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The link between exhaled NO and bronchomotor tone depends on the dose of inhaled steroid in asthma

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Summary
Background: Exhaled NO (FE_{NO}) is a steroid dose dependent eosinophilic inflammometer, but also a mediator of bronchomotor tone, but statistically significant relationships have infrequently been obtained with pulmonary function tests (PFT). The aim was to test the hypothesis that the relationships between FE_{NO} and PFT could be uncovered by inhaled corticosteroid (ICS) treatment, namely that a link between FE_{NO} and bronchodilator response (an index of bronchomotor tone) would appear under ICS.
Methods: Exhaled NO, forced expiratory flows and lung volumes were measured in atopic asthmatic children without recent (one month) respiratory symptoms.
Results: Two hundred and thirty children (mean ± SD, age: 11.2 ± 2.5 years, 69 girls) were included (% predicted, FEV_1: 100 ± 14; $FEF_{50\%}$: 76 ± 23; RV: 107 ± 29). The relationship between ICS dose (GINA classification) and FE_{NO} plateaued in children with an ICS dose higher than 200 μg beclomethasone equipotent daily dose: FE_{NO} (median [25th–75th percentiles]), 43 ppb [15–105] (no treatment, $n = 65$), 33 ppb [15–77] (low dose, $n = 70$), 23 ppb [12–57] (medium dose, $n = 57$) and 26 ppb [9–49] (high dose, $n = 38$). Statistically significant relationships between FE_{NO} and PFT were only observed in children receiving more than 200 μg/day

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ICS: with FEV_1 (medium ICS dose: $\rho = 0.43$, $p = 0.001$; high dose: $\rho = 0.32$, $p = 0.052$) and bronchodilator (400 μg salbutamol) response (medium dose: $\rho = 0.54$, $p = 0.001$; high dose: $\rho = 0.65$, $p = 0.002$).
Conclusions: A positive correlation between FE_{NO} and bronchomotor tone appears with increasing ICS doses in atopic children with clinically controlled asthma, which further suggests that children depicting the highest FE_{NO} values may have lesser steroid sensitivity.

Introduction

It is well known that inhaled corticosteroid (ICS) administration reduces exhaled NO fraction (FE_{NO}) in steroid-naïve subjects, and a dose–effect relationship has been observed in some studies.[1,2] These latter studies, based on a limited number of patients, also showed a plateau effect of ICS on FE_{NO}.[1,2] Although FE_{NO} and sputum or bronchial eosinophils positively correlated in several studies,[3,4] Jatakanon and colleagues reported a dissociation between FE_{NO} and sputum eosinophils with increasing dose of budesonide.[1] Other studies have also shown conflicting responses between exhaled NO and eosinophils under ICS treatment.[5,6] This delinking challenges the concept of exhaled NO as an ''inflammometer'' reflecting the eosinophilic inflammation and suggests that the increase in exhaled NO in asthma could also be related to other mechanisms. Accordingly, NO is a bronchoprotective mediator via its production by constitutive NO synthases (1 and/or 3).[7] The ability of exhaled NO measurement to assess this beneficial property is uncertain.

The absence of relationship between FE_{NO} and baseline pulmonary function tests is the rule. Nevertheless, using partitioning of exhaled NO in its proximal and distal sources, we were able to describe correlations between the distal source of NO and airflow limitation in asthmatic children under ICS treatment.[4,8]

Taking together, it seems realistic to suppose that the increase in exhaled NO due to allergic inflammation hides the contribution of constitutive NO synthases. Since steroid response is related to the down-regulation of epithelial inducible NO synthase 2, we hypothesized that the relationships between exhaled NO and bronchomotor tone would appear with increasing ICS doses. Our aim was therefore to describe in atopic children with clinically controlled asthma the relationships between exhaled NO and both airflow limitation and bronchodilator response, the latter being an indirect index of an increased bronchomotor tone.

Methods

Design of the study

We and other previously demonstrated that the main factors influencing FE_{NO} in asthmatic children are atopy, allergic exposure and recent upper or lower symptoms.[3,9] Consequently, a homogenous group of asthmatic children was studied: atopic children with clinically controlled asthma, i.e. without any recent symptoms were enrolled at winter time (to reduce the effect of seasonal allergen exposure). We further made subgroups of children according to ICS dose categories defined by GINA classification.[10]

Patients

Consecutive children with an established asthma, based on standard criteria (episodic symptoms of airflow obstruction are present, airflow obstruction is at least partially reversible and alternative diagnoses are excluded[10]) were eligible if they were addressed for pulmonary function testing for the regular follow-up of their asthma, if they were atopic based on previous skin prick tests (usual perennial allergens [*Dermatophagoides pteronnysinus*, *Dermatophagoides farinae*, *Alternariae*, dog, cat] and seasonal allergens [grass, olea, betula, fagaceae, weeds]), and if their asthma was clinically controlled for at least one month (absence of recent exacerbation, absence of any respiratory symptom [asthma control criteria of GINA guidelines, excepting lung function[10]]). Their treatment during the last three months was recorded (all children were treated). Children and their parents were informed of the prospective data recording, and our local ethical committee approved the protocol.

Exhaled NO ($FE_{NO,0.05}$)

Exhaled NO was measured online, using the Nitric Oxide Analyzer (NIOX; Aerocrine AB; Solna, Sweden: measurement at a constant 50 mL/s expiratory flow rate: $FE_{NO,0.05}$). Measurements were performed according to the ERS/ATS guidelines before lung function tests.[11]

Pulmonary function tests (PFT)

All PFT were performed without inhaled treatment (bronchodilator or long-acting bronchodilator/ICS association) on the day of the measurement by the same operator (BM). Spirometry and plethysmographic measurement of specific airway resistance and thoracic gas volume were performed according to international guidelines and as previously described.[12] The bronchodilator response (to salbutamol 400 μg) was assessed in children with $FEF_{25-75\%} < 70\%$ predicted, and was evaluated according to international recommendations.[13] Reference values were based on equations edited by Zapletal and Samanek,[14] as commonly done in Europe.[15]