

Review article

The role of small airways in monitoring the response to asthma treatment: what is beyond FEV₁?

The definition of asthma has evolved from that of an episodic disease characterized by reversible airways constriction to a chronic inflammatory disease of the airways, with at least partially reversible airway constriction. Increasing evidence supports the notion that small and large airways play a central role in asthma pathophysiology with regard to inflammation, remodeling and symptoms. The contribution of the distal airways to the asthma phenotype carries implications for the delivery of inhaled medications to the appropriate areas of the lung and for the monitoring of the response to asthma treatment. Asthma control is evaluated on the basis of symptoms, lung function and exacerbations. However, evidence suggests that dissociation between lung function and respiratory symptoms, quality of life and airway inflammation exists. In this study, common spirometric parameters offer limited information with regard to the peripheral airways, and it is therefore necessary to move beyond FEV₁. Several functional parameters and inflammatory markers, which are discussed in the present study, can be employed to evaluate distal lung function. In this study, extrafine formulations deliver inhaled drugs throughout the bronchial tree (both large and small airways) and are effective on parameters that directly or indirectly measure air trapping/airway closure.

**N. Scichilone¹, S. Battaglia¹,
D. Olivieri², V. Bellia¹**

¹Dipartimento di Medicina, Pneumologia, Fisiologia e Nutrizione Umana (DIMPEFINU), Sezione di Pneumologia e Medicina, University of Palermo, Palermo, Italy; ²Cardio-Pulmonary Department, Section of Respiratory Diseases, University Hospital, Parma, Italy

Key words: asthma; corticosteroids; lung function; small airways.

Nicola Scichilone
Dipartimento di Medicina, Pneumologia
Fisiologia e Nutrizione Umana
University of Palermo
via Trabucco 180
90146 Palermo
Italy

Accepted for publication 2 June 2009

The definition of asthma has evolved in the past decades: in the sixties asthma was considered as an *episodic* disease characterized by reversible airway obstruction; nowadays, asthma is regarded as a *chronic* disease based on a condition of chronic airway inflammation together with airway hyperresponsiveness, with at least partially reversible airway obstruction. The inflammatory and remodeling changes of the airways account for the clinical features of the disease, thus contributing to the asthmatic phenotype. The characterization of the inflammatory and clinical phenotypes has important prognostic and therapeutic implications, in that it can predict the course of asthma and guide the pharmacological approach. Since 2002, the GINA guidelines acknowledged that acute and chronic inflammation is irregularly distributed throughout the airways, and that the smaller airways (<2 mm) are also involved. This finding has implications for the problems of delivery of inhaled medications to the appropriate areas of the lung and for the monitoring of the response to treatment.

In the effort to meet the needs of patients and physicians, the management of asthma has progressively moved from bench to bedside; rather than pursuing the 'switch off' of inflammation, the goal of treatment has

become the best attainable control of asthma, defined as absence of symptoms, no exacerbations and no limitation of activities, together with normal lung function. Consequently, control is now considered the main determinant in the assessment of severity of asthma (1, 2), since the previously proposed classification based only on symptoms and lung function was applicable only to untreated patients. Several studies in recent years have shown that optimal control of asthma can be obtained in the majority of patients with inhaled steroids alone or in combination with long-acting β_2 agonists (3–5). However, epidemiological studies more closely depicting the situation in real life, clearly show that, overall, asthma is not adequately controlled, probably because patients studied in population cohorts behave differently from those recruited in randomized controlled trials. A recent publication (6) evaluated asthma control across European countries; the prevalence of uncontrolled asthma ranged from 20% to 67% among different countries, confirming previous observations (7, 8). Several possible explanations have been advocated to explain such a failure of asthma control; from a pathophysiological perspective, the involvement of the peripheral district of the bronchial tree, once defined 'the silent zone', and its response to

treatment have gained increasing evidence, and should not be ignored when monitoring asthma.

Monitoring response to asthma treatment

An effective preventive control of asthma and the maintenance of optimal pulmonary function are critical for the long-term management of patients with persistent asthma with a degree of severity ranging from mild to severe. The use of inhaled corticosteroids as first-line treatment for the management of patients with all levels of persistent asthma severity, is firmly established by current guidelines, and is of common daily clinical practice. However, many patients treated with inhaled corticosteroids still suffer from asthma symptoms and exacerbations necessitating use of relief medication. Solid evidence suggests treatment with combination therapy (inhaled corticosteroids plus long-acting β_2 agonists in a stepwise fashion) for patients with asthma not controlled by corticosteroids alone.

The current assessment of asthma control is described in Fig. 1. The evaluation of respiratory symptoms does not represent a difficult task and is commonly achieved through the recording of the patient's complaints as well as through the use of validated asthma questionnaires. Conventional lung function assessment is mostly useful in those patients who do not perceive their symptoms, especially older individuals, and in subjects who experienced a near-fatal episode of asthma attack. However, dissociation between lung function and respiratory symp-

toms, quality of life and airway inflammation has been demonstrated. Scichilone et al. (9) recently reported the observation that, in a group of mild-to-moderate-severe asthmatics, baseline FEV₁ was not correlated with severity of asthmatic symptoms. Similarly, Moy et al. (10) in a retrospective analysis from two clinical trials on asthmatics, in whom lung function assessment had been performed and the asthma quality of life questionnaire administered, concluded that lung function was not an independent predictor or determinant of quality of life at any level of asthma severity. Finally, Lehtimäki et al. (11) found that subjects with asthmatic symptoms but normal lung function had significantly higher alveolar NO concentrations than healthy and asthmatic controls, indicating that lung function was unrelated to peripheral inflammation. Taken together, these observations raise the question of whether conventional spirometry is the proper method to assess asthma control. If not, what is beyond FEV₁?

Although pharmacological treatment is able to control the disease in the majority of asthmatic patients, a subgroup of individuals experience poor quality of life and functionally and clinically uncontrolled asthma, despite optimal therapy. Little is known about the pathophysiological mechanisms underlying this phenotype, rendering the management of severe asthma a complicated task. A cross-sectional, observational study on severe asthmatics compared to nonsevere asthmatics (the ENFUMOSA project) (12) generated several hypotheses on the understanding of pathophysiological and phenotyping characteristics of severe asthma. One of

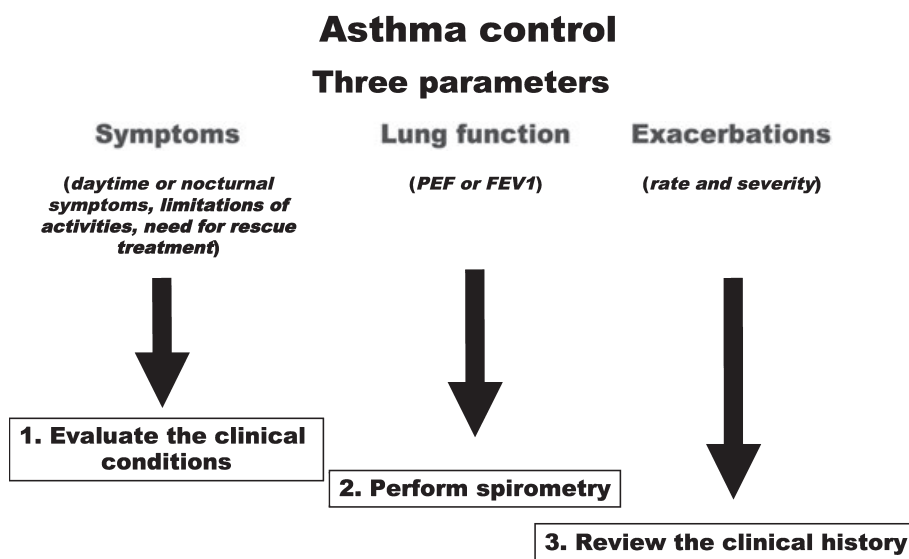


Figure 1. The assessment of asthma control focuses on three main domains: (i) symptoms (daytime and nocturnal symptoms, limitation of activities, use of rescue medications); (ii) lung function (PEF and/or FEV₁); and (iii) exacerbations (rate and severity). Following this assumption, a three-step approach is required as follows: (i) to examine the clinical conditions, (ii) to perform spirometry and (iii) to review the recent clinical history, to estimate respiratory symptoms, lung function and exacerbations, respectively.

the most interesting and challenging findings was the identification of air trapping, by means of significantly higher ratio of residual volume (RV) over total lung capacity (TLC), which suggests that structural and functional changes of peripheral airways contribute to the pathogenesis of severe asthma. In a recent study by Sorkness et al. (13) on 287 severe asthmatics and 382 nonsevere asthmatics, RV/TLC was significantly higher in the former at any given level of airway obstruction, as expressed by FEV₁/FVC ratio. A parallel trend was observed for FVC, which was significantly lower in the severe group, what may be assumed as an indirect measure of air trapping. Accumulating evidence confirms that, in asthma, chronic inflammation is irregularly distributed throughout the airways, including the smallest ones, and the parenchyma (14, 15). The awareness of this condition carries therapeutic implications, in that delivery of inhaled medications to the appropriate areas of the lung assumes a pivotal role for the achievement of the goals of asthma treatment. In this respect, the role of small airways abnormalities in the occurrence of asthmatic symptoms should be highlighted. Early closure of the smallest airways, perhaps due to uncontrolled inflammation, has been shown to characterize subjects with difficult-to-control asthma (16). Studies based upon computed tomography scanning (17–19), transbronchial biopsies (20–22) and autopsy specimens (23, 24) have confirmed the 'central' role of peripheral airways in severe or fatal asthma. Thus, the question is: can we look beyond FEV₁ for a more comprehensive assessment of the *severity* (diagnosis) and *control* (response to treatment) of asthma of asthma throughout the whole lung?

Monitoring response to asthma treatment: which procedure?

Even if inflammation and remodeling occurring at the level of airways whose internal diameter is smaller than 2 mm linked to clinical asthma phenotypes, changes in small airway function are difficult to assess with conventional spirometry; therefore, lung function testing may not be sufficient to properly assess and monitor asthma

control. Several functional parameters and inflammatory markers are available to monitor the response to asthma treatment; as summarized in Table 1, each procedure has both advantages and limitation, which may preclude their use in clinical settings. Noninvasive methods are preferred to assess airway and parenchymal changes and to follow-up patients with asthma over time. Among those, the spirometric index that has been classically proposed to indicate the involvement of the distal lung is vital capacity (VC). Since small airway obstruction often lead to complete obliteration, VC can be reduced more than FEV₁. As discussed earlier, an observational study (13) comparing severe and nonsevere asthmatics indicated that forced vital capacity (FVC) was significantly reduced at any level of airway obstruction and, as it is related to the residual volume, can be used as a physiological measure of air trapping. Similarly, the fall in FVC during methacholine bronchoprovocation tests has been established to suggest exaggerated airway narrowing due to early airway closure at the level of peripheral airways; the percent reduction in FVC at the provocative dose of methacholine causing 20% fall in FEV₁ (PD₂₀) has been demonstrated to be increased in moderate to severe asthma (25), again confirming the contribution of small airway dysfunction to asthma severity. Another physiological technique, impulse oscillometry, measures changes in airway resistance during tidal breathing; by varying the frequency, different districts of the bronchial tree can be assessed, and low oscillation frequencies (5 Hz) are supposed to measures resistance at the level of small airways. More complex measurements of small airway function, such as frequency dependent compliance and density dependent gas flow studies, are only available in research centers.

Among the available functional measures, the nitrogen single breath (sbN₂) test provides useful information to address changes that occur in the distal lung. After analysis of the sbN₂ wash-out curve, increased closing volume or closing capacity reflect air trapping due to small airways obstruction, and the N₂ washout slope is associated with severity of asthma (26). A study comparing asthmatics of various severity, but with normal FEV₁, with healthy volunteers, demonstrated that the uneven

Table 1. Lists of procedures that can be employed to assess small airway dysfunction

Procedure	Advantages	Limitations
NO measurement	High sensitivity for inflammation	Need for validity
Sputum induction	High reproducibility, high sensitivity for inflammation	Need for trained staff, time consuming
Transbronchial biopsies	'Gold standard'	Invasive
HRCT	High reproducibility	Side-effects, costs
Spirometry	Simplicity, high reproducibility	Poor correlation to severity
Oscillometry	Simplicity	Poor correlation to severity
Mch bronchoprovocation	High reproducibility, high sensitivity for diagnosis	Poor correlation to severity, time consuming
N ₂ wash-out	High reproducibility, high sensitivity for diagnosis	Need for trained staff
Asthma questionnaires, diary cards	High reliability, simplicity	Patient dependent

NO, nitric oxide; HRCT, high resolution computed tomography; Mch, methacholine; N₂, nitrogen.

ventilation expressed by the slope of phase III of the curve obtained by sbN₂ test represents an important indicator of poor asthma control and high exacerbation rate (27). Moreover, Battaglia et al. (28) showed that the slope of phase III and the closing volume correlated to fractional nitric oxide (NO) and 8-isoprostane in the exhaled air. These data suggest that the above-described functional parameters reflect small airway inflammation, and favor their role as complementary to spirometry in the monitoring of asthma.

Among the inflammatory markers of disease, NO in the exhaled air has been widely proposed. Fractional exhaled NO (FeNO) levels are increased in asthma even in mild and asymptomatic conditions (29, 30). It is likely that FeNO originates from the intrapulmonary airways in asthma (31), including peripheral lung (32–34) as confirmed by a recent *in vitro* study on NO gas phase release from differentiated small airway epithelial cells and alveolar type II cells (35). Battaglia et al. (28) demonstrated that FeNO is associated with functional evidence of small airway involvement in intermittent/mild persistent asthma, being the FeNO levels positively correlated with nonhomogeneous emptying of lung units, as reflected by a steeper slope of phase III of the sbN₂ test. Advances in technology have allowed to distinguish, *in vivo*, FeNO of proximal airways origin from that of distal airways/alveolar source, by measuring FeNO at different levels of constant flow exhalations on the basis of the two-compartment model (bronchial and alveolar) (34). Lehtimäki et al. (36) found higher levels of alveolar NO in patients with nocturnal asthma compared with non-nocturnal asthma, suggesting a more peripheral inflammation in the former. Other authors showed higher levels of alveolar NO in symptomatic *vs* asymptomatic children with asthma (37), and in patients with severe *vs* mild-to-moderate asthma (38). The latter observation was confirmed by van Veen et al. (26), who demonstrated that the alveolar component of NO is closely related to parameters of peripheral airway dysfunction in patients with severe asthma, but not in patients with mild-to-moderate asthma.

The accuracy of the two-compartment model has been recently challenged by newer mathematical models (39, 40), which take into account a process of back-diffusion from the bronchial to the alveolar compartment that can alter the measurements of NO concentration from peripheral lung. Human studies have been designed to assess which of these functional and/or biological indices better reflect the involvement of small airways in asthma.

A common approach to evaluate airway and parenchymal changes is through imaging methods. High-resolution computed tomography (HRCT) is capable of visualizing millimeter structures with high natural contrast. Axial images are acquired using thin sections, either 1.0- or 1.5-mm collimation, and the images are reconstructed using a high spatial frequency reconstruction algorithm. HRCT can allow to record images of the

bronchial tree *in vivo* to measure the airway wall thickness and lumen area that are correlated with histology. HRCT has been used to study changes in the airway structure in asthma. Quantitative assessment of the distribution of lung attenuation has been performed by using lung attenuation curve analysis as an indirect measure of changes in small airways caliber (41). Lee et al. (42) demonstrated that the HRCT prominence of centrilobular structures, which is an indicator of peribronchiolar inflammation, bronchiolar wall remodeling and intra-bronchiolar mucoid impaction, is significantly more represented in individuals with near-fatal asthma, as opposed to mild and moderate-to-severe asthmatics. To date, HRCT can be proposed as a sensitive procedure; however, further studies are required to assess its clinical usefulness.

Beyond FEV₁ for comprehensive assessment of response to treatment

The above-described methodologies have been demonstrated to be more accurate than FEV₁ in assessing the *severity* of asthma. The question therefore is raised on the opportunity to look beyond FEV₁ also for a more comprehensive assessment of the *response* to asthma treatment. The accumulating evidence that asthma is characterized by pathophysiological mechanisms leading to airway inflammation and remodeling throughout the entire bronchial tree has driven the development of extrafine inhaled formulations with the ability to reach both the large and small airways. In this scenario, extrafine inhaled formulations, which have a median aerodynamic diameter of 1 µm, not only deliver drugs to the small airways but may also be useful as tools for the investigation of changes in the small airways. Extrafine formulation of fluticasone was able to suppress eosinophilic inflammation both in central and peripheral airways of asthmatics (43). In a study performed in mild-to-moderate asthmatics (44), a 6-week course of extrafine fluticasone was demonstrated to significantly reduce the expression of smooth muscle actin in the peripheral airways, but not in the central ones, by transbronchial biopsies. These findings indicate reduction in the smooth muscle mass, which parallels improvements in small airway function. A reduction in air trapping, measured by HRCT, was documented in asthmatic patients receiving extrafine beclomethasone dipropionate (BDP) compared with patients receiving nonextrafine BDP (41). Extrafine BDP was also associated with a significant reduction in airway closure and no change in lung function after 3 months of treatment compared with nonextrafine fluticasone propionate (FP) (45). Furthermore, a greater increase in FVC was reported in asthmatic patients receiving BDP/formoterol (F) extrafine combination *vs* nonextrafine FP/salmeterol (S) (46), due to the improved peripheral deposition of the extra-

fine particles that characterize the BDP/F formulation. Since the improvement in FVC may reflect a reduction in air trapping associated with small airway obstruction, this finding seems to indicate a more efficient peripheral deposition of the extra-fine particles that characterize the BDP/F formulation. Preliminary data from a double blind, randomized pilot study comparing BDP/F extrafine with nonextrafine FP/S in patients with asthma also showed a significant reduction in airway closure at 12 weeks from baseline with the BDP/F extrafine combination but not with the nonextrafine FP/S (47).

Improvements in distal lung function were also demonstrated with agents other than corticosteroids, provided their ability to reach the distal lung. Changes of the sbN₂-test have been described after inhalation of formoterol or terbutaline, in nonallergic bronchial asthma (48). In a randomized, double blind study in mild asthmatics (49), oral montelukast resulted in significant changes in specific conductance and in residual volume, as opposed to placebo. Interestingly, these changes were associated with improvements in asthmatic symptoms, irrespective of modest FEV₁ changes. The study clearly demonstrated that, although FEV₁ is an important measurement in asthma patients, it does not provide complete information on the physiologic dysregulation associated with asthma.

Smith et al. (50) investigated whether the FeNO measurements may provide a method of adjusting inhaled corticosteroid (fluticasone) doses for patients with asthma. The authors performed a prospective, randomized, single blind, placebo-controlled trial that demonstrated that the FeNO-driven therapy resulted in a lower maintenance dose of inhaled corticosteroid needed to control asthma, as compared with the use of a dose-adjustment strategy based on conventional guidelines. However, the importance of these observations was lowered by another study (51), which found that an asthma treatment strategy based on the measurement of FeNO did not result in a reduction in the total amount of inhaled corticosteroid therapy, when compared with asthma guidelines based strategy. In addition, a recent study by Szeffler et al. (52) found that the addition of FeNO as an indicator of control of asthma resulted in even higher doses of inhaled corticosteroids, without clinically important improvements in symptomatic asthma control. None of the above-cited studies showed reductions in the exacerbation rate (50, 51) or improvements in asthma control (52).

With regards to NO of distal source, in mild-to-moderate asthma patients, alveolar exhaled NO decrease significantly with ciclesonide, delivered as a small-particle inhaled corticosteroid, and this suggests that the drug exerts anti-inflammatory effects on small airways (53). In children aged 6–12 years with moderate persistent asthma, alveolar NO concentration and bronchial NO flux were similar after therapy with extrafine

hydrofluoroalkane-beclomethasone or fluticasone dry powder inhaler (54). By contrast, in a study by Lehtimäki (55), inhaled fluticasone decreased bronchial NO flux from 3.6 ± 0.4 to 0.7 ± 0.1 nl/s ($P < 0.01$) but had no effect on alveolar NO concentration (before: 1.2 ± 0.5 ; after: 1.2 ± 0.1 ppb, $P > 0.05$) in agreement with the central deposition profile of this formulation.

Drugs administered orally should reach the small airways through systemic circulation; therefore, improvements on small airways functional parameters are expected. In this perspective, a small sample of subjects with asthma on inhaled corticosteroids was treated with a short course of oral prednisone, and this resulted in isolated significant decreases in NO alveolar concentration (56). The authors highlighted that despite treatment, including inhaled corticosteroids, patients with asthma may have ongoing separate airway and alveolar sites of NO inflammation, the latter responsive to oral corticosteroids.

It is important to emphasize that the improvements in parameters related to small airways function translate into improvements in health-related quality of life (QOL): extrafine BDP significantly improved QOL at 12 months compared with nonextrafine BDP ($P < 0.05$) in a nonblind, randomized trial of 473 asthmatics (57). However, Boulet (58) found that, in a large cohort of asthmatics of variable severity, the magnitude of improvement of respiratory symptoms following treatment with inhaled extrafine BDP was not correlated with measures of small airway function. This suggests that extrafine BDP mostly acts at the level of large or medium airways, or that the effects on proximal airways mask the contribution of the smaller airways to asthmatic symptoms. There is also the possibility that changes in small airways mainly affect other clinical or functional features, such as exercise tolerance or exercise-induced dynamic lung hyperinflation. Finally, changes in small airway function, primarily lung hyperinflation, could occur during induced or spontaneous bronchoconstriction, rather than in stable asthma.

In conclusion, monitoring asthma treatment should be based on a composite index derived from clinical and functional assessments. In selected patients, i.e. those with incomplete asthma control despite a good response in lung function, the involvement of peripheral airways is suspected, and therefore more sensitive procedures should be employed. In this regard, treatments targeting both large and small airways may be more beneficial in improving asthma control. Clinical studies suggest that extrafine formulations able to deliver inhaled drugs throughout the bronchial tree (both large and small airways) can be effective on functional and/or biological parameters measuring either directly or indirectly air trapping and airway closure. Further studies are needed to validate new procedures in the effort to properly monitor asthma treatment beyond FEV₁.

References

- Bousquet J, Clark TJ, Hurd S, Khaltaev N, Lenfant C, O'Byrne P et al. GINA guidelines on asthma and beyond. *Allergy* 2007;**62**:102–112.
- Humbert M, Holgate S, Boulet LP, Bousquet J. Asthma control or severity: that is the question. *Allergy* 2007;**62**:95–101.
- Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004;**170**:836–844.
- O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;**164**:1392–1397.
- Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;**368**:744–753.
- Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;**120**:1360–1367.
- Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;**6**:13.
- Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802–807.
- Scichilone N, Marchese R, Soresi S, Interrante A, Toghias A, Bellia V. Deep inspiration-induced changes in lung volume decrease with severity of asthma. *Respir Med* 2007;**101**:951–956.
- Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;**163**:924–929.
- Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Peripheral inflammation in patients with asthmatic symptoms but normal lung function. *J Asthma* 2005;**42**:605–609.
- European Network for Understanding Mechanisms of Severe Asthma. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003;**22**:470–477.
- Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. *J Appl Physiol* 2008;**104**:394–403.
- Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997;**100**:44–51.
- Tulic MK, Christodoulouopoulos P, Hamid Q. Small airway inflammation in asthma. *Respir Res* 2001;**2**:333–339.
- Kraft M. The distal airways: are they important in asthma? *Eur Respir J* 1999;**14**:1403–1417.
- Carr DH, Hibon S, Rubens M, Chung KF. Peripheral airways obstruction on high-resolution computed tomography in chronic severe asthma. *Respir Med* 1998;**92**:448–453.
- Newman KB, Lynch DA, Newman LS, Ellegood D, Newell JD Jr. Quantitative computed tomography detects air trapping due to asthma. *Chest* 1994;**106**:105–109.
- Park JW, Hong YK, Kim CW, Kim DK, Choe KO, Hong CS. High-resolution computed tomography in patients with bronchial asthma: correlation with clinical features, pulmonary functions and bronchial hyperresponsiveness. *J Investig Allergol Clin Immunol* 1997;**7**:186–192.
- Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. *Eur Respir J* 2002;**20**:254–259.
- Boulet LP. Transbronchial biopsy as a tool to evaluate small-airways disease in asthma. *Pros Eur Respir J* 2002;**20**:247–248.
- James A, Carroll N. Transbronchial biopsy as a tool to evaluate small-airways disease in asthma. *Cons Eur Respir J* 2002;**20**:249–251.
- Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;**154**:1505–1510.
- Tashkin DP. The role of small airway inflammation in asthma. *Allergy Asthma Proc* 2002;**23**:233–242.
- Yoo Y, Choung JT, Yu J, Kim do K, Choi SH, Koh YY. Comparison of percentage fall in FVC at the provocative concentration of methacholine causing a 20% fall in FEV(1) between patients with asymptomatic bronchial hyperresponsiveness and mild asthma. *Chest* 2007;**132**:106–111.
- van Veen IH, Sterk PJ, Schot R, Gauw SA, Rabe KF, Bel EH. Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. *Eur Respir J* 2006;**27**:951–956.
- Bourdin A, Paganin F, Prefaut C, Kieselers D, Godard P, Chanez P. Nitrogen washout slope in poorly controlled asthma. *Allergy* 2006;**61**:85–89.
- Battaglia S, den Hertog H, Timmers MC, Lazeroms SP, Vignola AM, Rabe KF et al. Small airways function and molecular markers in exhaled air in mild asthma. *Thorax* 2005;**60**:639–644.
- Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 1993;**6**:1368–1370.
- Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1693–1722.
- Massaro AF, Mehta S, Lilly CM, Kobzik L, Reilly JJ, Drazen JM. Elevated nitric oxide concentrations in isolated lower airway gas of asthmatic subjects. *Am J Respir Crit Care Med* 1996;**153**:1510–1514.
- Jorres RA. Modelling the production of nitric oxide within the human airways. *Eur Respir J* 2000;**16**:555–560.
- Pietropaoli AP, Perillo IB, Torres A, Perkins PT, Frasier LM, Utell MJ et al. Simultaneous measurement of nitric oxide production by conducting and alveolar airways of humans. *J Appl Physiol* 1999;**87**:1532–1542.
- Tsoukias NM, George SC. A two-compartment model of pulmonary nitric oxide exchange dynamics. *J Appl Physiol* 1998;**85**:653–666.
- Jiang J, Malavia N, Suresh V, George SC. Nitric oxide gas phase release in human small airway epithelial cells. *Respir Res* 2009;**10**:3.
- Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Increased alveolar nitric oxide concentration in asthmatic patients with nocturnal symptoms. *Eur Respir J* 2002;**20**:841–845.

37. Mahut B, Delacourt C, Zerah-Lancner F, De Blic J, Harf A, Delclaux C. Increase in alveolar nitric oxide in the presence of symptoms in childhood asthma. *Chest* 2004;**125**:1012–1018.
38. Berry M, Hargadon B, Morgan A, Shelley M, Richter J, Shaw D et al. Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. *Eur Respir J* 2005;**25**:986–991.
39. Condorelli P, Shin HW, Aledia AS, Silkoff PE, George SC. A simple technique to characterize proximal and peripheral nitric oxide exchange using constant flow exhalations and an axial diffusion model. *J Appl Physiol* 2007;**102**:417–425.
40. Kerckx Y, Michils A, Van Muylem A. Airway contribution to alveolar nitric oxide in healthy subjects and stable asthma patients. *J Appl Physiol* 2008;**104**:918–924.
41. Vanden Burgt JA, Busse WW, Martin RJ, Szefer SJ, Donnell D. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma. *J Allergy Clin Immunol* 2000;**106**:1209–1226.
42. Lee YM, Park JS, Hwang JH, Park SW, Uh ST, Kim YH et al. High-resolution CT findings in patients with near-fatal asthma: comparison of patients with mild-to-severe asthma and normal control subjects and changes in airway abnormalities following steroid treatment. *Chest* 2004;**126**:1840–1848.
43. Hauber HP, Gotfried M, Newman K, Danda R, Servi RJ, Christodouloupoulos P et al. Effect of HFA-flunisolide on peripheral lung inflammation in asthma. *J Allergy Clin Immunol* 2003;**112**:58–63.
44. Bergeron C, Hauber HP, Gotfried M, Newman K, Dhanda R, Servi RJ et al. Evidence of remodeling in peripheral airways of patients with mild to moderate asthma: effect of hydrofluoroalkane-flunisolide. *J Allergy Clin Immunol* 2005;**116**:983–989.
45. Thongngarm T, Silkoff PE, Kossack WS, Nelson HS. Hydrofluoroalkane-134A beclomethasone or chlorofluorocarbon fluticasone: effect on small airways in poorly controlled asthma. *J Asthma* 2005;**42**:257–263.
46. Papi A, Paggiaro P, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. *Allergy* 2007;**62**:1182–1188.
47. Scichilone N, Battaglia S, Sorino C, Paglino G, Martino L, Nicolini G et al. Effects on small airways of two different combination treatments for asthma. *Am J Respir Crit Care Med* 2009;**179**:A5070.
48. Hedenstrom H, Wegener T, Boman G, Wahlander L, Melander B. Effect of inhaled formoterol versus terbutaline on respiratory function in moderate bronchial asthma. *Allergy* 1992;**47**:158–163.
49. Kraft M, Cairns CB, Ellison MC, Pak J, Irvin C, Wenzel S. Improvements in distal lung function correlate with asthma symptoms after treatment with oral montelukast. *Chest* 2006;**130**:1726–1732.
50. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;**352**:2163–173.
51. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;**176**:231–237.
52. Szefer SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomized controlled trial. *Lancet* 2008;**372**:1065–1072.
53. Cohen J, Douma WR, ten Hacken NH, Vonk JM, Oudkerk M, Postma DS. Ciclesonide improves measures of small airway involvement in asthma. *Eur Respir J* 2008;**31**:1213–1220.
54. Robroeks CM, van de Kant KD, van Vliet D, Kester AD, Hendriks HJ, Damoiseaux JG et al. Comparison of the anti-inflammatory effects of extrafine hydrofluoroalkane-beclomethasone vs fluticasone dry powder inhaler on exhaled inflammatory markers in childhood asthma. *Ann Allergy Asthma Immunol* 2008;**100**:601–607.
55. Lehtimäki L, Kankaanranta H, Saarelainen S, Turjanmaa V, Moilanen E. Inhaled fluticasone decreases bronchial but not alveolar nitric oxide output in asthma. *Eur Respir J* 2001;**18**:635–639.
56. Gelb AF, Taylor CF, Nussbaum E, Gutierrez C, Schein A, Shinar CM et al. Alveolar and airway sites of nitric oxide inflammation in treated asthma. *Am J Respir Crit Care Med* 2004;**170**:737–741.
57. Juniper EF, Price DB, Stampone PA, Creemers JP, Mol SJ, Fireman P. Clinically important improvements in asthma-specific quality of life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate to approximately half the dose of extrafine beclomethasone dipropionate. *Chest* 2002;**121**:1824–1832.
58. Boulet LP. Comparative improvement of asthma symptoms and expiratory flows after corticosteroid treatment: a method to assess the effect of corticosteroids on large vs. small airways? *Respir Med* 2006;**100**:496–502.