EDITORIAL

Do measures of bronchial responsiveness add information in diagnosis and monitoring of patients with asthma?

G.F. Joos

Intermittent airflow limitation, bronchial hyper-responsiveness (BHR), airway inflammation and remodelling are key pathophysiological components of bronchial asthma [1]. BHR, an abnormal increase in airflow limitation following exposure to a stimulus, is present in almost all patients with clinically current asthma. Furthermore, patients with more severe asthma have more responsive airways than patients with mild disease and during exacerbations of asthma, for example during allergen exposure, increases in bronchial responsiveness do occur [2]. The measurement of bronchial responsiveness is widely available, well-standardized and can be applied in both research and clinical settings [3, 4]. Until recently, the evaluation of airway inflammation required bronchoscopy for taking bronchial biopsies and/or performing bronchoalveolar lavage (BAL). In recent years, noninvasive methods for the evaluation of airway inflammation have been developed: induced sputum and exhaled air are now increasingly applied in clinical studies and are becoming well-standardized tools that may also find application in the clinical setting [5–7].

Bronchial hyperresponsiveness and airways inflammation

It is frequently assumed that measures of bronchial responsiveness and airway inflammation can be used interchangeably. Very often, baseline bronchial hyper-responsiveness (before any therapeutic intervention) and airway inflammation are considered to be linked tightly together. A large number of studies have examined correlations between markers of airway inflammation (bronchoalveolar lavage, bronchial biopsy and/or sputum) and BHR at baseline. Although in some instances weak correlations have been found between one or more inflammatory markers and the degree of BHR, an almost equal number of studies did not find significant correlations between airway inflammation and BHR (reviewed in [8, 9]). For instance, in a study on 71 patients with chronic allergic asthma, CRIMI *et al.* [10] measured bronchial responsiveness and assessed airway inflammation. Multiple regression analysis revealed no significant correlations between the degree of bronchial

responsiveness to methacholine and the number of inflammatory cells in sputum, bronchoalveolar lavage and bronchial biopsy. Therefore, in a large sample of asthmatic patients, BHR was found to be independent of the numbers of inflammatory cells in the airway lumen or mucosa.

Factor analysis

When asthmatic patients are examined during the course of their disease, bronchial responsiveness and markers of airway inflammation cannot be considered as overlapping dimensions. For instance, Rosi *et al.* [11] applied the statistical method of factor analysis to a set of data obtained from 99 patients with stable asthma that underwent spirometry, sputum induction and histamine inhalation. Factor analysis allows the many parameters that characterize the disease to be reduced to a few independent factors, with each factor grouping associated parameters. Three different factors could explain 74.8% of variability. The first factor was airway function and age, the second BHR (provocative concentration causing a 20% fall in forced expiratory volume in one second for histamine) and the bronchodilator response to a β_2 -agonist, and the third factor was sputum eosinophilic cationic protein (ECP) and sputum eosinophilia. Therefore, airway function, baseline BHR and sputum outcomes were found to be independent factors that characterize or describe the status or condition of patients with chronic, stable asthma.

Hyperresponsiveness, induced sputum and exhaled nitric oxide

In this issue of the European Respiratory Journal, LEUPPI *et al.* [12] report on a cross-sectional study of patients with stable asthma under treatment with variable doses of inhaled steroids. Originally, 50 subjects were screened but only 31 were able to produce sputum. In addition to lung function, airway responsiveness to histamine (a direct stimulus) and to mannitol (an indirect stimulus) was measured, as well as exhaled nitric oxide (eNO) and inflammatory cells in induced sputum. A weak correlation between sputum neutrophilia and the bronchial response to mannitol was observed. However, no other significant correlations were found between either the inflammatory cells

collected in the sputum or eNO and bronchial responsiveness to histamine and mannitol.

Direct versus indirect challenges

It is therefore clear that BHR and noninvasive markers of airway inflammation measuring different aspects of asthma, both at diagnosis and during treatment. Although less specific than measuring a cell or a mediator, measures of bronchial responsiveness may better reflect the multiple pathophysiological aspects of asthma. Moreover, within the group of nonspecific bronchial stimuli, a distinction has to be made between direct and indirect stimuli. Direct stimuli (e.g. methacholine) cause airflow limitation by direct action on the effector cells involved in airflow limitation, whereas indirect stimuli (e.g. physical stimuli, adenosine) exert their action essentially on inflammatory and neuronal cells that act as an intermediary between the stimulus and the effector cells. Indirect challenges are less sensitive but more specific for the diagnosis of asthma [13]. Moreover, an indirect challenge may better reflect acute changes in airway inflammation induced by allergen avoidance [14] or by treatment with inhaled steroids [15, 16].

Diagnosis and monitoring

The monitoring of symptoms, airflow limitation and exacerbations is essential to asthma management [17]. Measures of bronchial responsiveness and airway inflammation (sputum induction, exhaled air, etc.) can be assessed at regular clinic visits and are increasingly included in studies evaluating asthma control [4, 5, 7]. It is well known that inhaled steroids slowly improve bronchial responsiveness to a direct stimulus [18]. SONT *et al.* [19] recently reported a study that incorporated measurement of bronchial responsiveness to methacholine in the adjustment of anti-inflammatory therapy. The treatment protocol, aimed at improving BHR to methacholine, in addition to improving symptoms and lung function, led to better asthma control, fewer exacerbations and reduced chronic airway inflammation (e.g. reduction in thickness of the reticular layer).

Conclusion

Studies like the one reported by LEUPPI *et al.* [12] in this issue of the Journal, are a reminder that bronchial hyperresponsiveness and noninvasive markers of airway inflammation are nonoverlapping dimensions. Recently, an enormous increase in studies focusing on induced sputum and/or exhaled air in the evaluation of patients with asthma has been seen, both at diagnosis and during treatment. Measures of bronchial responsiveness should not be ignored as they provide additional and useful information, which is probably not picked up by the noninvasive markers of airway inflammation. Evidently, more clinical research is needed on the long-term changes in

bronchial responsiveness occurring during treatment of asthma. An important consideration is whether the evaluation of bronchial hyperresponsiveness aids the achievement of better long-term control of asthma and, therefore, should be included in the stepwise approach to asthma treatment. Moreover, the value of incorporating indirect measures, in addition to direct measures of bronchial responsiveness has to be further explored. A European Respiratory Society Task Force on Indirect Airway Challenges is currently finishing a position paper on this important topic.

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