Original Article

Elevated Exhaled Nitric Oxide (NO) in Asymptomatic Asthmatics taking bronchodilators on demand with controlled Body Composition

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Abstract

Objective: Fractional Exhaled Nitric Oxide (FENO) is a recently introduced non invasive marker to measure inflammation and oxidative stress in the lung. This study aimed to measure FENO in Saudi asthmatic adult patients who had mild to moderate persistent asthma, on inhaled short-acting ? 2 agonists and compared them to healthy individuals matched for body composition without any evidence of obstructive airway disease.

Methods: As per selection criteria 61 subjects were selected. 30 subjects were known asthmatic and 31 were healthy individuals matched for age, height, weight, BMI and body composition. Forced expiratory volume in 1 s (FEV1), FVC, FEV1/ FVC, PEF, FEF25, FEF50 and FEF75 were measured by standard methods. FENO measurements were performed according to the ATS (American Thoracic Society) recommendations.

Results: Ventillatory function parameters FEV1 (p=0.0020), FVC (p=0.0030), PEF (p=0.0121), FEF25 (p=0.0241), FEF50 (p=0.0240) and FEF75 (p=0.1824) were significantly lower in asthmatic subjects compared to matched healthy control group. FENO was significantly higher (82.51 ± 39.26) in asthmatic subjects compared to control group (23.03 ± 8.56) p < 0.0000)

Conclusion: FENO levels are increased in patients with bronchial asthma with mild to moderate symptoms taking bronchodilators on demand only. It may be suggestive of the need for more accurate evaluation and early intervention with anti inflammatory drugs in a significant proportion of these patients (JPMA 59:147; 2009).

Introduction

In 1991, Gustafsson described the measurement of Nitric Oxide (NO) in the exhaled air of humans, rabbits, and guinea pigs leading to the eventual development of commercial instruments for the real-time measurement of Fractional Exhaled Nitric Oxide (FENO).[1] Later it was reported that airway inflammation is a central process in asthma and other lung diseases,[2] but monitoring inflammation is not yet included in current asthma guidelines despite evidences that this may improve control.[3]

FENO has been shown to correlate with other outcomes in mild asthma e.g., induced sputum eosinophilia[4] and bronchial reactivity[5] in non-steroid-treated subjects. NO diffuses across tissues to hollow organs such as the bronchus, where it remains stable in the gaseous phase. FENO levels can be measured within a few minutes online during slow exhalation or offline from samples collected in bags by Chemiluminescence procedure.[6]

FENO reflects the severity of the disease. Hence, several research groups have suggested that the noninvasive monitoring of FENO may be a useful tool in the diagnosis of airway inflammation.[7]

There is conflicting evidence on the effect of short-acting bronchodilators on FENO levels, although FENO does not significantly change after use of a long-acting β2 agonist.[8] Adherence to inhaled corticosteroids (ICS) and oral corticosteroids (OCS) after discharge in adults hospitalized for asthma exacerbations has been reported to be very poor (about 50 %).[9] A report from Italy stated that only 19% of the asthmatics on treatment, received daily treatment.[10]

Conventional measures of asthma severity have combined assessments of symptoms, amounts of β2-agonist used to treat symptoms, and lung functions. These measures do not assess airways inflammation, may not provide optimal assessment for guiding therapy and correlate poorly with eosinophilic inflammation on bronchial biopsies, or with FENO. FENO may be a quick and simple inflammatory marker with which to assess the impact of treatment changes on inflammation and thus to guide asthma therapy, although large long-term outcome trials are necessary to validate its usefulness. Routinely measuring FENO in our clinical settings still remains unclear, although current studies are encouraging that it runs in parallel to ongoing inflammation in a wide range of patients.[7]

Therefore the aim of study was to measure FENO in healthy Saudi asthmatic adult patients who had mild to moderate persistent asthma, and symptoms were controlled by inhaled short-acting β2 agonists on demand only and compared them to healthy individuals matched for body composition without any evidence of obstructive airway disease.

Patients and Methods

This study was conducted at the department of

Physiology of College of Medicine and King Khalid University Hospital, Riyadh, Saudi Arabia from Jan 2006 to April 2007. Written consent was obtained from all patients and the project was approved by the College of Medicine Ethics Review board.

Out of 90 individuals, 61 were finally selected for the study after fulfilling the selection criteria of the study.

Inclusion criteria for asthmatics included known asthmatic patients who had asthma for at least one year duration with mild to moderate symptoms. All recruited patients had mild to moderate persistent asthma, and symptoms were controlled by inhaled short-acting β2 agonists on demand only. Asthmatic patients taking oral or inhaled corticosteroids were excluded. Patients with chest cage or spinal deformities, smokers, chronic obstructive pulmonary disease and emphysema were also excluded.

Control group included healthy individuals who were non smokers, without any history of thoracic cage or spinal deformities, respiratory diseases or childhood asthma. They were matched for height, weight, BMI, body composition and occupation. Their height was measured in centimeters and weight in kilograms. BMI was calculated by the following formula;

BMI = Body Weight in Kilograms / Height (square meters)

The following studies were performed:

Body Fat Mass, lean Body Mass and Percent Body Fat

Composition of fat and protein mass in the body was measured by In Body Compostion Analyzer, manufactured by BIOSPACE, Korea and uses the principal of Bio-impedance for measuring these contents.

Ventilatory function parameters

Forced expiratory volume in 1 s (FEV1), FVC, FEV1/FVC, PEF, FEF25, FEF50 and FEF75 were measured by the Vitallograph (ALPHA, Ireland). All recordings were made in sitting position. At least three readings were obtained and the best of three was taken as the final result.

Exhaled NO measurements

FENO measurements were performed according to the present recommendations of American Thoracic Society [11] using a NOX EVA 4000 chemiluminescence analyzer (SERES-FRANCE) with a sensitivity of 1 ppb.

Using online visual monitoring the subjects were asked to inhale from residual volume to total lung capacity (TLC) and then, subjects performed a slow expiratory vital capacity manoeuvre with a constant standardized expiratory flow rate of 0.05 L/sec (± 10%) resulting in an expiration time of about 20 s, into a Teflon cylinder connected to 3-mm Teflon tubing, without the nose clipped.

To exclude nasal NO contamination a small expiratory resistance of 1 to 2 cm H_2O was applied. The subjects inspired from atmospheric air and expired in restricted-breath configuration set up.

The expiratory flow rate was measured by a pneumotachograph of data acquisition system BIOPAC MP-100 (biopac systems inc, USA). Plateau levels of FENO against time were determined and expressed as parts per billion (ppb).

Mean exhaled NO concentrations were determined between 5 and 15 s after start of the expiration. Three successive recordings at 1-min intervals were made, and the mean was used in analysis. NO concentrations were calibrated two to three times per week using a standard NO calibration gas.

The data was analyzed by computer software program Statistical Package for Social Sciences (SPSS Version 11). Data was expressed as mean ± SD for continuous variables and as percentages for categorical variables. Student's t-test was applied. A p value of 0.05 was taken as statistically significant and all tests were two tailed.

Results

A total of 61 subjects were studied. Table I shows clinical characteristics of control and asthmatics. There were no significant differences in age, height, weight, BMI, body fat, muscle mass and lean body mass between the two groups. Table II shows ventilatory function parameters between the two groups. FEV1, FVC, PEF, FEF25, FEF50 and FEF75 were significantly lower in asthmatic subjects compared to matched healthy control group.

Table I: Clinical Characteristics and Body Composition of Control and Asthmatic Subjects (n=61).

	Control n = 31	Asthmatics n = 30	P value
M/F	26/5	24/6	
Age (years)	34.13 ± 11.57	37.36 ± 13.85	0.4918
Height (cms)	170.69 ± 7.36	174.00 ± 9.70	0.2977
Weight (Kg)	83.98 ± 20.00	81.49 ± 15.36	0.7084
BMI	28.89 ± 5.95	26.99 ± 4.92	0.3527
% body FAT	28.01 ± 8.10	25.98 ± 9.07	0.5218
Fat Mass (Kg)	25.41 ± 12.10	21.87 ± 10.13	0.4029
Muscle Mass (Kg)	56.31 ± 9.21	55.86 ± 9.01	0.8971
LBM (Kg)	59.39 ± 9.84	59.64 ± 9.53	0.9446

Data is expressed as Mean ± SD
P value <0.05 is considered significant.

However, difference in FEV1/FVC was non significant, because these patients had mild to moderate asthmatic symptoms and were taking β2 agonists on demand only. FENO levels were significantly high (40 ppb) in asthmatic subjects

Table II Lung Function parameters and FENO of Control and Asthmatic Subjects (n=61).

PFTs	Control n = 31	Asthmatics n = 30	P value
M/F	26/5	24/6	
FEV1 Liters	3.64 ± 0.54	2.45 ± 0.93	0.0020 *
FVC Liters	4.28 ± 0.63	3.06 ± 0.97	0.0030 *
FEV1/FVC	84.89 ± 3.95	79.69 ± 9.69	0.1417
PEF L/min	644.67 ± 47.92	437.86 ± 220.97	0.0121 *
FEF 25 L/sec	8.88 ± 1.30	5.91 ± 3.40	0.0241 *
FEF 50 L/sec	4.43 ± 0.93	2.97 ± 1.57	0.0240 *
FEF 75 L/sec	1.36 ± 0.71	0.99 ± 0.48	0.1824
FENO ppb	23.03 ± 8.56	82.51 ± 39.26	0.0000 *

Data is expressed as Mean ± SD
* P value < 0.05 is considered significant.

compared to control group (15 ppb) $p < 0.0000$).

Discussion

In the past few years the definition of asthma has changed from that of a bronchoreactive airways disease to that of a TH-2-directed inflammatory disease involving both the large and the small airways.[12,13] Research on asthmatic inflammation in humans had been impeded by the lack of an easily performed, sensitive marker of inflammation.

Many asthmatic patients remain asymptomatic despite having an active ongoing airway inflammation. Such patients have a poor compliance to treatment and take medications irregularly on demand only. The prevalence of non compliance in asthmatics has been reported be very high.[9,10] The question of whether to further treat symptomatically controlled patients with asthma who have ongoing airways inflammation remains unclear.[14]

In asthma, where FENO promises to be very useful, it has been proposed to use this marker to diagnose asthma[15] to monitor the response to antiinflammatory medications,[16] to verify adherence to therapy,[17] and to predict upcoming asthma exacerbations.[18] It is also proposed that adjusting antiinflammatory medications guided by the monitoring of noninvasive markers, such as sputum eosinophils and FENO, could improve overall asthma control.

There are evidences for use of FENO for diagnosing asthma. In one study, Dupont et al[19] found that at a cutoff of 16 parts per billion (ppb), exhaled NO measurement is an accurate way to diagnose asthma in adults. However, later studies have regarded 50 ppb as the cut off appropriate level for asthma diagnosis.[20] However, this discrimination ability is poor. Our values are in higher ranges in accordance with the later studies.

There are evidences for use of FENO in assessing control and severity, titrating inhaled corticosteroids, and detecting ongoing airway inflammation.[21,22] The present study also supports the same findings that airway inflammation continues in asthmatic patients without steroid therapy. With the use of FENO measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.

Exhaled nitric oxide levels in patients with asthma are sensitive to treatment with inhaled corticosteroids and begin to decrease within 6 hours of treatment and plateau within 3 to 4 weeks.[23]

Measuring FENO has added another dimension to the determination of adverse respiratory effects because it allows detection of inflammatory responses in the absence of functional impairments.

The question of whether to further treat symptomatically controlled patients with asthma who have ongoing airways inflammation remains unclear and needs large longitudinal trials. An interesting study by Currie et al.[24] evaluated addition of montelukast to fluticasone dipropionate/salmeterol (FP/SM) or FP alone in adult asthmatics. Although montelukast addition did not improve lung function, a significant reduction in FENO and eosinophils was seen.[24] Changes in FENO may be an early indicator of loss of control as studied by Jones et al. who followed subjects who were withdrawn from their inhaled corticosteroids with FENO.[25]

Conclusion

FENO levels are increased in patients with bronchial asthma with mild to moderate symptoms taking bronchodilators on demand only. It may be suggestive of the need for more accurate evaluation and early intervention with anti inflammatory drugs in a significant proportion of these patients.

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