicians in centers specializing in PCD (6).

Table 1. nNO values in different respiratory diseases.

Nasal NO values (ppb)				
Healthy controls	Primary ciliary dyskinesia	Cystic fibrosis	Chronic rhinosinusitis without nasal polyposis	Non-CF-bronchiectasis
543-976	17-180	241-896	862-3601	516-1098

Table 2. nNO values according to age.

NEWBORN	46 ppb	IQR 29-69 ppb
AGE 2	238 ppb	IQR 203-389 ppb
AGE 4-5	283.5 ppb	SD +/- 107.4 ppb
AGE 5-6	294.3 ppb	SD +/-121.6 ppb
AGE >6	350.2 ppb	SD +/- 123 ppb
AGE 6-17	449 ppb	SD+/-115 ppb

*Rate of increase from newborn to age 2 is 5.4% monthly.

Clinical studies in children 5 years of age and older with PCD have demonstrated high accuracy of nNO measurement (43). As demonstrated by Leigh et al. in patients with suspected PCD, nNO < 77 ppb, when measured with a chemiluminescence NO analyzer while blowing into a mouth resistor, has a specificity and sensitivity greater than 95% for the diagnosis of PCD compared with electronic microscopy and/or genetic testing (44). Only chemiluminescence technology has been rigorously validated in clinical trials for the detection of PCD (43, 45). Although some small studies on electrochemical NO analyzers have been performed for nNO measurement in PCD, they are not recommended for nNO measurement in PCD (46, 47).

It is also very important that patients have a high pretest probability for PCD before nNO testing is performed, because nNO measurement in the general population results in poorer diagnostic accuracy. When population with high probability of PCD was tested sensitivity of the test was 93.6% (95% CI 78.5% to 99.0%) and specificity was 84.1% (95% CI 78.9% to 88.4%). Calculation of positive predictive value was 46% (95% CI 30.2% to 54.5%) and for negative predictive value was 99.1% (96.6% to 99.9%) (48). To improve diagnostic accuracy, it is strongly recommended that the nNO test be repeated in two separate examinations at least two weeks apart (40). The nNO levels in patients with PCD remain low over time (44).

nNO IN CYSTIC FIBROSIS

Cystic fibrosis (CF) is a genetic condition inherited in an autosomal recessive manner. It results from various mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator gene). This gene is responsible for encoding a channel that allows the movement of chloride and bicarbonate ions. Individuals with mutation can have a variety of medical conditions that affect the respiratory, endocrine, gastrointestinal, pancreatic, biliary, and reproductive systems (49).

Within the domain of respiratory afflictions, children affected with CF confront the exigencies of enduring chronic bronchitis concomitant with bronchiectasis, intractable rhinosinusitis, and iterative ear infections. The quantification of nNO in the context of cystic fibrosis reveals levels that are understandably diminished compared to those in typically healthy children. However, these levels still register lower than those observed in cases of chronic rhinosinusitis, albeit surpassing those encountered in PCD. Güney et al. have measured the referral values of nNO by using nasal quiet exhalation method with chemiluminescence analyzer in children with PCD, CF and healthy children. They found the mean nNO values were respectively 10.4 ± 8.3, 22.8 ± 18.7 and 21 ± 8.9 ppb.

nNO was statistically significantly lower in PCD when compared to CF and healthy controls ($p<0.05$) (50).

DISCUSSION

The assessment of nasal nitric oxide (nNO) remains, in part, a research modality characterized by the absence of established normative benchmarks and uniform protocols tailored to distinct age cohorts and diverse analyzers, considering the array of respiratory maneuvers employed. Moreover, the outcomes of nNO measurements can be subject to the impact of environmental variables concerning environmental level of NO, thereby circumscribing the practicability of this method to specialized facilities. We still need to obtain normative data for young children and infants, electrochemical analyzers and tidal breathing techniques. It would also be useful to increase the number of studies on how to manage high ambient NO levels. Additional research will hopefully improve the clinical appliance of nNO measurement in everyday practice, but current knowledge can be used for the benefit of patients as nNO is a completely noninvasive method.

CONCLUSIONS

nNO is a noninvasive, clinically applicable test for use in pediatric allergic rhinitis, chronic rhinosinusitis, acute rhinosinusitis, primary ciliary dyskinesia and cystic fibrosis. It can be used as a complementary method in the diagnosis of these respiratory diseases and as a monitoring tool during the treatment of allergic rhinitis, acute and chronic rhinosinusitis.

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