

Editorial

Maximal airway plateau responses and eosinophils in cough variant asthma

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Accepted for publication 29 January 2004

In 1979, Carrao et al. described six patients with persistent cough and without airflow obstruction, but who had methacholine airway hyperresponsiveness (1). In all subjects the cough improved with regular inhaled bronchodilator therapy, and the term cough variant asthma was coined to describe these patients, who were thought to have a 'forme fruste' of asthma. What then differentiates cough variant asthma from classic asthma and what mechanisms underlie the differences in clinical characteristics? Clearly, there is no difference in airway responsiveness between the two groups as measured by PC₂₀ (sensitivity of concentration–response): both demonstrate bronchial hyperresponsiveness. In both conditions, there is a degree of eosinophilia observed in induced sputum or bronchoalveolar lavage fluid or in submucosal biopsies (2–5), and the degree of eosinophilia in cough variant asthma is usually similar to that of asthma. Another feature of cough variant asthma is subepithelial fibrosis, albeit to a lesser degree than that of asthma (5). One issue is whether cough variant asthma can convert into classic asthma, and indeed 17–37% of patients with cough variant asthma do so (6–8).

A research group in Seoul, Korea, has reported that the cough variant asthma patient with a high degree of sputum eosinophilia or with an absent or elevated maximal response plateau on the dose–response curve to methacholine has a higher chance of developing asthma (9, 10). However, the degree of bronchial hyperresponsiveness measured classically by the PC₂₀ was not predictive (10). In the current issue of *Allergy*, the Korean group extends their observations by examining the relationship between airway inflammation and the airway plateau response or the lack of a plateau response (11). They confirm that equivalent degrees of eosinophilic inflammation as measured by eosinophil counts and levels of eosinophil cationic protein in sputum, and of methacholine

PC₂₀ responsiveness. The sputum eosinophil response was not related to PC₂₀, as has been shown before in some studies (12, 13). In both cough variant asthma and classic asthma, Yoo et al. report that those with a maximal plateau response had a lower sputum eosinophil and ECP levels than those in whom a plateau response could not be achieved. There were significantly more in the cough variant asthma group that achieved a maximum response plateau than those in the classic asthma group.

What is the significance and relevance of this new work? Maximum plateaus on concentration–response curves for FEV₁ were first described by Woolcock et al. (14), and for flows on partial flow-volume curves by Sterk et al. (15). A plateau response is characterized by small limited airway narrowing, despite progressively higher doses of bronchoconstrictor agonists. Nonasthmatic subjects showed plateaus, which were absent in asthmatics, particularly the more severe ones (14). This maximal capacity of the airways to narrow can be regarded as a more important feature of airway hyperresponsiveness than the widely-used PC₂₀ because it is this capacity of excessive airway narrowing that determines the extent of airflow obstruction that leads to asphyxia and death in asthma exacerbations. In nonasthmatic subjects, during induced bronchoconstriction, the maximal activation of airway smooth muscle at the plateau is balanced by lung forces such as the pulmonary elastic recoil (16). Other neural, humoral or mechanical forces may prevent further constriction, and in more severe asthma, these mechanisms may become deficient, preventing a maximal plateau response to be achieved. The determinants of unlimited response during airway smooth muscle contraction in severe asthma are multiple, and include the amount of muscle and behavioural changes, inflammatory, geometric and airway adventitial factors. Yoo et al. report in their current paper that there was a close relationship between activated eosinophils and the

maximal response achieved during methacholine challenge in cough variant asthma, but not in their patients with classic asthma. Interestingly, in patients with allergic rhinitis without asthma, sputum eosinophilia was also related more closely to the maximal plateau response rather than to the PC₂₀ (17). It would be of interest to examine the airway response of patients with eosinophilic bronchitis presenting with cough, but with a normal PC₂₀ (18).

There is the intriguing possibility that the eosinophil may be implicated in the conversion of cough variant asthma into classic asthma, perhaps by removing the plateau response. One cannot make any definite conclusion from this essentially observational study, but there is supportive

evidence in that an anti-inflammatory treatment, inhaled corticosteroids, improves the maximal response to methacholine while β -adrenergic agonists do not (19, 20). Similarly, an inflammatory stimulus, allergen challenge, increased the maximal response to methacholine in those with a late asthmatic response (21). Perhaps the role of eosinophils is in the early phase of asthma development particularly in causing loss of the plateau response rather in the later phase of maintenance of asthma.

These studies do not tell us why patients with cough-variant asthma present predominantly with a predominant cough, but this is another story. Studying cough variant asthma may provide us with mechanistic clues about the development of classic asthma.

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