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Pathophysiology of airway hyperresponsiveness in patients with nasal polyposis

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Reactivity;
Sensitivity

Summary
Background: It has been hypothesized that airway hyperresponsiveness (AHR) is characterized by sensitivity (strength of stimulus) and reactivity (responsiveness to stimulus); the latter could be the intrinsic characteristic of AHR. The underlying mechanisms leading to AHR could be 1) airway inflammation, 2) reduction of forces opposing bronchoconstriction, and 3) structural airway changes/geometric factors.
Objective: Our main objective was to assess the relationships between reactivity in patients with nasal polyposis and these three mechanisms using measurements of 1) bronchial and bronchiolar/alveolar NO, 2) bronchomotor response to deep inspiration, and 3) forced expiratory flows and an index of airway to lung size, i.e. $FEF_{25-75\%}$/FVC.
Methods: Patients underwent spirometry, multiple flow measurement of exhaled NO (corrected for axial diffusion), assessment of bronchomotor response to deep inspiration by forced oscillation technique and methacholine challenge allowing the calculation of reactivity (slope of the dose–response curve) and sensitivity (PD_{10}).
Results: One hundred and thirty-two patients were prospectively enrolled of whom 71 exhibited AHR. Airway reactivity was correlated with alveolar NO concentration (rho = 0.35; $p = 0.017$), with airflow limitation ($FEF_{25-75\%}$: rho = −0.40; $p = 0.003$) and with an index of airway size to lung size ($FEF_{25-75\%}$/FVC: rho = −0.38; $p = 0.005$), of which only alveolar NO remained the only independent factor in a stepwise multiple regression analysis (variance 25%). Airway sensitivity was not correlated with any pulmonary function or exhaled NO parameter.

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Conclusion: In patients with nasal polyposis, alveolar NO is associated with airway reactivity, suggesting that bronchiolar/alveolar lung inflammation may constitute one intrinsic characteristic of increased responsiveness.

Introduction

Airway hyperresponsiveness (AHR), the tendency of the airways to narrow too much and too easily in response to various stimuli, is a universal feature of asthma, although it is not exclusive to this disease. Airway inflammation and structural airway changes can lead to this heightened airway response. Accordingly with these statements made by Boulet,[1] inflammation and structural changes might be associated with a change in smooth muscle mechanical properties and/or a reduction of forces opposing bronchoconstriction, such as reduced airway-parenchymal interdependence. Other factors, such as "geometric factors" (eg, airway caliber related to lung size), can also modulate the degree of AHR.[2] Nevertheless, the mechanisms by which all these potential factors modify airway function are still unclear. The two major functional components of AHR are airway reactivity and sensitivity, which can be obtained from a dose—response curve to methacholine. Accordingly to Sterk and Bel, reactivity could constitute the intrinsic characteristic of AHR (responsiveness of the airways to stimulus), while sensitivity could be related to extrinsic factors as allergic exposure (strength of triggering stimulus).[3] Consequently, one may hypothesize that the relationships between reactivity/sensitivity and the potential modifiers of AHR deserve to be studied.

Although the increase in exhaled NO commonly observed in atopic subjects with or without symptoms has classically been attributed to eosinophilic inflammation (one dimension of asthma), the relationships between fractional exhaled NO (FE_{NO}) and both AHR[4] and bronchodilator response[5] suggest a specific link between NO and another dimension of asthma, namely an increased airway tone. Consequently, one may also hypothesize that a link between exhaled NO and airway reactivity would be evidenced in patients with AHR. For this demonstration, partitioning of exhaled NO in its bronchial and bronchiolar/alveolar origins is mandatory since a single expiratory flow measurement at 50 mL/s mainly reflects the bronchial contribution to FE_{NO},[6] which is mainly linked to bronchial inflammation,[7] while alveolar NO should better represent airway responsiveness.[8,9]

The aim of our cross-sectional physiological study was to assess the relationships between airway reactivity/sensitivity and 1) bronchial/alveolar NO origins (using multiple flow exhaled NO measurement), 2) reduction of forces opposing bronchoconstriction (using bronchomotor response to deep inspiration [DI]), 3) structural airway changes/geometric factors (using forced expiratory flows and a crude assessment of airway to lung size, i.e. $FEF_{25-75\%}$/FVC).[2,10] These three pathophysiological factors were chosen because they may constitute three dimensions of airway hyperresponsiveness accordingly to Boulet,[1] even if there is some links between them.

Patients with nasal polyposis were enrolled because the prevalence of non atopic asthma is elevated, which may favour the discrimination of the role of NO that is not associated with allergic inflammation.

Patients and methods

Design

All consecutive patients suffering from nasal polyposis (diagnosis based on endoscopic examination and on computed tomography, as previously described [10]) referred for baseline pulmonary function testing were eligible with the exception of those suffering from another respiratory disease than asthma or from a severe cardiac disease. Patients were divided according to the presence of AHR, and further divided in symptomatic (asthmatic) and asymptomatic subjects. Our patient database has been declared to our regulatory agency for computer data collection (Commission Nationale Informatique et Libertés, *n°* 1391593v0), and approval from our local Ethics Committee was obtained. All patients were informed of the prospective recording of clinical and physiological data.

Diagnosis of confirmed asthma

The diagnosis of confirmed asthma was based on the fact that symptoms of recurrent episodes of airflow obstruction and AHR (based on PD_{20}) were both present, and alternative diagnoses were excluded, as recommended by GINA guidelines.

Pulmonary function tests

The tests were conducted in the following order and are summarized in Fig. 1.

Exhaled nitric oxide measurements

Exhaled NO was measured using a chemiluminescent nitric oxide analyser (ENDONO 8000, Seres, Aix en Provence, France) before performing spirometry (Fig. 1). Maximum

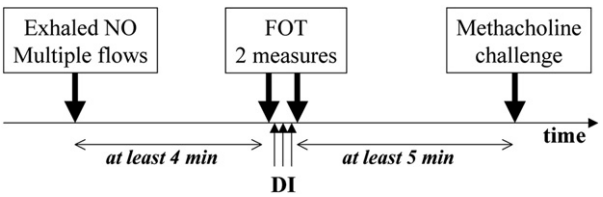

Figure 1 Sequence of investigations. The bronchomotor effect of deep inspiration (DI) is of short duration (median 65 s [range, 35—120 s]) as previously demonstrated.[8]