



Small airway disease in asthma: pathophysiological and diagnostic considerations

Marco Contoli^a, Pierachille Santus^b, and Alberto Papi^a

Purpose of review

The aim of the current review is to summarize the evidence of small airway abnormalities in asthma, the proposed diagnostic tools for small airway abnormalities and the clinical implications of small airway abnormalities in asthma.

Recent findings

Pathological abnormalities in the peripheral membranous bronchioles less than 2 mm in diameter (i.e. small airways) can be very frequently detected in asthma patients across severity: from mild to the more severe clinical manifestations of the disease. Interestingly, not only are small airway abnormalities present in asthma, but there is evidence that the magnitude of small airway abnormalities correlates with the severity of the disease. So far no unanimously accepted method and/or algorithm is available for small airway abnormality detection; however, some functional techniques and inflammatory markers have been used as surrogates of small airway dysfunction.

Summary

Clinicians, and not only researchers, must consider small airways when approaching asthma patients, particularly when dealing with patients with a 'difficult-to-treat phenotype'. The identification of subgroups of asthma patients with prominent small airway disease is not merely speculative, and carries pathophysiological and therapeutic implications.

Keywords

asthma, diagnosis, inflammation, small airways

INTRODUCTION

Asthma is a chronic inflammatory disease of the whole bronchial tree from the central to the more peripheral airways [1]. Pathological abnormalities in the peripheral membranous bronchioles less than 2 mm in diameter (i.e. small airways) can be very frequently detected in asthma patients across severity [2]: from milder to the more severe clinical manifestations of the disease [3–5]. Interestingly, not only are small airway abnormalities present in asthma, but there is evidence that the magnitude of small airway abnormalities correlates with the severity of the disease [6,7], suggesting that small airway abnormalities can drive the clinical manifestation of the disease. So far no unanimously accepted method and/or algorithm is available for small airway abnormalities detection; however, some functional techniques and inflammatory markers have been used as surrogates of small airway dysfunction.

The aim of the current review is to summarize the evidence of small airway abnormalities in asthma, the proposed diagnostic tools for small

airway abnormalities and the clinical implications of small airway abnormalities in asthma.

ASSESSMENT OF SMALL AIRWAYS IN ASTHMA: INFLAMMATION

The small airways represent a region of the airways not easily reachable. In order to directly study biomarkers of small airways, peripheral specimens derived from invasive techniques such as surgical resection and transbronchial biopsies are needed.

^aSection of Internal and Cardio-Respiratory Medicine, Department of Medical Sciences, Research Centre on Asthma and COPD, University of Ferrara, Ferrara and ^bDipartimento di Scienze della Salute, Pneumologia Riabilitativa, Fondazione Salvatore Maugeri, Istituto Scientifico di Milano IRCCS, University of Milan, Milan, Italy

Correspondence to Prof Alberto Papi, Section of Internal and Cardio-Respiratory Medicine, Department of Medical Sciences, Research Centre on Asthma and COPD, University of Ferrara, Italy, Via Savonarola 9 – 44121, Ferrara, Italy. Tel: +39 0532236908; fax: +39 0532210297; e-mail: ppa@unife.it

Curr Opin Pulm Med 2015, 21:000–000

DOI:10.1097/MCP.000000000000122

KEY POINTS

- Small airways are relevant sites for pathological abnormalities in asthma.
- A correlation has been documented between the magnitude of small airway abnormalities and the severity of the clinical manifestation of asthma.
- Despite the lack of unanimous consensus on the gold standard to assess small airways, several assays can provide information on different aspects of small airway abnormalities.

Although in the past such invasive techniques have proven to be fundamental for assessing the disease of small airways in asthma, and are still performed in explorative studies, they obviously are not applicable in daily clinical practice. By the means of these invasive techniques, it has been shown that inflammation and remodelling, key elements in the disease of asthma, also occur in the peripheral airways of asthma patients. Intense inflammatory cell infiltrate, luminal plugging and airway structural abnormalities have been demonstrated in post-mortem tissue of peripheral airways from patients who died from a severe exacerbation [8–11]. Increased eosinophils and T-helper 2 polarized-CD4⁺ T lymphocytes and higher number of inflammatory cells in small versus large airways [3] have been shown via transbronchial biopsies or in surgical specimens of severe asthma patients undergoing lung resection. Remodelling is also a well known characteristic of the central airways of asthma patients [3]. However, features of remodelling, such as increases in the thickness of adventitial, submucosal and muscle layers and of the reticular basal membrane, have also been demonstrated in peripheral airways of severe asthma patients or patients who died from asthma [12,13]. Very few studies have directly assessed small airways of mild asthma patients. In these studies, airway inflammation, airway remodelling and enhanced matrix deposition have been shown also in the small airways of mild asthma patients, suggesting that small airways are a relevant site of pathological abnormalities across all the levels of severity of the disease [4,14].

Ethical concerns have limited the extensive use of invasive techniques to directly explore small airway abnormalities in asthma, particularly in the mildest forms of the disease. To overcome such limitations, more sophisticated techniques have been developed to indirectly assess small airway disease.

Peripheral airway inflammation can be indirectly examined by measuring nitric oxide

concentrations in single-breath exhaled air at different flow rates [15,16]. With this technique, using a mathematical model, it is possible to discriminate between the bronchial and alveolar nitric oxide levels and therefore to indirectly evaluate peripheral airway inflammation. Alveolar nitric oxide has been related to markers of peripheral airway inflammation such as eosinophil cationic protein levels and eosinophil counts in bronchoalveolar lavage of asthma patients [17].

ASSESSMENT OF SMALL AIRWAYS IN ASTHMA: PATHOPHYSIOLOGY

Although small airways have very little impact on airflow resistance in normal conditions, there is evidence that their abnormalities significantly contribute to increasing airflow resistance in asthma patients. In a pivotal study, Wagner *et al.* [18] demonstrated that, by inserting a bronchoscope with a catheter at the tip to measure airway resistance, the peripheral resistance of accessible airways of asthma patients was 10-fold higher than in controls. The same authors showed the higher response of peripheral airways of asthma patients towards histamine as opposed to controls [19]. More recently, van der Velden *et al.* [20] found that, in a sheep model of asthma, the peripheral airway responses to allergic (house dust mite) and nonallergic (methacholine) stimuli, measured directly with the use of a wedged bronchoscope, was more evident in the presence of asthma. Given the invasive nature of the methodology, other functional measurements specifically assessing the role of small airways were more recently developed.

From a functional point of view, small airway abnormalities lead to peripheral heterogeneity of the ventilation and to premature airway closure and air trapping. Functional tests have been used to indirectly assess these abnormalities.

It has been documented that in asthma, residual volume correlates with both peripheral airway resistances (directly assessed by endobronchial catheterization) [21] and parameters of air trapping evaluated by high-resolution computed tomography (CT) scan [22]. Thus, increased residual volume, and more precisely residual volume over total lung capacity (residual volume/TLC) ratio above the upper limit of normal obtained from a reference equation, is considered a valid surrogate of air trapping. Additionally, forced vital capacity (FVC) has been shown to correlate inversely with residual volume/TLC [23], indicating that reduction in FVC can be considered a marker of air trapping that must be complemented with lung volume measurements.

Other lung function parameters have been proposed and investigated as markers of small airway function. One of them is forced expiratory flow (FEF) between 25 and 75% of FVC (FEF_{25–75}), although the literature supporting its validity is not conclusive and conflicting data have been presented. Serial measures of FEF_{25–75} are highly variable, and FEF_{25–75} levels are influenced by large airway obstruction and volume changes. Additionally, this parameter did not correlate with neither other measures of air trapping (FVC and residual volume/TLC) [23] nor with small airway inflammation as determined by lung biopsies obtained through bronchoscopy [24]. Taking in account the considerations made, modifications from normality of FEF_{25–75} should be interpreted with caution as a reflection of small airway impairment, both because of its intrinsic variability and dependence on lung volume changes.

The single-breath nitrogen washout test (SBWT) is a test dating from the 1960s that can measure peripheral ventilation inhomogeneity (slope of phase III) and airway closure (closing capacity), and thus it represents another functional test that has been extensively used to indirectly measure small airway functional abnormalities in asthma patients. The technique implies an expiration to residual volume before slowly inhaling a 100% concentration of oxygen to TLC. The individual then slowly expires to residual volume again and the tracing of nitrogen concentration is registered. The record originated is made by a first steep increase of nitrogen due to anatomical dead space of upper airways, then a plateau is reached reflecting the emptying of conductive and medium size airways (phase III). A final steep increase in nitrogen concentration (phase IV) that normally occurs at the 25% of vital capacity represents the closing volume, the lung volume that reflects the complete occlusion of the gravity-dependent small airways. When the residual volume is summed to closing volume, closing capacity is obtained and referred as the percentage of TLC (closing capacity/TLC%) [25]. Recently, a new way of assessing small airway alterations in a noninvasive way using the multiple breath nitrogen washout test (MBWT) has been described. With respect to SBWT, MBWT has several major advantages as it is hardly affected by gravity [26], and it is not affected by airway closure below functional residual capacity, which is known to affect SBWT phase III [27]. Moreover, it is capable of distinguishing the origin of ventilation heterogeneity, and the implication of small airways. In fact, two different variables are detected, the S_{cond} (index of conductive ventilation heterogeneity) and S_{acin} (index of acinar ventilation heterogeneity)

[28,29]. In asthma, MBWT has been employed in airway challenging [30] and it showed a good relation in detecting small airway abnormalities independently of airway inflammation measured by exhaled nitric oxide [16]. Finally, a recent study showed a correlation between functional parameters of air trapping (including increased residual volume) and of heterogeneity of peripheral airway ventilation and closure [including increase in the slope of phase III by nitrogen washout test (dN₂), and closing capacity] with levels of alveolar nitric oxide in severe asthma patients [31], supporting that in lung periphery airway inflammation and functional abnormalities are interrelated. These techniques are rarely used in daily clinical practice. However, they are capable of offering a reliable picture of small airway conditions in asthma. The ability of interpretation of their numerous signals, together with other recent noninvasive techniques, will bring novel insights in small airway pathophysiology.

Among the more recent noninvasive techniques to assess small airway abnormalities, the forced oscillation technique (FOT) and impulse oscillometry (IOS) have become quite popular and largely adopted not only in research settings but also in clinical practice. They are noninvasive versatile tests that imply little patient collaboration and represent one of the most important current research lines in lung physiopathology. FOT measures the impedance of the respiratory system to forced pressure oscillations produced by a loudspeaker. The impedance includes two parameters: resistance (Rrs) and reactance (Xrs). Rrs is related to airway calibre, Xrs depends on the distributed inertance and stiffness of the respiratory system [32]. To derive its measures, FOT uses the superimposition of pressure fluctuations on the airway during patient's tidal breathing. Goldman *et al.* [33] confirmed the hypothesis that Rrs at frequencies higher than resonance reflects large airway mechanical properties, whereas that at frequencies below resonance reflects the added influence of small airways. It, therefore, appears simple to study peripheral airway effects by comparing low-frequency and high-frequency Rrs [33]. Low-frequency Xrs appeared to be a useful and sensitive index of peripheral airway function; in fact, it is modified by asthma treatment and related achievement of clinical control. [33]. The functioning principle of IOS is similar to FOT, as it derives directly from it and delivers a regular square wave of pressure five times per second emitting a continuous spectrum of frequencies that allows the determination of the mechanical behaviour of respiratory system [32]. The so-called frequency dependence, an increase of Rrs at lower frequencies (<10–15 Hz), has

been demonstrated in various obstructive lung diseases such as asthma, but is also related to small airway obstruction [33–35]. There is no doubt that FOT and IOS provide an advantage over spirometry because of the ease with which these tests can be performed, requiring little or no cooperation at all from the patients. Moreover the amplitude of the oscillation does not alter the mechanical properties of the respiratory system, thus making this technique ideal in monitoring bronchoactive responses. The main weakness remains the inability to distinguish between obstructive and restrictive pattern [36]. CT has emerged as a useful tool to noninvasively assess peripheral airway disease in patients with asthma. The cardinal CT sign of peripheral airway disease in asthma is the presence of pulmonary decreased attenuation areas, which are more conspicuous and extensive on expiratory CT scans. These areas reflect air-trapping, which may be either secondary to transient small airway obstruction or spasm or caused by fixed peripheral remodelling [37–39]. There are two systems for quantifying air-trapping on CT: the visual score and the densitometric analysis. The major disadvantage of a subjective approach is the variation between observers, and the densitometric analysis, despite its limitations, has been the technique of choice in recent scientific investigations and pharmaceutical trials. Specifically, either mean lung density or -850 HU cut-off CT density has been used to quantify air trapping in asthmatic subjects. CT imaging of pulmonary ventilation patterns in patients with asthma has evolved over the past decade with the introduction of more sophisticated techniques. Although the direct assessment of peripheral remodelling by CT measurements is still limited, due to the difficulty in accurately measuring the distal small airways (typically <2 mm diameter), computer-assisted three-dimensional analysis of the airway tree structure is currently advancing the evaluation of small airway disease [40]. Although current evidence indicates that small airway obstruction could be routinely assessed using CT scanning, this technique does have some limitations, including lack of standardization of the technical parameters of the CT scanner, lack of consensus on the best index for small airway disease assessment, and exposure of subjects to ionizing radiation. Indeed, the regular assessment of small airway disease via CT imaging is still not part of the routine clinical practice for asthmatic patients.

SMALL AIRWAY DISEASE IN ASTHMA: THE CLINICAL RELEVANCE

Small airway abnormalities can be detected across all levels of asthma severity from the mild to the more

severe clinical manifestation of the disease. There is evidence of a correlation between the degree of small airway abnormalities/impairment and the severity of asthma. A study comparing the characteristics of small airway inflammation in severe vs. moderate asthma patients in transbronchial biopsies showed a more pronounced neutrophilic inflammation in the small airways of patients with severe asthma [5]. Indirect parameters of peripheral airway inflammation, such as alveolar nitric oxide, were found to be elevated in patients with uncontrolled asthma despite regular treatment compared with mild-to-moderate controlled asthma patients and normal controls [17]. Similarly, alveolar nitric oxide was higher in patients with steroid-dependent asthma compared with nonsteroid-dependent asthma patients [31] and in patients with uncontrolled compared with controlled asthma [41[¶]]. Similarly, there is evidence of a correlation between functional parameters reflecting small airway impairment and the severity of the disease. In particular, enhanced air trapping with increased residual volume/TLC ratio has been reported in severe patients when compared with mild-to-moderate asthma patients with a similar degree of airflow limitation as assessed by FEV₁ [23]. Additional studies have evaluated functional parameters of small airway abnormalities in relation to asthma severity/control. Using the SBWT, in 't Veen *et al.* [42] found that increased closing volume and closing capacity were the only pulmonary function variables that discriminated between patients with difficult-to-control asthma (i.e. experiencing frequent exacerbations despite regular and maximal inhalation treatment) and patients with stable asthma. Moreover, Bourdin *et al.* [43] found that an increase in the dN2 of the washout curve was associated with poor asthma control, high exacerbation rate and with the need for a high daily dose of inhaled corticosteroids in a cohort of asthma patients with normal FEV₁. Very recently, small airway dysfunction, also when assessed by the IOS technique, has been shown to be associated with poor disease control and a history of asthma exacerbations [44[¶]]. In some studies, small airway involvement was assessed in specific phenotypes of severe difficult-to-control asthma such as nocturnal asthma. In transbronchial biopsies, Kraft *et al.* [21] found that the number of inflammatory cells was significantly higher in the distal airways of patients with nocturnal asthma compared with nonnocturnal, controlled asthma patients.

Taken together, these data indicate that more severe pathological abnormalities, leading to premature airway closure and peripheral air trapping, occur in the airways of severe asthma patients compared with moderate or controlled asthma patients.

It has been recently proposed that not only are small airway abnormalities prominent in severe asthma patients, but also that enhanced small airway abnormalities could be a characterizing feature of a specific subgroup/phenotype of asthma patients linked by poor response to treatment such as asthma patients with fixed airflow obstruction and elderly asthma patients [7].

CONCLUSION

Small airways, that is, the peripheral membranous bronchioles less than 2 mm in internal diameter are an important site of inflammation and structural abnormalities in asthma. Small airway abnormalities significantly contribute to increase airflow resistance in the airways of asthma patients. Despite no unanimous consensus on the algorithm to assess small airway function and structure, several noninvasive techniques can detect and quantify small airway disease/dysfunction. By the mean of these techniques, small airway abnormalities can be very frequently detected in the population of asthma patients across all levels of severity of the disease [2]. Interestingly, there is published evidence of enhanced small airway abnormalities/dysfunction in patients characterized by severe manifestation of the disease and/or poor response to treatment [7].

Taken together, these data support the concept that clinicians, and not only researchers, must consider small airways when approaching asthma patients, particularly when dealing with patients with a 'difficult-to-treat phenotype'. The identification of subgroups of asthma patients with prominent small airway disease is not merely speculative, and carries pathophysiological and, even more importantly, therapeutic implications. If a small airway phenotype is identified, a more aggressive approach should be proposed in order to assess and treat the abnormalities at the level of small airways. Further studies are required in this direction.

Acknowledgements

None.

Financial support and sponsorship

The Research Centre on Asthma and COPD, Section of Internal and Cardio-Respiratory Medicine, Department of Medical Sciences, of the University of Ferrara, Italy, received unrestricted grants for research from Fondazione Chiesi and Fondazione Maugeri.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Contoli M, Bousquet J, Fabbri LM, *et al.* The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. *Allergy* 2010; 65:141–151.
2. Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? *Ann Allergy Asthma Immunol* 2012; 109:185–189.
3. Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. *Eur Respir J* 2002; 20:254–259.
4. Hamid Q, Song Y, Kotsimbos TC, *et al.* Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997; 100:44–51.
5. Wenzel SE, Szefler SJ, Leung DY, *et al.* Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med* 1997; 156:737–743.
6. van der Wiel E, ten Hacken NHT, Postma DS, *et al.* Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. *J Allergy Clin Immunol* 2013; 131:646–657.
7. Contoli M, Kraft M, Hamid Q, *et al.* Do small airway abnormalities characterize asthma phenotypes? In search of proof. *Clin Exp Allergy* 2012; 42:1150–1160.
8. Dolhnikoff M, da Silva LFF, de Araujo BB, *et al.* The outer wall of small airways is a major site of remodeling in fatal asthma. *J Allergy Clin Immunol* 2009; 123:1090–1097.
9. Mauad T, Silva LFF, Santos MA, *et al.* Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med* 2004; 170:857–862.
10. den Otter I, Silva LFF, Carvalho ALN, *et al.* High-affinity immunoglobulin E receptor expression is increased in large and small airways in fatal asthma. *Clin Exp Allergy* 2010; 40:1473–1481.
11. Caramori G, Oates T, Nicholson AG, *et al.* Activation of NF-kappaB transcription factor in asthma death. *Histopathology* 2009; 54:507–509.
12. Ebina M, Takahashi T, Chiba T, Motomiya M. Cellular hypertrophy and hyperplasia of airway smooth muscles underlying bronchial asthma. A 3-D morphometric study. *Am Rev Respir Dis* 1993; 148:720–726.
13. Kuwano K, Bosken CH, Pare PD, *et al.* Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148:1220–1225.
14. Nihlberg K, Andersson-Sjoland A, Tufvesson E, *et al.* Altered matrix production in the distal airways of individuals with asthma. *Thorax* 2010; 65:670–676.
15. Tsoukias NM, Shin HW, Wilson AF, George SC. A single-breath technique with variable flow rate to characterize nitric oxide exchange dynamics in the lungs. *J Appl Physiol* 2001; 91:477–487.
16. Lehtimäki L, Kankaanranta H, Saarelainen S, *et al.* Extended exhaled NO measurement differentiates between alveolar and bronchial inflammation. *Am J Respir Crit Care Med* 2001; 163:1557–1561.
17. Berry M, Hargadon B, Morgan A, *et al.* Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma. *Eur Respir J* 2005; 25:986–991.
18. Wagner EM, Liu MC, Weinmann GG, *et al.* Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990; 141:584–588.
19. Wagner EM, Bleecker ER, Permutt S, Liu MC. Direct assessment of small airways reactivity in human subjects. *Am J Respir Crit Care Med* 1998; 157:447–452.
20. van der Velden J, Barker D, Barcham G, *et al.* Assessment of peripheral airway function following chronic allergen challenge in a sheep model of asthma. *PLoS One* 2011; 6:e28740.
21. Kraft M, Martin RJ, Wilson S, *et al.* Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. *Am J Respir Crit Care Med* 1999; 159:228–234.
22. Ueda T, Niimi A, Matsumoto H, *et al.* Role of small airways in asthma: investigation using high-resolution computed tomography. *J Allergy Clin Immunol* 2006; 118:1019–1025.
23. Sorkness RL, Bleecker ER, Busse WW, *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.
24. Sutherland ER, Martin RJ, Bowler RP, *et al.* Physiologic correlates of distal lung inflammation in asthma. *J Allergy Clin Immunol* 2004; 113:1046–1050.
25. Robinson PD, Latzin P, Verbanck S, *et al.* Consensus statement for inert gas washout measurement using multiple- and single-breath tests. *Eur Respir J* 2013; 41:507–522.
26. Prisk GK, Guy HJ, Elliott AR, *et al.* Ventilatory inhomogeneity determined from multiple-breath washouts during sustained microgravity on Spacelab SLS-1. *J Appl Physiol* 1995; 78:597–607.
27. Verbanck S, Schuermans D, Meysman M, *et al.* Noninvasive assessment of airway alterations in smokers: the small airways revisited. *Am J Respir Crit Care Med* 2004; 170:414–419.

28. Dutrieue B, Vanholsbeeck F, Verbanck S, Paiva M. A human acinar structure for simulation of realistic alveolar plateau slopes. *J Appl Physiol* 2000; 89:1859–1867.
 29. Verbanck S, Thompson BR, Schuermans D, *et al.* Ventilation heterogeneity in the acinar and conductive zones of the normal ageing lung. *Thorax* 2012; 67:789–795.
 30. Verbanck S, Schuermans D, Van Muylem A, *et al.* Ventilation distribution during histamine provocation. *J Appl Physiol* 1997; 83:1907–1916.
 31. van Veen IH, Sterk PJ, Schot R, *et al.* Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. *Eur Respir J* 2006; 27:951–956.
 32. Smith H, Reinhold P, Goldman M. Forced oscillation technique and impulse oscillometry. *Eur Respir Mon* 2005; 31:72–105.
 33. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. *Respir Physiol Neurobiol* 2005; 148:179–194.
 34. Castro-Rodriguez JA, Daszenies C, Garcia M, *et al.* Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: a 5-year follow-up. *Pediatr Pulmonol* 2006; 41:947–953.
 35. Delacourt C, Lorino H, Herve-Guillot M, *et al.* Use of the forced oscillation technique to assess airway obstruction and reversibility in children. *Am J Respir Crit Care Med* 2000; 161:730–736.
 36. Oostveen E, MacLeod D, Lorino H, *et al.* The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J* 2003; 22:1026–1041.
 37. Newman KB, Lynch DA, Newman LS Jr, *et al.* Quantitative computed tomography detects air trapping due to asthma. *Chest* 1994; 106:105–109.
 38. Gono H, Fujimoto K, Kawakami S, Kubo K. Evaluation of airway wall thickness and airtrapping by HRCT in asymptomatic asthma. *Eur Respir J* 2003; 22:965–971.
 39. Laurent F, Latrabe V, Raheison C, *et al.* Functional significance of air trapping detected in moderate asthma. *Eur Radiol* 2000; 10:1404–1410.
 40. Montaudon M, Lederlin M, Reich S, *et al.* Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings. *Radiology* 2009; 253:844–853.
 41. Scichilone N, Battaglia S, Taormina S, *et al.* Alveolar nitric oxide and asthma ■ control in mild untreated asthma. *J Allergy Clin Immunol* 2013; 131:1513–1517.
- This study provides the evidence of the clinical relevance to evaluate small airway dysfunction in patients with uncontrolled asthma.
42. in 't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *Am J Respir Crit Care Med* 2000; 161:1902–1906.
 43. Bourdin A, Paganin F, Préfaut C, *et al.* Nitrogen washout slope in poorly controlled asthma. *Allergy* 2006; 61:85–89.
 44. Pisi R, Tzani P, Aiello M, *et al.* Small airway dysfunction by impulse oscillometry ■ in asthmatic patients with normal forced expiratory volume in the 1st second values. *Allergy Asthma Proc* 2013; 34:e14–20.
- This study provides the evidence of the clinical relevance to evaluate small airway dysfunction in poor-controlled asthma patients.