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Asthma in the elderly: The role of exhaled nitric oxide measurements

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Summary

Asthma in the elderly is poorly understood because only a small minority of asthma studies have investigated this patients group. Fractional Exhaled Nitric Oxide (FENO) has been extensively studied in children and adults with asthma, but little is known about FENO in elderly asthmatics. We studied the role of serial measurements of FENO in elderly subjects with asthma.

Thirty stable asthmatics 65 years old and older were followed for one year with evaluations at baseline and every three months. We looked for associations between FENO and subjects' demographics, comorbidities, asthma treatment, spirometric values and Asthma Control Test (ACT) scores. FENO was not elevated in our study subjects throughout the study period (mean < 30 ppb). FENO significantly increased and FEV1% decreased between first and last study visit, while ACT scores and steroid dose remained unchanged. No significant correlation was found between FENO and FEV1/FVC, other spirometric values, inhaled steroid dose or ACTscores at any time point. No associations of FENO were found with age, sex, Body Mass Index (BMI), atopic status, disease duration, presence of rhinitis or gastroesophageal reflux disease (GERD), or other medications used. Moderate asthma exacerbations did not consistently cause an increase of FENO.

In stable elderly asthmatic patients, FENO was not elevated and did not correlate with subjects' demographics, comorbidities, treatment, symptoms or spirometric values. Routine measurements of FENO may not be clinically valuable in elderly asthmatics.

Keywords

Asthma; FENO; Elderly

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People older than 65 years of age are a rapidly growing demographic group and will account for over 20% of the U.S. population by the year 2050.[1] Most studies on asthma have not included elderly asthmatics who are more likely to be underdiagnosed, undertreated, and hospitalized when compared to their younger counterparts.[1] Pulmonary function tests and monitoring asthmatic symptoms may be less reliable in the elderly because of other potential causes of respiratory impairment and delayed awareness of bronchoconstriction. Elderly asthmatics have an increased mortality compared to their non-asthmatic counterparts.[1]

FENO has been proposed as a marker of airway eosinophilic inflammation, but the role of FENO measurements in patients with asthma remains unclear. To our knowledge, no study has addressed the value of serial FENO measurements in older asthmatics. Therefore, we performed such measurements every three months for one year in a group of elderly, stable asthmatic patients. We looked for associations between FENO and subjects' demographics, comorbidities, asthma treatment, spirometric values and ACT scores.

Thirty subjects 65 years old and older with asthma followed in an Allergy and Immunology practice in suburban Philadelphia were included in the study. Twenty-five study subjects were lifetime nonsmokers and five smoked for less than 10 pack-years. The study was approved by the Main Line Hospitals Institutional Review Board.

The presence of atopy was verified by allergy skin tests. Spirometric values were obtained by KoKo Spirometer (nSpire Health, Inc, Longmont, CO). FENO was measured online in triplicate determinations by NIOX MINO (Aerocrine, New Providence, NJ) according to the ATS/ERS guidelines and reported in ppb as the mean of the three values.

Statistical analysis was performed using STATA v10 (College Station, TX). Descriptive variables were expressed as means and standard deviation, Multiple linear regression was used to test association between groups of variables and group differences were tested using unpaired t-tests. Significance was accepted at alpha Z 0.05 with no adjustment for multiple comparisons.

Table 1 shows the study subjects' characteristics at baseline. We found that FENO was not elevated (mean < 30 ppb at each of the four study visits) and there were no significant differences between any of the values of FENO, FEV_1% and ACT scores at each study visit and the ones obtained at the previous visit. However, there was a significant increase in FENO (to 27 ± 14.5 ppb, $p = 0.02$) and a decrease of the $FEV_{1\%}$ (to 71.3 ± 15.8%, $p = 0.005$) between the first and the last visits, while ACT scores (22.1 ± 2.8 vs. 22.3 ± 3.3) and inhaled steroid dose (353 ± 363 vs. 375 ± 374 mcg/day) were unchanged.

We found no association between FENO and age, sex, BMI, atopic status, disease duration, rhinitis, or GERD ($p > 0.34$ for all measurements).

We found no association between FENO and inhaled steroid dose, treatment with a long-acting bronchodilator, leukotriene antagonist, or nasal steroid ($p > 0.18$ for all measurements). FENO was higher in the subjects who were not receiving inhaled steroids (36.8 ± 16.1 vs. 24.2 ± 19.2 ppb, visit 3, n = 6 and 24, respectively), whereas ACT (20.8 vs.

21.3) and $FEV_{1\%}$ (71.9% vs. 73.5%) were unchanged. This difference did not reach statistical significance ($p = 0.11$), possibly due to the small number of untreated subjects.

We found no association between FENO and ACT scores or spirometric values, except for $FEV_{1\%}$ and $FEF_{25e75\%}$ at visit 2 ($p < 0.04$). When ACT scores were ≤19 (17.2 ± 1.5, n = 5), FENO was low (11.6 ± 3.9 ppb) and the $FEV_{1\%}$ was 91.6 ±24.4% (steroid dose 712 ± 557 mcg/day). When the FEV_1 was <80% (n = 12), FENO was similar as compared to when it was >80% (17.2 ± 11 vs. 18.9 ± 16.2 ppb, respectively, $p = 0.73$).

A few moderate asthma exacerbations occurred during the study period (8 out 120 study visits, mean steroid dose 316 ± 493 mcg/day). At the time of these exacerbations the ACT scores were significantly lower compared to the prior visit (13.3 ± 4.9 vs. 21.4 ± 4, $p < 0.02$). FENO (34.5 ± 29 vs. 24.8 ± 14.7 ppb) and $FEV_{1\%}$ (69 ± 13% vs. 76.6 ±23.4%) showed a trend for increase of FENO and decrease of the FEV1%, but these did not reach statistical significance ($p > 0.19$ for both).

Neither the baseline data, nor the results of the analysis of associations were affected by limiting the statistical analysis to the lifetime non smokers (data not shown).

Our results showing that FENO is not elevated in elderly asthmatics are in agreement with a very recent study in elderly asthmatics half of whom were on inhaled steroids whose FENO was about 20 ppb.[2] We did not find an association between FENO and subjects' demographics including age or with atopic disease as in a recent study that found similar FENO levels in older and younger asthmatic adults.[3] However, in another report FENO was positively associated with the number of positive skin tests.[4]

In adult asthmatics, FENO was found to be negatively but weakly associated with the inhaled steroid dose.[5] In contrast, in elderly asthmatics we did not find an association between FENO and steroid dose or other anti-asthmatic drugs. However, we cannot rule out that in our subjects inhaled steroids may inhibit FENO independent of their dose.

In adult patients with asthma, FENO has been negatively, but weakly associated with ACT scores[6] and inconsistently with lung function. In our elderly subjects, FENO was not associated with ACT scores or with spirometric values except at visit 2. Our results are in agreement with a very recent study in younger asthmatics on inhaled steroids.[7]

Only a few moderate asthma exacerbations occurred during the study period. While FENO increased and $FEV_{1\%}$ decreased, these values did not reach statistical significance, possibly because of the small number of observations. However, a very recent study in adult subjects on inhaled steroids similarly showed that FENO does not consistently increase during severe asthma exacerbations.[8]

Limitations of our study include the relatively small number of subjects, almost exclusively caucasians, and that most subjects were well controlled on inhaled steroids. However, our results are in agreement with several recent studies and our study schedule reproduces a relatively typical "real life" clinical scenario.

In conclusion, our study shows that in stable elderly asthmatics on inhaled steroids FENO is not elevated and routine measurements of FENO may not be clinically valuable. Our results need confirmation in larger cohorts of elderly asthmatics including subjects untreated with inhaled steroids and those experiencing severe exacerbations.

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Table 1

Subjects' characteristics at baseline.

Female/male	18/12
Age, yr (range)	71.6 ± 4.9 (65–84)
BMI (range)	25.6 ± 3.8 (19–34)
Atopy	21/30
Duration of disease, yr (range)	35 ± 20.3 (2–70)
Inhaled steroids (dose)	26/30 (384 ± 378 mcg/day)
Long acting bronchodilator	20/30
Leukotriene antagonist	11/30
Theophylline	2/30
Prednisone	2/30
Inhaled anticholinergic	1/30
Nasal steroids	15/30
Rhinitis	27/30
Nasal polyps	2/30
GERD	12/30
Heart disease	3/30
ACT score	22.1 ± 2.8
FENO (ppb)	18.2 ± 14.3
FEV_1 (%)	84.9 ± 20.3
FEV_1/FVC	0.71 ± 0.08
$FEF_{25–75\%}$	64.2 ± 29.5

Results are expressed as the mean ± S.D. Of the two subjects on prednisone at baseline, in one it was discontinued shortly after the initial visit, in the other it was reduced from 10 mg/day to 2.5 mg/day for the rest of the study period.