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Daniel Menzies, Arun Nair, Brian J. Lipworth

Department of Medicine and Therapeutics, Asthma & Allergy Research Group, Ninewells Hospital and Perth Royal Infirmary, University of Dundee, Scotland, UK

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Non-Invasive Measurement of Airway Inflammation in Asthma

Daniel Menzies, M.B.Ch.B, Arun Nair, M.B.B.S., and Brian J. Lipworth, M.D.

Asthma & Allergy Research Group, Department of Medicine and Therapeutics, Ninewells Hospital and Perth Royal Infirmary, University of Dundee, Scotland, UK

Assessing the severity and control of a patient’s asthma is of great importance to ensure that pharmacotherapy is optimized. Measures such as lung function, symptoms, and reliever use have traditionally been used as objective means of undertaking this assessment, but until now the level of airway inflammation has not been quantified. As asthma is primarily an inflammatory disorder, it would be desirable to include a measure of this process when evaluating disease control. The following article outlines methods of non-invasively measuring asthmatic airway inflammation and highlights their potential role in clinical practice.

Keywords: asthma, inflammation, nitric oxide, airway hyper-responsiveness

INTRODUCTION

Modern asthma management involves titrating pharmacotherapy against disease severity in a stepwise fashion to ensure that the dose and type of medication used is appropriate for the individual patient. As asthma is primarily an inflammatory disorder, inhaled corticosteroids (ICS) form the foundation of most treatment strategies and are used in all but the mildest forms of the disorder (1, 2). A structured guideline-based approach has been adopted in an attempt to maximize the benefit-risk ratio obtained from use of medications such as corticosteroids, which can cause side-effects including suppression of the hypothalamic-pituitary-adrenal axis, reduced bone mineral density, skin bruising, cataracts, and growth impairment in children (3, 4). Accurately adjusting the dose of ICS is particularly important as many of these adverse effects are dose dependent, although the pharmacokinetic properties of individual drugs also play a role (5, 6). To minimize unwanted effects while maintaining effective control of a patient’s asthma, it is therefore important that disease severity is carefully assessed to facilitate appropriate alterations in pharmacological treatment. Traditionally, this severity assessment has relied on patients’ perceptions of their symptoms, amount of reliever use, and objective measures of airway calibre such as FEV$_1$ and PEF (1, 2). Although these tools are inexpensive and readily available, they also have a number of disadvantages. Measurements of airway patency and subjective symptoms are all distant from the underlying inflammatory process that characterizes asthma, and as such may not truly reflect disease activity. This is particularly true for mild to moderate asthmatics and also in children, in which fluctuations in airway diameter may not occur despite unsuppressed airway inflammation (7, 8). This could potentially lead to many patients with unchecked indolent inflammation throughout the lung, resulting in frequent exacerbations and eventually irreversible damage due to airway remodeling. Recently, an alternative inflammation-based approach to asthma management has been proposed in which treatment decisions are based not purely on pulmonary function and symptoms but are also a measure of inflammatory disease activity. This current article outlines some of the available methods for assessing asthmatic airway inflammation and highlights the relevance of these techniques to this novel strategy.

AIRWAY HYPER-RESPONSIVENESS

Airway hyper-responsiveness (AHR) to agents such as histamine, methacholine, and adenosine monophosphate is characteristic of asthma and has been used for a number of years to help establish the diagnosis and as a research tool to monitor response to pharmacological interventions (9). Recent studies have shown that the degree of hyper-reactivity to these agents is directly linked to underlying bronchial inflammation and that airway remodelling can be attenuated by appropriate pharmacological intervention with inhaled corticosteroids even in mild asthmatics (10).

Methacholine Challenge

Ward et al. demonstrated that in mild to moderate asthmatics (FEV$_1$ > 90%, not on regular inhaled corticosteroids), treatment with fluticasone propionate 750 g daily led to significant improvements in AHR to methacholine and bronchoalveolar lavage inflammatory cell counts at 3 months, and a reduction in reticular basement membrane thickness at 12 months when compared with placebo (10). Furthermore, regression analysis suggested that much of the change in hyper-responsiveness was attributable to reduction in reticular basement membrane thickness, demonstrating the interrelationship of the parameters. In another prospective 2-year longitudinal study by Sont et al., it was shown that using AHR as an adjunct to guide the prescribed dose of inhaled corticosteroid in mild to moderate asthmatic patients led to an 1.8-fold reduction in mild exacerbations when compared to the
conventional spirometry-based approach (0.23 and 0.43 exacerbations per year per patient, respectively (Figure 1)) (11). The clinical improvement in the AHR group was accompanied by a concomitant significant reduction in sub-epithelial reticular basement thickness at the end of the 2-year follow-up period. Together these studies suggest that AHR reflects underlying airway inflammation and may be a useful guide on which to base treatment decisions leading to fewer exacerbations and less airway remodeling over time. However, both these studies used methacholine PC20 as a surrogate of airway inflammation, which is impractical for everyday clinical practice because of the time and resource required to carry out the challenge test. An abbreviated form of this testing regimen using PC10 instead of PC20 has been validated that is both shorter and may have less potential for adverse reactions, but this too would no doubt prove to be unwieldy for everyday use given the equipment and expertise required (12).

Adenosine Monophosphate (AMP) and Mannitol Challenges

Challenge testing with indirect stimuli with agents such as AMP and mannitol may confer theoretical and practical advantages over direct stimuli like methacholine. AMP exerts broncho-constrictive effects by ligand-dependant release of inflammatory mediators from epithelial-associated mast cells and, as such, airway narrowing is proportional to the degree of inflammatory cell mucosal infiltration (13). Inhalation of mannitol leads to an alteration in mucosal osmolarity, and secondary release of inflammatory mediators again from mast cells (14, 15). Therefore, these tests are intrinsically dependent on primary airway inflammation to mediate their downstream constrictor effects and represent a more physiological model of asthmatic airway narrowing than their directly irritant counterparts of methacholine and histamine challenge. Indeed it has been shown previously that AMP PC20 reflects airway eosinophilia more closely than methacholine PC20, and further that AHR to AMP is strongly correlated with response to mannitol (16, 17). In addition to these physiological reasons, mannitol challenge is inherently more attractive as a practical measure of asthmatic airway inflammation than other tests because it requires little specialist equipment apart from a spirometer and a hand-held dry powder inhaler, while retaining the sensitivity of direct airway challenge with histamine (14, 18). These practical aspects to the test suggest it may be easily transferable to a primary care setting as a routine measure of airway inflammation. Mannitol challenge demonstrates good repeatability and is able to identify asthmatic subjects who are responsive to other indirect challenge tests such as hypertonic saline, eucapnic hyperventilation, and exercise (14, 19, 20). Inhaled steroid therapy has been shown to significantly attenuate airway sensitivity to inhaled mannitol with an associated reduction in symptoms and inhaled β-2 receptor agonist use (21). It has also been shown to be a good predictor for the failure of ICS drug reduction among asthmatic subjects (22). Mannitol responsiveness is also attenuated by histamine antagonists; however, it is unaffected by leukotriene receptor antagonists (LTRA) (20). Together these observations underscore the ability of mannitol responsiveness to accurately reflect underlying airway inflammation and disease activity. Despite the potential utility of this test, no longitudinal studies have been conducted to evaluate this as a tool to monitor or guide asthma therapy.

Exercise and Eucapneic Voluntary Hyperventilation (EVH)

Physical stimuli such as exercise and EVH have also been used as indirect bronchial challenges. Jones et al. reported the significance of an exercise induced decrease in FEV1, paving the way for diagnostic techniques aimed at identifying exercise-induced asthma (23, 24). EVH is based on the principle that exercise per se is not essential to provoke bronchoconstriction, and similar changes in airway resistance can be obtained by voluntary respiratory maneuvers (25, 26). This has lead to the standardization of EVH as a diagnostic test for exercise-induced asthma in athletes and is currently recommended as a standard laboratory test by the International Olympic Committee (27). Exercise testing may also have a potential role for deciding on the appropriate dose of ICS based on airway inflammation. In a placebo-controlled study in moderate to severe asthmatic children evaluating the dose response effects of inhaled budesonide, it was observed that protection against exercise-induced asthma required higher doses of budesonide when compared with symptom control, indicating that exercise challenge testing has a better sensitivity than conventional spirometry-based measures for detecting ongoing disease activity (28). In a further dose-response study designed to evaluate the effects of medium- and high-dose (200 µg or 800 µg daily) HFA-BDP on exhaled nitric oxide and exercise-induced bronchoconstriction in children with mild asthma, it was observed that medium dose of HFA-BDP reduced exhaled nitric oxide and improved lung function and exercise tolerance compared with placebo, with no additional benefit conferred by the higher dose (29). These studies suggest that exercise challenge and EVH may play a role as a surrogate of underlying disease activity, particularly in children and patients with exercise-induced asthma.

Exhaled Biomarkers of Respiratory Tract Inflammation

Nitric Oxide

Numerous authors have reported that the fraction of exhaled nitric oxide (FENO) measured in the expired breath of asthmatics is elevated, due to effects on inducible nitric oxide synthase, and reflects airway inflammation (30). In the appropriate clinical context, measurement of FENO has
been shown to have similar diagnostic sensitivity to methacholine challenge for the diagnosis of asthma with a positive predictive value of more than 80%, although this was in steroid-naïve patients (Figure 2) (31). In addition, FENO positively correlates with other markers of asthmatic inflammation including sputum and peripheral eosinophil count, AHR, eosinophil cationic protein, and bronchial wall thickness on computed tomography scan supporting its value as a surrogate of underlying disease activity (32–34). FENO reliably varies with corticosteroid therapy and can therefore also serve as a marker of treatment response, and elevated levels in treated asthmatics may herald a subsequent loss of asthma control, suggesting that serial monitoring may facilitate prevention of exacerbations (35–37). However, prospective dose titration studies have consistently revealed a rather shallow dose response curve on FENO, with a plateau at approximately 400 µg daily of BDP equivalent in patients with mild to moderate asthma (38, 39). Indeed in one such dose-ranging study of mild to moderate asthma, there was maximal suppression of FENO at a dose of 100 µg daily of extra fine hydrofluoroalkane-beclometasone dipropionate (HFA-BDP) (40). On this basis, one could reliably use FENO in a clinic setting to assess compliance with inhaled steroid therapy in patients who are not controlled on low to medium doses.

Measurement of FENO is quick, painless, and non-invasive with a high degree of reproducibility and tolerability among subjects making ideal for use in routine clinical practice. Two trials have used adjuvant FENO measurements in treatment algorithms and compared this with conventional strategies. In the first trial, 85 children were randomized to treatment decisions based on either FENO or symptoms for one year, with significant improvement in AHR in the FENO group without any difference in exacerbation rate or average daily dose of inhaled corticosteroid (41). In addition, no difference was found in either symptom scores or FEV₁ between the two strategies, although the patients recruited had comparatively mild asthma to begin with. This suggests that in mild to moderate asthmatics in which symptoms and spirometry are well preserved and therefore insensitive measures of disease activity, an inflammation centred approach to management can effectively attenuate the underlying inflammatory process. This could in turn have beneficial effects on long-term airway remodeling. A similar study carried out by Smith et al. in an adult asthmatic population again using FENO to titrate dose of inhaled corticosteroid over 1 year failed to demonstrate a difference in exacerbation rates between the two strategies, although there was a trend toward an improvement using the FENO strategy; but on this occasion the total daily dose of

![Figure 2](image_url)
inhaled corticosteroid was significantly reduced in the FE\textsubscript{NO} cohort compared with the reference strategy (reduction in daily dose fluticasone propionate of 270 \(\mu g\) per day, 95% CI 112 \(\mu g\)-430 \(\mu g\), \(p=0.003\) [Figures 3 and 4] (42). These initial studies have demonstrated the potential utility of FE\textsubscript{NO} measurements as an adjuvant to traditional measures of disease severity, although neither has convincingly established that this approach can reduce exacerbation rate, which could be regarded as the most clinically relevant outcome measure. Furthermore, both of these studies were undertaken in university teaching hospitals under the supervision of highly trained respiratory personnel. Even with the development of less expensive portable hand-held nitric-oxide analyzers, exactly how this translates into a primary care setting where tools such as this would arguably be of most value remains to be established. Further work is also required to identify appropriate cut off values of FE\textsubscript{NO} to set as targets for optimizing anti-inflammatory therapy. For example, in the above study by Smith et al. a target value of 15 ppb was used to guide inhaled steroid dose adjustment, which is much higher than a previously suggested cut off value of 7 ppb to separate normal from asthmatic subjects at the same mouth flow rate of 250 mL/second (31).

**FIGURE 3.**—Comparative exacerbation rate and severity between treatment strategy (conventional outcomes or measured exhaled nitric oxide) after 1 year. Reproduced from reference (42).

**FIGURE 4.**—Comparative daily dose of inhaled corticosteroid between treatment strategy (conventional outcomes or measured exhaled nitric oxide) over 1 year. Reproduced from reference (42).

**Alveolar and Nasal Nitric Oxide**

Asthma affects the entire respiratory tract from the naopharynx to the alveoli, and quantification of nitric oxide levels from these two sites has gained increasing interest. Alveolar nitric oxide can be determined by measuring FE\textsubscript{NO} at a variety of flow rates, then using regression analysis to identify the small airway component, whereas nasal nitric oxide can be directly measured via a nasal olive (43, 44). Preliminary work into targeting these components of asthmatic inflammation in the unified airway has revealed interesting results. Lehtimäki et al. showed that inhaled fluticasone propionate reduced bronchial but not alveolar nitric oxide (45), and Gelb et al. further demonstrated that 30 mg of oral prednisolone for 5 days could normalize elevated alveolar nitric oxide levels in patients already receiving inhaled corticosteroids (46). Similarly, it has been shown that topical nasal corticosteroids attenuate nasal nitric oxide levels in the unified allergic airway (47). These techniques are at present research tools but will hopefully lead to greater future understanding of asthmatic inflammation and pave the way for treatments directed at the airway as a whole. Moreover, with the availability of extra-fine HFA inhaled steroid formulations and systemic nonsteroidal anti-inflammatory agents (e.g., LTRA and phosphodiesterase 4 inhibitors), it will be relevant to assess respective effects on tidal and alveolar NO to evaluate their putative effects on the small airways in asthma.

**Exhaled Breath Condensates**

A number of biomarkers have been identified in the exhaled and cooled breath of asthmatics, including eicosanoids and isoprostanes (both products of arachidonic acid metabolism) and hydrogen peroxide (48). The pattern of relative production of each of these biologically active metabolites in a variety of lung diseases including asthma is steadily being unraveled, and it appears that it may hold promise as non-invasive disease marker. The eicosanoid predominant fingerprint of cytokine production in exhaled air would seem to substantiate further our current knowledge of leukotriene-driven inflammatory pathways in asthma and may in the future provide greater insight into asthmatic airway biology. Exhaled breath condensate isolates may also act as markers of asthma severity and unlike FE\textsubscript{NO} appear to be less affected by treatment with corticosteroids or LTRA (49, 50). This lack of treatment response may provide further clues to the pathogenesis of asthmatic inflammation but makes this technique less attractive as a potentially clinically applicable weapon in the armoury for disease management. As yet, measurement of these markers remains restricted to research institutions.

**INDUCED SPUTUM**

Eosinophils are undoubtedly strongly implicated in the pathogenesis of asthma (51). It is established that eosinophils activated by IL-5 can degranulate and release a variety of cytokines and proteins that are directly toxic to the respiratory epithelium causing inflammation and eventually airway remodeling. There is also emerging evidence that the eosinophil may play a role not only as a disease effector but may mediate the inflammatory process at a more fundamental level by preferentially modulating T-cell maturation into the Th2 subset (52). Sputum from asthmatic subjects contains a
preponderance of eosinophils that can be used both to assist diagnosis and to guide treatment. It has been shown that a raised sputum eosinophil count is the most robust predictor of response to corticosteroid therapy and like \( \text{FE}_{\text{NO}} \) can also predict impending loss of asthma control (53, 54).

In a landmark trial, Green et al. used these observations to titrate corticosteroid treatment against sputum eosinophil count or a conventional index of asthma severity (55). Patients randomized to the “sputum” limb of the trial had treatment increments if their induced sputum eosinophil count was greater than 3%, and this approach was compared with the current British Thoracic Society guidelines. At the end of 1 year there was nearly a fivefold reduction in exacerbation rate in favor of the sputum-based group, with similar reductions in other markers of airway inflammation including \( \text{FE}_{\text{NO}} \), methacholine AHR, and total induced sputum eosinophil count (Figures 5 and 6). However, there were no differences in spirometric indices, peak flows, symptoms, quality of life, or reliever use between the groups, again suggesting that these markers are ineffective methods by which to monitor disease progression (Figure 7). Furthermore, there was no significant difference in either the average daily dose of corticosteroid used or second line therapies required between the groups, suggesting that this inflammation-based approach facilitated a more targeted use of pharmacotherapy, not simply treatment bias toward the sputum cohort. Despite the encouraging results of this trial, sputum analysis remains an inaccessible and impractical test for the majority of patients and will remain a specialist investigation.

**OTHER POTENTIAL INFLAMMATORY BIOMARKERS**

**Peripheral Blood Eosinophils**

Although eosinophils mediate the majority of their effects by degranulating in the asthmatic respiratory tract mucosa, it is undoubtedly more convenient to sample them while en-route from the bone marrow to the airways in the peripheral blood stream. Studies evaluating the effects of treatment with inhaled steroids and LTRA on surrogate inflammatory markers have shown that peripheral blood eosinophils, while being less sensitive than sputum eosinophils, demonstrate a significant reduction in number in response to treatment with low-dose inhaled steroids and LTRA, possibly reflecting systemic disease burden (56, 57). However, it is probably more likely that activated status of eosinophils in the eventual target tissue is more important than absolute levels in the bloodstream. This hypothesis is supported by data from a trial of IL-5 monoclonal antibody (mepolizumab) in which peripheral and broncho-alveolar lavage fluid eosinophil count was significantly (median reduction in peripheral eosinophil count 100%, IQR 67–100%, \( p = 0.004 \)) attenuated in asthmatics by three doses of the drug each separated by 4 weeks, without any concomitant reduction in either clinical outcome measures or AHR (58). Analysis of bone marrow and bronchial biopsy specimens in the same study showed reduction in eosinophil counts inferior to that observed in other body compartments, possibly in part explaining the lack of response seen by other authors in previous trials using the same drug (59). Although the lack of response to anti-IL-5 treatment is undoubtedly more complex than absolute cell numbers alone, these observations suggest that measurement of total peripheral eosinophil count is of limited value in asthmatics acting mainly as a marker of the presence of disease and overall systemic activity, but not truly representing airway-specific allergic inflammation.

**Eosinophilic Cationic Protein**

Degranulation of eosinophils leads to release of numerous pro-inflammatory and immunogenic mediators including eosinophilic cationic protein (ECP). ECP can be detected in a variety of body fluids, although the majority of reports have concentrated on quantification in serum, sputum, or broncho-alveolar lavage specimens (60). Measurement of this secretory protein has theoretical advantage over absolute eosinophil count as it serves as a marker of granulocyte activity rather than simply documenting the absolute
number of inflammatory cells present (61, 62). Moreover, from a practical standpoint, it is technically less demanding to undertake ECP measurement than for example a sputum differential count, which even with abbreviated techniques, requires isolation and staining of samples (63). ECP values obtained from sputum, serum, and bronchoalveolar lavage fluid have been shown to positively correlate not only with each other, but also with other indices of asthmatic inflammation such as AHR, lung function, and overall disease severity (60, 64). Importantly, ECP also fluctuates in parallel with other markers of pulmonary inflammation in response to appropriate pharmacotherapy and may also positively predict exacerbations and response to anti-inflammatory treatment (62, 65). In an open label study designed to evaluate the effects of low-dose fluticasone/salmeterol combination on surrogate inflammatory markers in moderate persistent asthmatics, ECP and eosinophils in sputum exhibited greater sensitivity when compared to serum markers in gauging disease activity and airflow inflammation (56). These observations have led to speculation that ECP could be used in a similar way to sputum eosinophil count or FE\textsubscript{NO}, to more efficiently decide the dose of anti-inflammatory medication for asthmatics. The single trial to date failed to show a clear benefit of this approach using ECP as a surrogate biomarker, although in part this may be because it was underpowered to demonstrate a difference in exacerbation rate and overly reliant on markers of airway caliber such as FE\textsubscript{V\textsubscript{1}} for the primary outcome variable (66). As such, ECP measurement can be regarded as an additional valuable method by which clinicians can gauge eosinophilic activity, assess asthma severity, and monitor and predict response to treatment. However, there is no evidence to advocate use of this marker as a guide for treatment alteration.

**Urinary Leukotrienes**

The cysteinyl-leukotrienes are clearly implicated in the pathogenesis of asthma, orchestrating the inflammatory cellular immune response and acting as direct bronchoconstrictors (67). Levels of leukotriene E4 can be quantified relatively easily by enzyme-linked immunosorbent assay (ELISA) and a number of reports have investigated urinary levels of this eicosanoid in asthmatic patients (68, 69). It has been shown previously that the level of urinary leukotriene E4 becomes transiently elevated in response to airway challenge with mannitol and oral aspirin challenge and following acute exacerbations of asthma (15). A weak but statistically significant correlation ($r = 0.43$, $p < 0.001$) between urinary leukotriene levels and improvement in airflow limitation has also been demonstrated in asthmatics having an acute exacerbation (70). However, there have been conflicting reports about the validity of urinary measurements when compared with other established measures of airway inflammation. In particular, some authors have presented data suggesting a positive association between asthma severity and urinary leukotriene levels, whereas others have found the opposite (34, 71). Likewise, studies designed to investigate potential associations between urinary eicosanoid excretion and airway inflammation have revealed conflicting data to support a correlation between this parameter and other markers of respiratory tract inflammation including sputum leukotriene levels (72). Although of limited value in monitoring asthma severity, one potential interesting application of this assay may be to investigate response to leukotriene receptor antagonists and to help further characterize asthma phenotypes. In one study, response to bronchial challenge with either oral aspirin or house dust mite in sensitive asthmatics was examined, and airway blood and urinary inflammatory biomarkers were compared (73). Whereas both groups exhibited an
increase in sputum and urinary eicosanoid concentration, in association with an immediate allergic response, both the baseline and post-challenge levels were significantly greater (3.3 fold) in the aspirin-sensitive group. This is in agreement with previous studies that have also documented higher urinary leukotriene levels in aspirin-sensitive asthmatics, suggesting derangement of arachidonic acid metabolism in this subpopulation of patients (74). Recent work has also suggested that leukotriene production may be influenced by genetic polymorphisms of the C4 synthase gene (75). To date little work has specifically looked at urinary leukotriene excretion in response to severity, exacerbations, or treatment of asthma in the context of promoter genotype.

CONCLUSION

Increasingly physicians are beginning to appreciate the potential utility of measuring airway inflammation in asthmatic patients, not simply as a research tool but also as a means by which to guide treatment. Recent studies have demonstrated that encompassing measures of airway inflammation into decision algorithms may offer superiority over the traditional spirometry and symptom-based approach currently used. Treatment dictated by inflammation can lead to fewer exacerbations and less steroid use because of better dose titration in response to impending loss of disease control while simultaneously reducing the chance of overtreatment. What remains to be established is which marker of inflammation is most suitable for everyday clinical practice, particularly in a primary care setting. Airway hyper-responsiveness and induced sputum cells counts undoubtedly closely mirror bronchial inflammation and in the trials to date have produced encouraging results. However, their utility is undermined by the obvious practical implications of undertaking such tests in routine practice. The use of a simple dry powder inhaler to perform mannitol bronchial challenge would seem to best suited to primary care and studies are now under way to assess whether this can be used to titrate inhaled steroid therapy as an aid to reducing exacerbations. Nitric oxide measurement is quick and easy to perform, providing a more attractive practical alternative, particularly with the newer portable devices, but the studies to date have failed to show improvement in exacerbation rate, arguably the most important endpoint. Most of the other candidate surrogates of disease activity are time-consuming, prohibitively expensive, or too distant from the underlying airway inflammation to present viable alternatives, although some of these biomarkers may be useful for research to provide information about the pathobiology of asthma and the response to pharmacotherapeutic agents. The challenge will be to develop a technique of measuring asthmatic inflammation that is allied closely enough to the underlying process to accurately facilitate treatment titration, while remaining quick and inexpensive enough to become a practical tool for everyday use.

REFERENCES


NON-INVASIVE MEASUREMENT OF AIRWAY INFLAMMATION IN ASTHMA 413


