Original Article

Effects of age, gender, and environmental exposures on exhaled nitric oxide level in healthy 12 to 18 years Qatari children

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Abstract:

CONTEXT: Fractional exhaled nitric oxide (FENO) is a useful noninvasive diagnostic tool for asthma and some other pediatric respiratory diseases. Factors affecting FENO level are variable in different populations and studies.

AIMS: To estimate the normal values of exhaled nitric oxide for Qataris 12 to 18 years of age. Other objectives were to measure the correlation of anthropometric and other potential factors with FENO levels.

SETTINGS AND DESIGN: Community-based, cross-sectional study.

METHODS: A total of 438 Qatari national school children from both genders were randomly recruited in cross-sectional study. Of them, 203 were non-atopic and hence included in the statistical analysis. Questionnaires including personal data, demographic data, and other factors that may affect FENO level were distributed.

STATISTICAL ANALYSIS USED: Comparison of means done using *t*-test. We performed Spearman's rho test to measure correlations. Data analysis was done using PASW 18.0 Release 18.0.0, 2009.

RESULTS: The geometric mean of FENO levels for all subjects was 14.1 ppb (upper level CI 95% - 36.3 ppb). FENO was significantly higher in males ($R^2 = -0.254$, $P<0.0001$) and was negatively correlated with increasing age for the whole study population ($P=0.036$). This decline was interrupted by a significant upraise at the age of 15 years ($P=0.0462$) which seems to be driven by the males ($P=0.0244$). FENO levels were lower in subjects exposed to cats ($P=0.019$). We could not find significant correlation between FENO and other factors studied.

CONCLUSIONS: Estimated FENO level with 95% CI in Qatari children, which is probably close to those in other Gulf countries, will be helpful clinically. The lower level of FENO with female gender, increasing age, and exposure to cats needs to be further studied to establish the association and to understand the underlying mechanisms.

Key words:

Age, cat, children, exhaled nitric oxide, females, fractional exhaled nitric oxide, gender, males, puberty

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Fractional exhaled nitric oxide (FENO) measurement is useful in screening for or monitoring treatment of asthma and probably some other respiratory diseases. FENO is measured using a noninvasive technique. It can be measured either online, or off-line, by collecting the exhaled breath in an inert bag and analyzing it remotely.

Knowing normal values in healthy subject is essential for clinicians and researchers seeking to apply FENO measurements in everyday practice. Many attempts have been made to establish such reference values.[1-5]

The early reports have used the online gold standard method.[2,6-8] Later studies compared online with offline methods, and showed that the results of both are comparable.[9-12] The recently introduced hand-held machine has been studied as well and compared with the laboratory-based online device results and found to be comparable.[13-15]

In addition, some studies showed gender and age variation in the normal values of the FENO,[1,2,16-18] while this was not observed in other studies.[8]

Most of the studies revealed internationally comparable results; however, some studies have shown different values in different populations in the form of higher FENO levels among Asians.[3,16,19]

To our knowledge, there are no published reference values of FENO among children in the Arabian Gulf or Middle East region. One study from Saudi Arabia tried to establish normative values for FENO in adults.[20]

Because of the wide variation of FENO level among different ethnic groups, the normal FENO

levels for our population cannot be accurately determined, so that clinical decisions related to individual's FENO level can be confidently taken. Our primary objective was to estimate normal values of exhaled nitric oxide for Qatari children 12 to 18 years of age. Other objective was to evaluate the contribution of potential factors listed in ATS/ERS latest statement in 2005[21] on FENO level in those children.

Methods

Study subjects and protocol

This is a cross-sectional study. We planned to recruit 175 healthy Qatari children—25 for each of the 7 age groups between 12 to 18 year of age—who attend intermediate and secondary schools in Qatar. We estimated that the return rate of the consent form is about 40% based on previous studies of FENO among school children.[19] We considered that the chance of any child having any of the four atopy presentations—physician diagnosed asthma, wheezing, allergic rhinitis, or eczema ever—is 48% based on a previous study in the State of Qatar that involved 3 500 schoolchildren.[22] As the age group in that study does not exactly match the age groups in the current study, we presumed the prevalence of atopy to be around 50% in the targeted age group. Therefore, we intended to recruit 730 children to get 350 children tested in order to have the 175 healthy children needed.

Healthy, non-atopic, Qatari national children, 12- to 18-year-old were included.

The children were excluded from the study if they have any of the following:

History of wheezing; physician diagnosed asthma; allergic rhinitis; or eczema ever according to modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires. In addition, those who smoke primarily or had respiratory tract infections within one week or have chronic respiratory disease were excluded.

The schoolchildren were selected from two boys and four girls intermediate and secondary schools in the State of Qatar. Written informed consents and questionnaires were distributed to the randomized schoolchildren to be completed by the students' parents. Exhaled nitric oxide was measured for all children whose parents signed the written consent form.

The study was approved by the ethical committee of the Medical Research Center at Hamad Medical Corporation, Doha, Qatar.

Data analysis was done using PASW 18.0 Release 18.0.0, 2009.

Fractional exhaled nitric oxide measurements

Nitric oxide measurements were performed using a portable nitric oxide analyzer (MINO; Aerocrine AB; Smidesvägen, Sweden), the result of which correlates well with those obtained using an established laboratory analyzer.[13-15]

The measurement protocol was in accordance to the ATS/ERS latest recommendations in 2005.[21] Accordingly, the ambient NO was reported in each of the locations of the test daily.

Subjects were asked to empty the lungs and take a fast and deep breath through the NO-scrubber to total lung capacity. The child was then asked to exhale slowly and steadily through the filter over 6 seconds at a flow rate of 50 ± 5 ml/s with the help of incentive animation to provide at least two approved FENO measurements within 10% or 2 ppb of each other, with a maximum of six trials. The tests were done at the same time of the day between 8 and 11 am to avoid the diurnal variation of FENO level reported by some investigators,[23] although it has been disputed by others.[24] Another reason for choosing this time is that all physical education lessons were scheduled in the afternoon; therefore, this will ensure the absence of strenuous exercise for at least 1 hour before the test. The data were collected over a 5-month period from November 2008 to March 2009.

Ambient NO was measured each day and in each location using same machine, i.e., MINO; so, we can confidently measure correlation between ambient and exhaled nitric oxide levels.

Questionnaires

Questionnaires included personal, demographic, and contact information.

Furthermore, a modified ISAAC questions were used to verify whether the child has any of the four cardinal features of atopy: Eczema, physician diagnosed asthma, wheezing, and allergic rhinitis. The subject was considered non-atopic if the answer is "NO" to all of the four questions.

In addition, the questionnaire included questions about the frequency and duration of the exposure of the child to passive smoking, and if the child is exposed regularly to animals and the presence of any food or drug allergy.

The children were asked before the test about performing exercise within one hour of the test, food ingested within 3 hours, and history of cold within one week to decide about inclusion and for later correlation.

The questionnaires were translated into Arabic by a professional translator. A translated Arabic version of the questionnaire was revised by a bilingual consultant pediatric pulmonologist, and then back-translated by a bilingual physician who was unfamiliar with the original English version. Both translators made necessary corrections after considering the minor differences that occurred.

Results

Subjects

We distributed 754 informed written consent forms. We received 438 (57.2%) filled and signed consent forms. Of them, 418 (95.4%) completed the questionnaires. 212 subjects were excluded. Five of them had chronic respiratory diseases, three smoke primarily, and the rest had at least one of the four cardinal symptoms of atopy. Those with recent upper respiratory infections were retested in a later date. Three subjects could not perform the test; therefore, a total of 203 were included in the statistical analysis. The success rate of test performance was 99.2%. No adverse effects were reported during or after measurements. Baseline characteristics of the subjects are shown in Table 1.

Table 1: Baseline characteristics of healthy subjects

	Weight (Kg)	Height (cm)	BMI (Kg/m²)	BSA (m²)	Ambient NO (ppb)	FENO (ppb)
Mean (Range)	60.3 (29-155)	159 (135-185)	23.6 (13.2-61.3)	1.6 (1.1-2.5)	22.8 (5-114)	16.7 (5-90.5)

FENO = Fractional exhaled nitric oxide

Fractional exhaled nitric oxide levels

Data were skewed to the right, so data analysis was performed after log transformation and geometric mean was used for analysis. Readings above two standard deviations from the geometric mean were considered outliers and were excluded from statistical analysis.

The geometric mean of FENO levels for all subjects was 14.1 ppb with a 95% confidence interval for the upper FENO level of 36.3 ppb. FENO concentration was significantly higher in males than in females (*t*-test), with a difference in means of 5.8 ppb (95% CI 2.7-8.9 and $P<0.002$) [Table 2]. In addition, there was a negative correlation of FENO with increasing age using Spearman's rho Correlation ($R^2=-0.19$; $P=0.0007$) [Figure 1].

Using Mann-Whitney test, we noticed a significant rise of FENO at the age of 15 compared with 14 years old for all of the subjects ($P=0.046$) [Figure 2]. This seemed to be due to the effect of male subjects mainly who had a similar rise of FENO at the age of 15 with a *P* value of 0.024. However, for the females, there was a trend toward increase of FENO at the age of 14 years, but it was not statistically significant ($P=0.35$).

A negative correlation was noticed between FENO levels and exposure to cats with a mean FENO levels for those exposed to cats of 13.4 ppb and those not exposed of 20.5 ppb ($P=0.019$).

There were no correlations between FENO levels and each of weight, height, Body Mass Index (BMI), Body Surface Area (BSA), ambient NO, cigarette exposure, food allergy, drug allergy, or animal exposure excluding cats (chicken, sheep, dog, camel, horse, pigeon, and other birds).

The presence of outliers and respiratory tract infections within one week of FENO measurement did not affect the results.

Discussion

Using locally or regionally obtained normative data of FENO in children is very important when it comes to comparative studies and utilization of this clinical tool in clinical practice; therefore, we elected to study our local population. The number of subjects we studied was reasonably high, taking into consideration the previous studies of normal FENO level among children and the total population of the state of Qatar.

To minimize the effect of ethnic variation, only Qatari nationals were included in this study. Ethnic differences in FENO are well established in many studies.[1,19,25] Buchvald *et al*.[1] showed that FENO is lower in Whites compared with the Blacks and Asians, although the number of non-whites was small, and this was confirmed by Kovesi *et al*.[19] The only published study for normative FENO values in the Arabian Gulf region is from Saudi Arabia for adult subjects.[20] This study showed mean FENO levels of 22.79 ppb+/-8.13 which are comparable with the international figures, but higher than ours (14.1 ppb). The FENO level of our study population seemed to be higher

Table 2: FENO arithmetic mean and SD according to age and gender in healthy subjects

Age (years)	No. of subjects	Males no. (%)	FENO geometric mean (ppb)	SD (ppb)
12	9	7 (77.8)	19.4	10.4
13	28	9 (32.1)	14.4	8.6
14	36	16 (44.4)	15.7	10.3
15	34	14 (41.2)	17.1	14.7
16	45	18 (40)	11.9	13.3
17	33	13 (39.4)	12.4	6.4
18	18	3 (16.7)	12.9	7.0
Males	80	80 (100)	16.2	15.2
Females	123	0 (0)	12.9	6.6
Total	203	80 (39.4)	14.1	11.2

FENO = Fractional exhaled nitric oxide

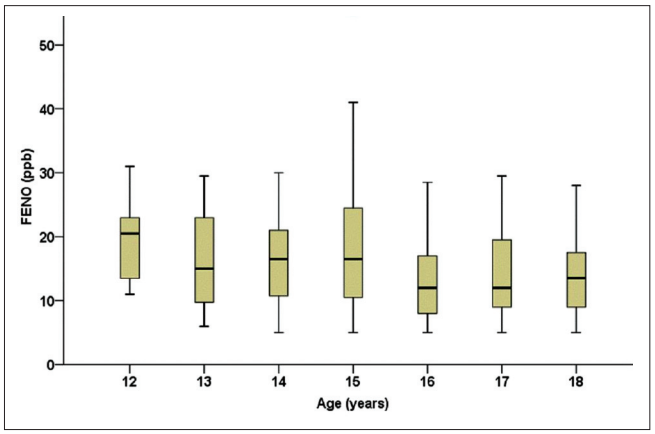

Figure 1: Box-plot. FENO levels (ppb) for each age group

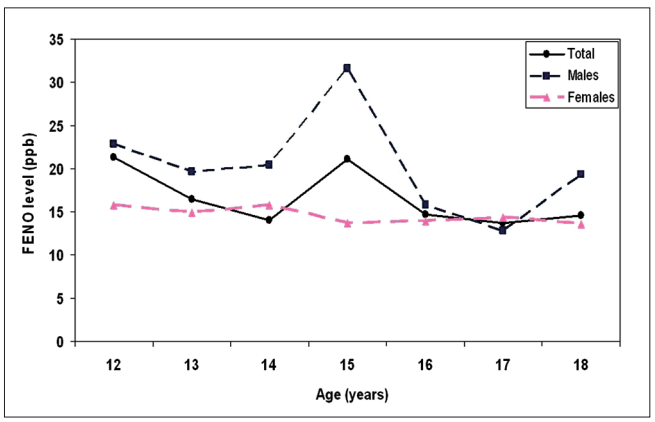

Figure 2: FENO changes with age for the whole population and for each gender separately

than in whites[1,4,19] but lower than in Asian children[19,25,26] of the same age groups and using same measurement protocol [Figure 3]. However, our values are closer to Caucasians than Africans and Asians. This is similar to the findings of Kovesi *et al*. on children of Arabic descent (Personal Communication).

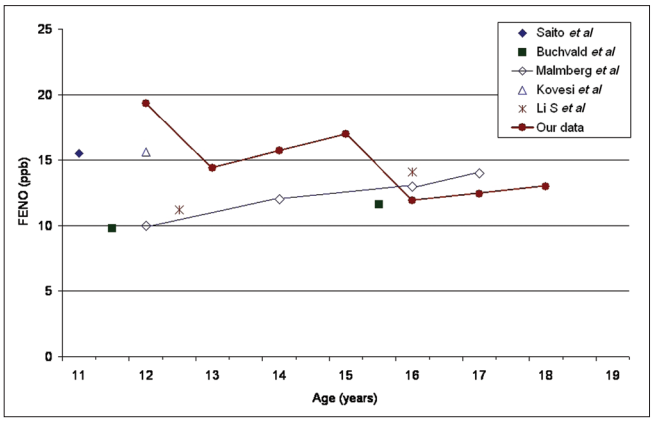

Figure 3: Age-related FENO values from different publications (Saito *et al*.,[25] Buchvald *et al*.,[1] Malmberg *et al*.,[4] Kovesi *et al*.,[19] Li *et al*.[26])

The cause of such ethnic differences is still not clear. It may be related to the rate of NO production by the alveolar or bronchial cells. Genetic studies among adults suggested an association between FENO and polymorphisms in the Nitric Oxide Synthase (NOS).[27,28] In children, there is a recent evidence of an association between NOS polymorphism and atopy as well as asthma and FENO level.[25,29,30] Another explanation for the ethnic difference in FENO levels may be related to the difference in the alveolar surface area that affect the amount of NO produced and hence exhaled. This may be explained by correlation of FENO with the weight, surface area,[1,4] height,[1,4,19] and pulmonary function test parameters[4,25,31] in different studies among children. In our study, we did not show any statistically significant relationship between FENO and any of these variables.

Interestingly, gender difference in FENO was only found among Asians in most of the epidemiologic studies performed on children.[16,19] We found similar gender difference among Qatari children; therefore, gender should be considered while interpreting FENO results among our population. Genetic polymorphism of NOS performed by Leung *et al*.[32] failed to explain this difference, which may indicate that the difference is due to hormonal or anatomic factors. The stimulatory effect of testosterone[33-35] and the inhibitory effect of estrogen on FENO may indicate a hormonal cause of this gender difference, while higher pulmonary surface area among males[36] may point toward anatomic effect.

Many studies found a positive correlation between FENO and increasing age among children,[1,4,19] while others failed to prove such association.[16,37] Unlike all previously published data, our study showed a negative rather than positive correlation of FENO with age. This is probably why FENO levels are higher than those reported in other studies for the younger age group (12-15 years) but lower for the older age group (16-18 years). In general, FENO levels tend to be higher in adults than in children.[18] Whether this is due to the difference in lung size or increased endogenous production of NO related to NOS activity is still controversial. The first theory is supported by the finding that FENO level is affected by height and body surface area rather than age, both in adults and children.[4,19,38] In addition, among children, a positive correlation was found between FENO and BMI.[1,16,18] The other theory is supported by the notion that FENO continue to increase during adulthood despite fixed or even declining lung volume.[38] However, in our study, no association was noticed between FENO and weight, height, BMI, or BSA using both univariate and multivariate regression analysis. Inadequate sample size to show such correlation is possible; however, our sample size was larger than some of other studies that revealed significant correlation.[4] Therefore, FENO among our population may be affected by factors other than anthropometric measures.

The downward trend of FENO with age was interrupted by higher levels at age 15 years for boys, before the curve resumes its downward trend. A similar phenomenon was noticed among Asian children in a report by Kovesi *et al*.; in that study, there was a drop in FENO level at 9 to 10 years, while there was a rise at 10 to 12 year olds. In our study, we did not look for clinical or hormonal changes related to puberty, which is the possible mechanism. Testosterone surge at puberty may explain the increased level in our male subjects at 15 years. To the authors' knowledge, there are no longitudinal cohort studies to monitor the FENO changes around puberty and correlate them to the hormonal changes.

Interestingly, there was no relationship between FENO level and cigarette smoke exposure, which was explained by NOS3 polymorphism difference which mediate cigarette effect on FENO in a previous study.[39]

Among the environmental exposures, we included in the questionnaires that affect FENO level, only cat exposure had a significant negative effect on FENO level. Similar correlation had been reported by some studies;[40] however, most of the others revealed opposite results.[39,41] In another study of indoor factors affecting FENO, dogs were associated with a significant reduction in FENO, but cats were not.[42] This may be explained by the hygiene hypothesis which correlates early animal exposure to reduced atopic propensity later in life. The same study observed, as we did, no relationship between environmental tobacco exposure and FENO.

We could not determine the sample size accurately without having a preliminary data to determine the approximate standard deviation of FENO level and prevalence of exclusion criteria, especially atopy, among our population. Moreover, the collection of samples took 5-month period and hence spanned two seasons, which may affect the results. However, such effect was not detected when data were stratified according to the month of sampling. The sample size targeted according to pre-study data to measure FENO reference values for the age range studied with 95% confidence was accomplished. However, given the standard deviation observed in the study and success rate of performing FENO, the sample size needed to determine reference FENO levels for each age group is estimated to be 45 subjects. Therefore, we intend to recruit 315 subjects in a follow-up study to achieve this aim for the 7 age groups.

In conclusion, the results of our study, which is the first for children in the region, revealed higher FENO levels than in Whites, but lower than Asians for the targeted age group with the same gender trend of Asians. Interestingly, we documented

a previously unreported negative correlation of FENO with age, uprising level around puberty for males, and negative correlation with exposure to cats. Further studies in the region are needed to verify such associations. In addition, after the follow up study, we will formulate an equation for normative FENO levels for each age group in our population, taking in consideration the abovementioned variables that affect measured FENO values to use them in the daily clinical practice.

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