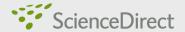
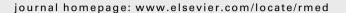


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Effects of allergen exposure on methacholine and AMP-induced air trapping in pollen-sensitive subjects

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KEYWORDS

Adenosine 5'monophosphate;
Allergens;
Air trapping;
Airway responsiveness;
Methacholine

Summary

Background: The effect of pro-inflammatory stimuli on bronchoconstrictor-induced air trapping has not been studied.

Objective: To determine the effect of natural allergen exposure, a pro-inflammatory stimulus, on methacholine- and adenosine 5'-monophospate (AMP)-induced air trapping.

Methods: Airway responsiveness to methacholine and AMP before and during the pollen season was obtained in 25 subjects with pollen allergy and in 10 healthy controls. The response was expressed by the sensitivity (PC_{20} value) and by the slope and intercept of the FVC values recorded at each step of the challenge against the corresponding FEV_1 values.

Results: The slope and intercept FVC versus FEV_1 values for both methacholine and AMP were significantly higher in subjects with pollen allergy than in healthy controls. In the group with pollen allergy, both methacholine and AMP PC_{20} values decreased significantly during the pollen season. However, the mean (95% CI) slope FVC versus FEV_1 values for methacholine were 1.00 (0.84–1.16) before the pollen season and 0.99 (0.86–1.12, P=0.90) during the pollen season. Similar results were obtained with AMP.

Conclusions: Although the air trapping induced by both methacholine and AMP is significantly greater in subjects with pollen allergy than in healthy controls, natural allergen exposure is associated with a selective increase in airway sensitivity without concomitant changes in bronchoconstrictor-induced air trapping. These findings suggest that the information provided by the bronchoconstrictor-induced change in FEV₁ and FVC is not equivalent and may be complementary. © 2010 Elsevier Ltd. All rights reserved.

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Introduction

Airway hyperresponsiveness can be defined as the tendency of the airways to narrow too easily and too much in response to a wide variety of provoking stimuli. 1 Therefore, airway responsiveness can be studied by constructing concentration-response curves to pharmacological bronchoconstrictors, and the response must be characterized by at least two abnormalities: a leftward shift (increased sensitivity) and an upward displacement (excessive airway narrowing) of the dose-response curve. However, during routine bronchoprovocation procedures, the response is generally expressed as the provocation concentration of agonist that caused a decrease in forced expiratory volume in 1 s (FEV₁) of 20% (PC₂₀ or sensitivity), whereas the potential for excessive airway narrowing is only exceptionally identified $^{2-4}$ owing to the inherent risks of provoking an excessive decline in FEV₁.

Clinically and for research purposes, airway responsiveness is measured by bronchial challenge, usually with methacholine or histamine. Both agonists predominantly induce bronchoconstriction though a direct effect on airway smooth muscle. In contrast, adenosine 5'-monophosphate (AMP) acts indirectly, causing primed mast cell degranulation and the release of pro-inflammatory mediators (histamine and leukotrienes) with subsequent smoothmuscle contraction. Since mast cells are believed to play a predominant role in atopic asthma, the bronchial response to AMP may be a more direct marker of allergic airway inflammation than direct bronchoconstrictors. ^{7,8}

On the other hand, it has long been appreciated that during bronchoconstriction induced by acetylcholine or methacholine, residual volume (RV) increases^{9,10} and forced vital capacity (FVC) decreases¹¹ significantly. The conventional explanation for why the FVC decreases during induced bronchoconstriction is that change in the smooth muscle tone causes an increase in air trapping. Assuming that during induced bronchoconstriction total lung capacity (TLC) remains constant, 12 this air trapping could be measured by the dose-dependent decline in FVC. Furthermore, because lung volume is a major determinant of the bronchoconstrictor response, 13 it has been suggested that changes in FVC may give relevant additional information as they correlate with the maximal degree of airway narrowing¹⁴ and may reveal information about the underlying asthma pathogenesis that is not apparent from the changes in FEV₁. 15 All these previous investigations were performed with direct bronchoconstrictor agents (histamine, acetylcholine or methacholine), but little information is available on AMP-induced air trapping. 16

There is convincing evidence that, in sensitized subjects with pollen-induced rhinitis or asthma, natural exposure to pollen during the season provokes an increase in airway responsiveness to both methacholine^{17,18} and AMP. ^{19,20} However, the influence of natural antigenic exposure on the magnitude of air trapping, as measured by the decrease in FVC remains to be further documented.

The aim of this study was to determine the effect of a pro-inflammatory stimulus, such as allergen exposure, on methacholine- and AMP-induced air trapping. To this end, we performed methacholine and AMP inhalation challenges in patients with pollen-induced allergic rhinitis associated or not with mild asthma both before and during the pollen season

Subjects and methods

A total of 35 subjects volunteered for this study. Twenty-five patients with seasonal allergic rhinitis, with or without mild asthma were recruited from the allergy clinic of our institution. Asthma was identified by the presence of asthmatic symptoms plus airway hyperresponsiveness with a methacholine PC20 of less than 8 mg/ml (n=8) if the FEV1/FVC was 70% or greater or an improvement of the FEV1 from predicted of 15% or greater after 200 μ g of inhaled salbutamol if the FEV1/FVC was less than 70% (n=2). Subjects with allergic rhinitis were defined as those individuals with a characteristic history of seasonal rhinitis during the pollen season and no history of asthma.

Skin-prick tests showed positive response (≥3 mm wheal diameter) to grass and/or olea europea and/or parietaria judaica pollens in all of the subjects. Seven subjects were also sensitized to perennial allergens, although they had no symptoms out of the pollen season. A control group of 10 healthy nonatopic subjects was also studied. These subjects were recruited from volunteers in the laboratory and among students. Selection criteria for this group included no history of asthma, allergic rhinitis, atopic eczema, or other relevant disease.

All 35 subjects were nonsmokers, had baseline FEV₁ \geq 70% predicted and FEV₁/FVC \geq 60%, and no subjects had a history of chronic bronchitis, emphysema, or respiratory tract infections during the 4 weeks before the study. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all the participants.

Study design

The study was performed between January and June 2009. Patients were first evaluated between mid-January and the end of February (pre-seasonal evaluation), before the pollen season had begun in Valencia, Spain. During this period, patients had 3 laboratory visits. At the first visit, all patients were evaluated for suitability and spirometry was performed. At each of the next 2 visit (3–7 days apart), spirometry and concentration-response studies with either methacholine or AMP were performed on separate days, with the order of challenge randomized. Patients returned to the laboratory at the height of the pollen season (seasonal evaluation) between April and June. During this period, patients attended 2 laboratory visits. At each visit, spirometry and concentration-response studies with either methacholine or AMP were performed.

The pollen season period was estimated according to atmospheric pollen counts obtained in the Valencia area. ²¹ In our region, pollen counts between 27 and 60 grains/m³ for *grass* and between 30 and 345 grains/m³ for *olea europea* were recorded from May to June. Urticaceae (*Parietaria judaica*) pollen levels were high from the end of March to the beginning of July, with pollen counts between 23 and 59 grains/m³.

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