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Nasal NO: normal values in children age 6 through to 17 years

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ABSTRACT: The present study is an assessment of normal values of nasal nitric oxide (nNO) in healthy children.

Healthy children aged between 6–17 yrs were recruited from three schools in Rotterdam (The Netherlands). Breath was held for 10 s, while air was extracted from one nostril at 700 mL·min^{-1}. The mean nNO value at the response plateau after 7–10 s was recorded and the average of three measurements was used.

In total, 340 children participated; the male:female ratio was 156:184. Three reliable measurements were available in 85% of the children. The nNO concentrations were distributed normally (mean 449 ppb, SD 115). They were not associated with sex, passive smoking or body mass index. In children aged <12 yrs nNO correlated positively with age, history of adenoidectomy and ambient NO. In children aged ⩾12 yrs ambient NO was the only significant modifier. Prediction rules for nNO values in children were formulated.

In conclusion, the current study presents normal values for nasal nitric oxide in children, which can be used to assess the value of nasal nitric oxide in respiratory illnesses.

KEYWORDS: Children, nasal nitric oxide, normal values

Nitric oxide (NO), a potent biological mediator, was first demonstrated to be present in orally exhaled air by GUSTAFSSON *et al*. [1]. Two years later ALVING *et al*. [2] observed the presence of NO in the human nasal airways, and in the paranasal sinuses, in much higher concentrations compared with the lower airways. Studies in healthy adults indicate that NO in nasal air is mainly produced in the epithelial cells of the nasal cavity, particularly in the paranasal sinuses [3]. NO is known to be involved in the local host defence of the upper airways and acts as an airborne messenger and as a regulator in mucociliary function in the nasal airway [4–7]. In addition nasal NO (nNO) is affected by inflammation of the upper airways [8–12].

Measurement of nNO can easily be performed and can be used to screen for disease or to monitor treatment effects. However, the uses of nNO measurements within clinical practice are still limited. On the one hand, the effects of different physiological and pathological conditions on nNO still require further research. On the other hand, there is a lack of consensus on measurement techniques, which consequently lead to different findings of nNO concentrations in different airway illnesses, such as sinusitis [10, 13], polyposis nasi [8, 10] and (allergic) rhinitis [9, 14–16]. Exceptions are cystic fibrosis (CF) [17–22] and primary cilliary dyskinesia [23–26]. It is well established that the nNO levels in these patients are extremely low and are independent of the measurement methods used.

There is only one study on normal values of nNO in healthy children [27]. The assessment of normal values of nNO may be important for determining the role of nNO as a marker of inflammatory disorders of the upper airways. The reported effects of inflammation on nNO are not consistent [10, 13, 25, 28–32]. The conclusions of the various studies may differ because of methodological factors, including different sampling methods, sampling flow-rate and the influence of ambient NO. In previous studies, the effects of airway diseases and treatment on nNO have been compared with normal nNO levels obtained from relatively small control groups, which are not suitable to assess normal values, and do not necessarily represent a sample of the general population [11, 14, 33]. Therefore, the current authors aimed to collect normal values for nNO in a large population of healthy children aged between 6–17 yrs, using a previously validated method [34].

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METHODS

Subjects and setting

Children (aged 6–17 yrs) from two primary and one secondary school were invited to participate. All parents and children ($\geqslant$12 yrs of age) were asked to fill out a questionnaire based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire [35, 36]. This was extended with questions on inclusion and exclusion criteria and potential confounders (sex, age, height, weight, body mass index (BMI), history of ear, nose and throat surgery and passive smoking). The inclusion criteria were: age 6–17 yrs, written consent from parents and the child (aged $\geqslant$12 yrs). Exclusion criteria were: physical exercise immediately before the NO measurement; active smoking; allergy and/or asthma (based on ISAAC core questionnaire); airway influencing medication (*e.g.* inhaled corticosteroids, nasal decongestives); chronic airway disease (*e.g.* CF, primary ciliary dyskinesia); and recent (<3 months) adeno- and/or tonsillectomy.

Nasal NO measurements

The nNO was measured with a NIOX chemiluminescence analyser (Aerocrine, Solna, Sweden). The air was sampled with a flow of 700 mL·min^{-1} from the nostril with the best patency [34]. Calibration of the equipment was performed every 14 days using 100% nitrogen to zero and with a certified calibration gas (NO, 2120 ppb). The NO signal was sent to a computer data acquisition program (NIOX, nasal mode; Aerocrine) that displayed real-time measurements.

The nNO was measured during breath-hold after a deep inspiration. An NO-inert olive was placed firmly against one nostril. The olive was connected to an adjustable vacuum pump (custom made) to obtain a flow of 700 mL·min^{-1} [34]. From a side port a sampling tube was led to the NIOX. Subjects were asked to take a deep breath and hold it for 10 s. The average nNO concentration was calculated at the plateau between 7–10 s after breath-hold (fig. 1). Preliminary experiments indicated that with this technique, the soft palate was closed as evidenced by absence of CO_2 in the aspirated air. Any leakage was evident from an increase in CO_2 and a sudden drop in nNO. The manoeuvre was performed in triplicate. To obtain three correct measurements a maximum of six attempts were made. Before every measurement the ambient NO concentration was recorded. The Ethical Committee of the Erasmus Medical Centre (Rotterdam, The Netherlands) approved the study protocol.

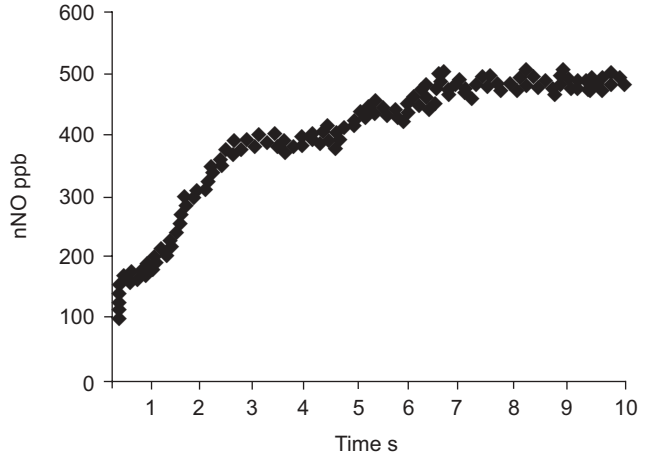

FIGURE 1. Example of on-line nasal nitric oxide (nNO) measurement during 10 s of breath-hold and aspiration flow of 700 mL·min^{-1}.

Statistical methods

The nNO concentrations were expressed as the mean of three measurements. For the analysis of the relationship between nNO and potential confounders, univariate analyses were performed. When the univariate analysis appeared to be significant ($p<0.10$; 90% confidence interval) the variables were included in a multivariate analysis. For the multivariate analysis different linear and quadratic models were used to test nNO concentrations in healthy children as a function of covariates. Algorithms were formulated to predict normal nNO in healthy children by fitting linear and quadratic models.

RESULTS

Study population

In total, 1,343 subjects were invited by letter to participate, and of these, 606 children (58%) responded. The response at the secondary school (36%) was lower than at the two primary schools (61% and 57%, respectively). In total, 340 children (56%) aged between 6–17 yrs met the inclusion criteria and were enrolled (156 male and 184 female; fig. 2). There were 266 (44%) children excluded from the study (128 wheezed, 154 sneezed, 66 smoked, 69 other health disorders; numbers overlap). Most children were Caucasian (92.4%). The mean (SD) BMI was 18.5 (3.1). A total of 41 (12.1%) of the enrolled children had a history of adenoidectomy, but none occured 3 months prior to the measurements being taken.

Nasal NO values

From the study population, 289 children successfully performed the nNO measurements (mean age 11.6 yr), with 51 (15%) having problems with performing the measurements (mean age 11.2 yr), including difficulties in maintaining an adequate palatal closure and failure to achieve a stable plateau. This group was not significantly different from the whole study group. The values of nNO were normally distributed (mean 449 ppb; SD 115; fig. 3). The ambient NO ranged from 5–182 ppb, with a median of 43 ppb. The nNO values were independent of sex, passive smoking, height, weight or BMI.

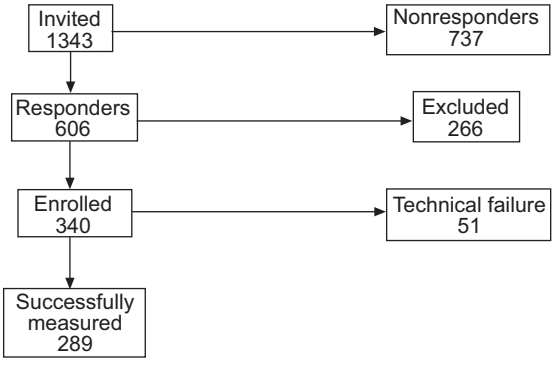

FIGURE 2. Flow chart of the study.

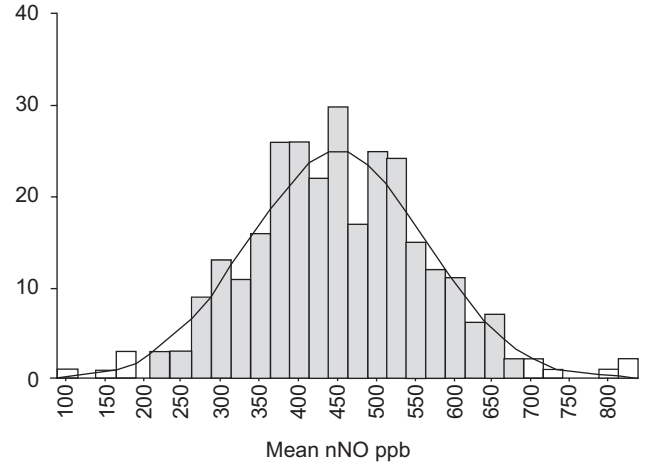

FIGURE 3. Distribution of mean nasal nitric oxide (nNO) values (ppb) in healthy children aged between 6–17 yrs. ■: 95% of the subjects. Mean=449.3; standard deviation=114.9; n=289.

Several models were fitted to describe the relationship between nNO and age and other covariates. Plotting nNO against age suggested an increase towards a plateau at older age (<12 yrs; fig. 4). Therefore, a quadratic model was fitted but did not appear to contribute significantly in describing the relationship. A standard linear model did not fit the data sufficiently. Subsequently, a linear model depending on age, with two different slopes connecting at one point was fitted with a non-linear least squares method. The model predicted the intersection of the two slopes at the age of 11.2 yrs. Taking into account the interaction with age the current authors proposed to stratify for age in two groups in the algorithm for predicting nNO.

In children aged <12 yrs the mean nNO value correlated positively with age (adjusted $\beta=11.5$; $p<0.01$), was modified by a history of adenoidectomy in the past (adjusted $\beta=-57.5$; $p=0.02$), and correlated positively with ambient NO (adjusted $\beta=0.50$; $p<0.01$). These associations were nonsignificant in children aged ⩾12 yrs except for ambient NO. Two prediction rules for nNO value in healthy children were derived. The equations predict the mean nNO concentration corrected for age in years, history of adenoidectomy (yes=1 and no=0) and ambient NO (in ppb) in healthy children (on the condition of the inclusion criteria described previously).

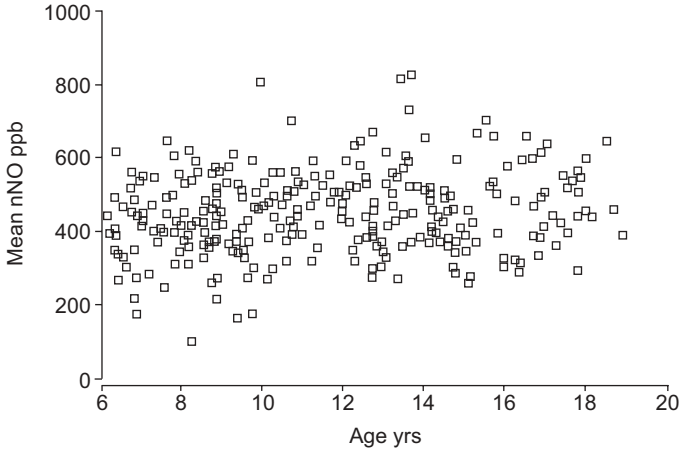

FIGURE 4. Nasal nitric oxide (nNO) values in healthy children by age.

Prediction rule for nNO age <12:

$$\text{nNO} = 314.6 + 11.5 \times \text{age} - 57.5 \times \text{history of adenoidectomy} + 0.5 \times \text{ambient NO}$$

Prediction rule for nNO age ⩾12:

$$\text{nNO} = 452.6 - 2.9 \times (\text{age} - 12) - 16.0 \times \text{history of adenoidectomy} + 0.5 \times \text{ambient NO}$$

For example, the approximate nNO concentration of a child aged 10 yrs who has never had an adenoidectomy and has an ambient NO of 15 ppb will be:

$$314.6 + (11.5 \times 10) - (57.5 \times 0) + (0.5 \times 15) = 437.1 \text{ ppb}$$

DISCUSSION

The present study assessed nNO in a large group of healthy children. In 289 children aged 6–17 yrs, nNO was normally distributed and depended on ambient NO and, only in those aged <12 yrs, on age and history of adenoidectomy. Sex, passive smoking, BMI, weight and height did not influence nNO. The current study is one of the first studies on normal values of nNO conducted in a large number of healthy children.

In the majority of the clinical studies on nNO, comparisons are made with small ''normal'' control groups. There is only one study [27] that formally intended to establish normal nNO values in children. DAYA *et al*. [27] assessed nNO values in 30 healthy children, 18 males and 12 females aged between 3.2–17.6 yrs, and found a considerable variability, which may be ascribed to the racial heterogeneity (17 Caucasian, seven Oriental and six Black children) and the small size of the study group. In addition to this, there were only between one and four children assigned to each age category. The children were recruited from siblings or friends from patients attending an otolaryngology clinic, and may not represent a sample of the general population. Moreover, age and other potential confounders such as ambient NO were not taken into account.

On the basis of the current literature children with airway morbidity, recent infections (<1 week) and recent adeno- and/or tonsillectomy (<3 months) were excluded [3, 8, 10, 11, 13, 14, 16, 29, 30, 33, 37–47]. This also applied for smoking and children using airway-influencing medication. Physical exercise immediately before the measurements was not allowed. Sex, age, height, weight, BMI, history of adenoidectomy, passive smoking and ambient NO were considered as covariates.

In the current study, age was positively associated with nNO. The association was significant and especially evident in children <12 yrs of age. Radiological anatomy of the paranasal sinuses shows that sinuses reach their final size in 12-yr-olds [48, 49]. Due to this, and in combination with the results of the multivariate modelling, the data with a break at the age of 12 yrs was analysed. The association between nNO and age in children <12 yrs was approximately three times stronger when compared with children aged ⩾12 yrs. In the latter

group the association was no longer significant, indicating that age is an interaction factor. These findings are in agreement with the hypothesis that nNO concentrations are correlated with the anatomical development of the paranasal sinuses [48, 49]. An additional factor, explaining the association between age and nNO might also be the increase of the nasopharyngeal airway during pre- and early adolescence while adenoid regresses. The altered volume influences the intranasal flow and, perhaps, nNO measurements.

Adenoids develop during infancy and reach a maximal size between 2–14 yrs [50]. In the present study nNO was significantly lower in children with a history of adenoidectomy. This association was only found in children aged <12 yrs, probably because after this age adenoids regress rapidly, making children with an adenoidectomy comparable with children without. Besides, removal of adenoids is more likely in case of chronic respiratory infections, which might cause elevated nNO [14, 29, 30].

Little is known about how to deal with the influence of ambient NO on nNO. A significant relation was found between ambient and nNO, ambient NO was ~10% (median 43 ppb) of the mean nNO. Therefore, the presented absolute levels and the calculated output (ppb × sample flow) may have been overestimated. This is a problem in the assessment of nNO as a diagnostic tool or monitoring tool in case of, for example, allergic rhinitis where there might be only subtle changes in nNO, in contrast with, primary cilliary dyskinesia or CF where nNO is much lower than in healthy subjects. Several investigators have simply subtracted ambient NO from nNO [16, 43] without justification. The present data show that ambient NO and nNO are not simply additional, but that correction for nNO can be made by subtracting 0.50 ppb per ppb of ambient NO. The fact that a relationship with ambient NO was found, which other studies have not, could be explained by the large range of ambient NO values (5–182 ppb) in the present study, whereas in most previous studies ambient NO did not exceed 20 ppb [9, 10, 14, 33].

Further studies in other populations should confirm whether the current prediction rules, subtracting 50% of ambient NO, have general validity. For the moment it seems prudent to include healthy controls in any studies exploring nNO in disease.

The present study used questionnaire-based information for inclusion, without physical examination and/or laboratory tests to confirm the health status of the studied subjects. The validity of such findings can be questioned. However, physical examination is not sensitive to detect allergic disease, and the questionnaires used are well validated in the ISAAC study and showed good agreement with objective tests of allergy [35, 36].

In conclusion, a normal reference range for nasal nitric oxide in healthy school children was established, and an algorithm developed to predict normal nasal nitric oxide on the basis of age, ambient nitric oxide and a history of adenoidectomy. Establishing the normal range of nasal nitric oxide in 6–17-yr-old, healthy children is important for the investigation of the nasal nitric oxide measurement as a screening, or even diagnostic test for various inflammatory conditions of the upper airways, such as allergic rhinitis, cystic fibrosis or primary ciliary dyskinesia.

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