



The role of small airway disease in asthma

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Purpose of review

This review provides an update on the importance of the peripheral 'small' airways in asthma. As the small airways account for less than 10% of total airway resistance, thus having little impact on standard lung function measures such as forced expiratory volume and peak flow, they have been referred to as the 'silent zone'.

Recent findings

The study has revealed that small airway involvement is present in all stages of asthmatic disease, being related to important clinical phenotypes such as nocturnal asthma, exercise-induced asthma, and difficult-to-control asthma, including those with the risk of repeated asthma exacerbations. **Uncontrolled small airway inflammation is related to airway remodeling and progression of the disease, with a more rapid decline in the lung function.** Moreover, studies on both children and adults have shown that the involvement of the small airways represents a crucial step in asthma development. New tools have been developed and old tools have been refined, providing an opportunity to better understand small airway inflammation and dysfunction.

Summary

Small airway inflammation is present in all stages of asthmatic disease and plays an important role in many key clinical conditions/phenotypes. In order to control the disease, we need to target small airway inflammation, which is not only difficult to reach by standard inhaled medications but also to some extent different. A better understanding of the important role small airways are playing in asthma will show that the 'silent zone' is by far not silent at all.

Keywords

asthma, imaging, optical coherence tomography, physiology, small airways, treatment

INTRODUCTION

The small airways, defined as distal airways with an internal diameter of less than 2 mm, have traditionally been referred to as the 'silent zone' [1]. Although the central airways account for more than 90% of the airway resistance, they only represent less than 10% of the total lung volume. Consequently, owing to the trumpet shape of the accumulated airway diameter (Fig. 1), small changes in airway diameter within the central airways have a great impact on flow measures, such as peak flow (PEF) and forced expiratory volume in 1 s (FEV1), as well as producing lung sounds (wheeze) audible with or without a stethoscope. During recent years, increased attention has been devoted to the important role of small airways in the pathophysiology of asthma, revealing that distal airways are 'not that silent' after all. The clinical consequence of small airway disorder is more related to functional aspects, having impact on physical function and quality of life. The involvement of small airways in asthma pathophysiology has been known for several years [2], and it is clear that inflammation is not just present in the distal

airways. The intensity of inflammation may be even higher in the peripheral compared with central airways [3]. In the present review the focus will be on the role of small airways in a number of important clinical entities such as asthma exacerbations, nocturnal asthma, and exercise-induced asthma. In addition, the importance of small airways in asthma development will be clarified.

FROM RHINITIS TO ASTHMA

Asthma and rhinitis are closely linked conditions and more than three-quarters of all patients with asthma report concomitant rhinitis [4]. It is also

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KEY POINTS

- Small airways, referred to as the silent zone, are not that silent after all.
- Small airway dysfunction increases the risk of asthma exacerbations and is a prominent feature in clinical entities such as nocturnal asthma and exercise-induced asthma.
- In order to adequately control the disease, it is also important to control the inflammation within the small airways.

known that approximately 45% of those with allergic rhinitis without being diagnosed as having asthma have bronchial hyperresponsiveness (BHR) to methacholine or histamine indicative of disorder within the lower airways, even in those not showing any clinical signs and symptoms [5]. Moreover, individuals with allergic rhinitis suffer an increased risk of developing clinical asthma over time [6]. Rhinitis patients with nonspecific BHR do not perceive induced bronchoconstriction to the same degree as those patients with rhinitis with concomitant asthma [7]. By using forced impulsocillometry (IOS) during methacholine challenge, it became clear that patients with asthma had an increased reactivity and resistance within the distal airways compared with those with rhinitis and BHR only, despite a similar decrease in FEV1 [8]. Further studies measuring fractional exhaled nitric oxide (FeNO) revealed an increased nitric oxide diffusivity and

increased alveolar nitric oxide concentration (CalvNO) in patients with asthma compared with those with rhinitis with or without BHR [9]. So far, a number of noninvasive studies have indicated that in contrast to patients with rhinitis without low airway disorder, the airways of patients with asthma are characterized by extended inflammation and pathology from central to more distal airways. These noninvasive observations were further supported by bronchoscopy studies with bronchoalveolar lavage (BAL) and bronchial and transbronchial biopsies. Although the inflammatory pattern in the central airways did not differ between patients with asthma and rhinitis, a profound difference was found within the peripheral airways, with the most prominent changes being an increase in the IgE-receptor-positive mast cells and surface-bound IgE in patients with asthma compared with rhinitis patients and healthy controls [10[¶]]. Another interesting observation in patients with asthma is the presence of features of airway remodeling, that is, fibrosis within the distal airways and collagen deposition within the alveolar septa. This was associated with an increased number of fibroblast progenitor cells, both in the biopsies and in BAL fluid [11,12]. These findings indicate that important aspects of distal airway remodeling occur early, already in very mild disease.

ASTHMA EXACERBATIONS

Asthma exacerbations affect quality of life and impose high costs on society. Moreover, patients with frequent exacerbations have an increased

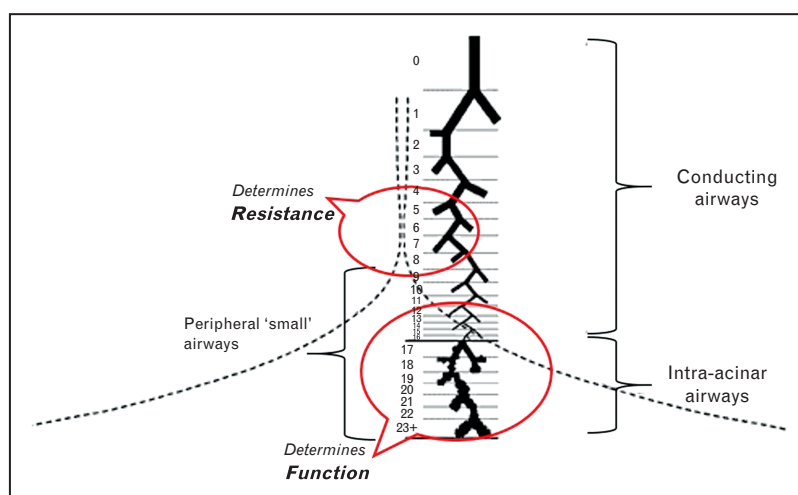


FIGURE 1. Illustration of the bronchial tree, in which the accumulated diameter of the airways increases exponentially in the peripheral small airways starting around generation 8. Although the central airways represents less than 10% of the volume, small airway caliber changes have great impact on airway resistance measured as impairment of flow (peak flow, forced expiratory volume).

annual decline in lung function, indicating a higher degree of airway remodeling [13]. However, the degree of lung function impairment is a rather poor predictor of future risk of having an asthma exacerbation, whereas the best predictor seems to be a history of a recent exacerbation during the last 6 months [14]. Thus, patients with an increased risk of getting exacerbations seem to represent a specific clinical phenotype. In the study by in't Veen *et al.* [15], patients with moderate-to-severe clinically stable asthma were compared with patients with similar degree of clinical severity, but with a history of frequent (≥ 2) exacerbations during the last 12 months. The groups did not differ with regard to lung volume measures, such as FEV1 and total forced expiratory volume, but differed with regard to small airways physiology, showing a pathological nitrogen washout curve with elevated closing volume (CV/VC) and closing capacity (CC/TLC) (Fig. 2) [15]. A similar study was conducted some years later by Bourdin *et al.* [16]. Thus, it seems that disorder within the distal airways is associated with an increased risk of exacerbations and a more progressive course of the disease. The mechanisms are not entirely clarified. From high-resolution computed tomography (HRCT) studies, patients with asthma seem to have an increased reactivity within the peripheral airways, responding with bronchoconstriction upon deep inspiration [17]. Our group has demonstrated increased small airway reactivity

by endoscopy using optical coherence tomography (OCT). With this technique, a rotating Doppler probe scans the conducting and most distal airways from patients and controls at a scanning length of 5.4 cm. A typical pattern seen in patients with asthma compared with controls was spontaneous bronchoconstriction at different levels leaving trapped gas behind (Fig. 3a and b). This phenomenon can further be illustrated by HRCT technique revealing signs of air trapping by comparing inspiratory and expiratory slides. Air trapping is seen in all stages of asthma, but most commonly in patients with more severe disease [18]. Moreover, air trapping has proven to be a major risk factor for future asthma exacerbations [19].

NOCTURNAL ASTHMA

Nocturnal awakening due to insufficiently controlled asthma is regarded as a minor exacerbation that occurs in a few hours during the night. FeNO studies have shown that patients with nocturnal asthma have distal airway inflammation identified by increased CalvNO, even when measured outside the nocturnal event [20]. It is reasonable to assume that these differences would be even more pronounced if recording was done during the night. In one study measuring prebronchodilator and post-bronchodilator FeNO, a significant increase of FeNO was seen during the night in the nocturnal

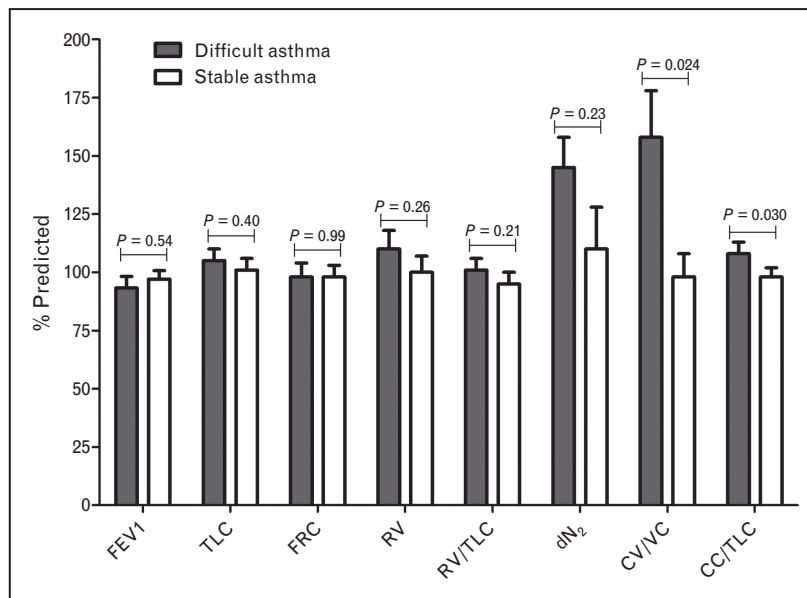


FIGURE 2. Difficult to treat asthma with 2 or more exacerbations during the last year were compared with patients with severe asthma with similar degree of treatment but no exacerbations during the last year. Those with a history of repeated exacerbations had significantly increased closing volume (CV/VC) and closing capacity (CC/TLC) as measured by single breath nitrogen washout curve. Adapted with permission [15]. This document was published in 2000. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

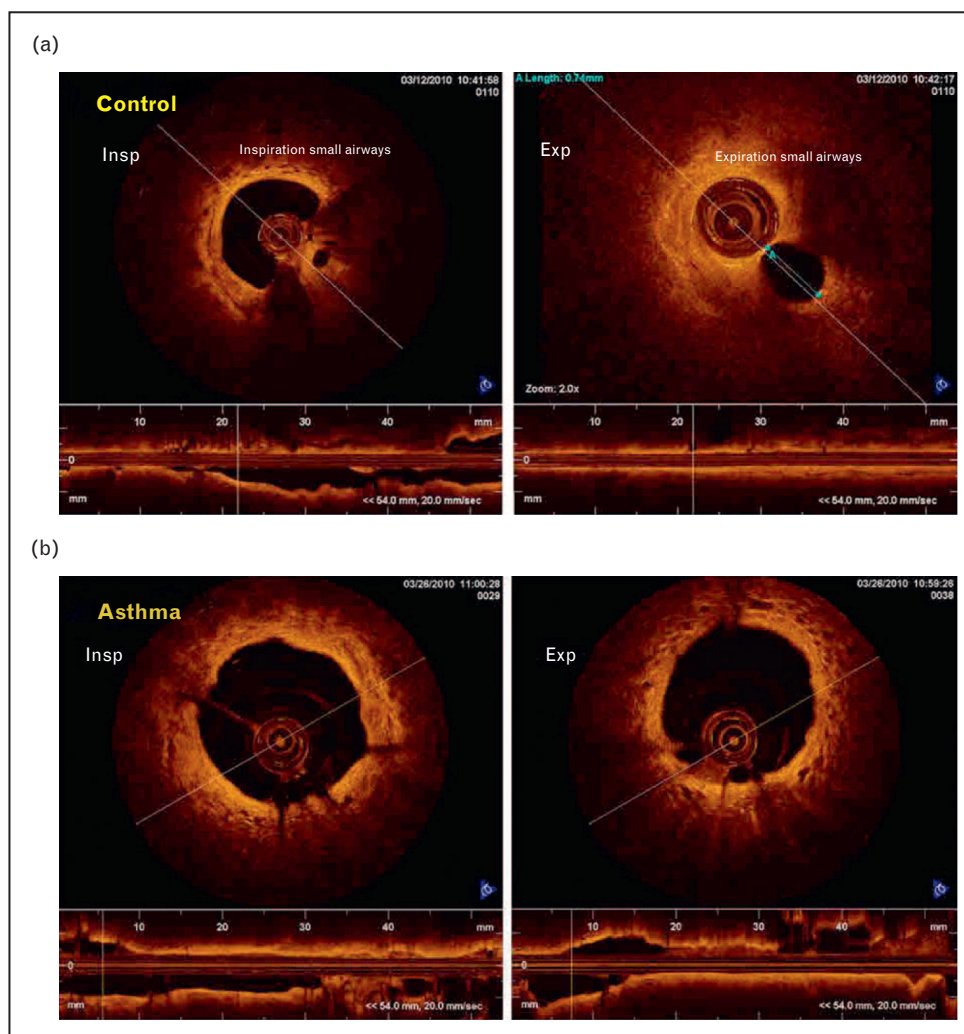


FIGURE 3. (a) Optical coherence tomography (OCT) in a healthy control. The probe is scanning an area of 5.4 cm. At expiration, all airways collapse around the catheter. (b) OCT in a patient with moderate active asthma. When the patient is asked to perform a deep exhalation, only parts of the conductive airways collapse around the catheter leaving trapped gas in the distal airways.

awakening group compared with those without nocturnal awakening [21]. Thus, nocturnal asthma seems to be characterized by a circadian inflammatory pattern, being increased during night. These changes are driven by a number of neurohormonal mechanisms making the individual more susceptible to biological stress during the night [22,23].

In the study by Kraft *et al.* [24], asthmatic patients with or without nocturnal awakening were investigated using bronchoscopy, with bronchial and transbronchial biopsies on two separate occasions, that is, at 4 p.m. and 4 a.m. Focusing on the number of eosinophils, no clear differences could be seen between the groups in the bronchial biopsies. In contrast, substantially higher eosinophil numbers were seen in both groups in the transbronchial biopsies, obtaining alveolar tissue, with considerably more in those samples from patients with

nocturnal awakening (Fig. 4) [24]. Moreover, the increased eosinophilic inflammation was associated with an increased peripheral airway resistance [25], and there was even a close relation between the degree of decrease in FEV1 and the number of infiltrating eosinophils and CD4-positive T lymphocytes in the alveolar tissue [26].

UNCONTROLLED ASTHMA

From real-life studies [27], as well as from randomized clinical trials [28], it is clear that only a limited number of patients with asthma are totally controlled and less than 50% achieve acceptable clinical control based on symptom registration and rescue medication use. A number of reasons for this lack of control can be listed as low adherence to therapy (adherence), wrong use of inhaler devices

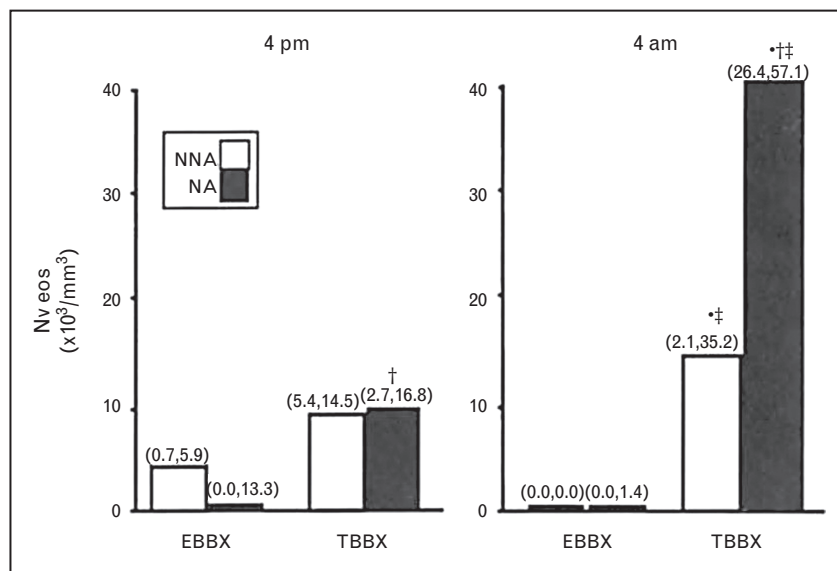


FIGURE 4. Central and peripheral (alveolar) biopsies were taken from patients with or without nocturnal asthma at daytime, in the afternoon, and in the early morning when they occasionally had a nocturnal attack with drop in lung function. EBBX, endobronchial biopsy; NA, nocturnal asthma; NNA, non-nocturnal asthma; Nv eos, number per volume of eosinophils; TBBX, transbronchial biopsy. Adapted with permission [24]. This document was published in 1996. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

(adherence), and uncontrolled comorbid conditions (comorbidity). In our own study, we compared symptomatic (uncontrolled) asthmatic patients, being treated with inhaled corticosteroids (ICS) with or without a long-acting β -2 agonist, with well controlled patients [29[¶]]. Although central bronchial biopsies did not show any evident differences in inflammatory pattern between controlled and uncontrolled patients (Asthma Control Test < 17), the inflammation differed considerably within the peripheral airways. Patients with uncontrolled asthma were characterized by a substantial increase in IgE receptor and IgE-positive mast cells [29[¶]]. Moreover, there was also an increased Th2-driven inflammatory activity within the peripheral airways, which was associated with the degree of BHR to methacholine and clinical symptoms (in preparation). These results are in line with reports by others showing that patients with uncontrolled asthma have increased CalvNO [30], unaffected by high doses of ICS but systemic administration (i.e., oral steroids) can be effective [30].

EXERCISE-INDUCED ASTHMA

Exercise-induced asthma is often referred to as exercise-induced bronchoconstriction (EIB) with a drop in FEV1 of more than 12% after a short and intensive (6–8 min) exercise challenge, ideally at more than 85% of maximum capacity [31]. However, although exercise-induced symptoms (EIS) are common in

asthma, there is a poor relation between EIS and EIB [32], indicating that other mechanisms than just a drop in FEV1 may be involved. The trigger factor in exercise-induced asthma is hyperventilation, and this may be even more extensive if the inspired air is cold and/or dry [33]. Experimental studies on animal have shown that distal airways are vulnerable to dry-air hyperventilation (animal dry-air ventilation) and peripheral airway resistance increases considerably in patients with asthma after the same stimuli [34,35]. Clara Cell protein 16 (CC16) is produced by epithelial cells in the bronchiole and may as such act as a biomarker for disturbances within the peripheral airways. Indeed, we have found that hyperventilation, in contrast to other stimuli such as mannitol challenge, induce increased levels of CC16 in urine [36]. Disturbances within the peripheral airways, associated with some degree of air trapping, may lead to delayed emptying of the peripheral airways followed by dynamic hyperinflation during exercise [37] (Fig. 5).

THERAPEUTIC IMPLICATIONS

Considering that small airways dysfunction is present in the majority of the clinical asthma phenotypes, it is of utmost importance to treat and control small airway inflammation to achieve optimal disease control. There is also a scientific rationale to the belief that controlling small airway inflammation could have an impact on the course of

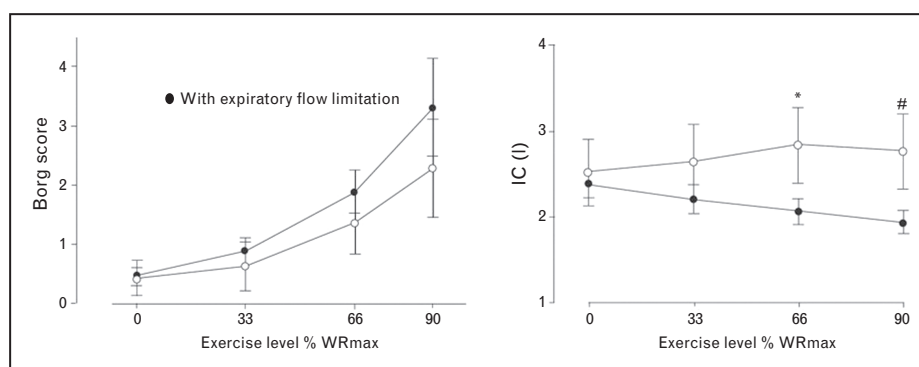


FIGURE 5. Dynamic hyperinflation in patients with exercise-induced symptoms compared with asthmatic controls. The increasing symptoms on a certain work load were associated with decreased inspiratory capacity (IC). Adapted with permission [37].

the disease, because clinical studies performed with standard inhaled medication do not prevent accelerated decline of lung function [38], or have an obvious impact on the natural course of the disease [39]. In a recent study analyzing the effect of ICS treatment on FeNO in patients with uncontrolled, steroid-naïve asthma, only those with normalization including the CalvNO achieved adequate clinical control [40]. These findings, in parallel to the aforementioned study by Berry *et al.* [30], indicate the presence of small airway inflammation which is responsive to steroids; however, it is difficult to reach by the inhaled route.

One strategy to overcome this obstacle is to use ultrafine ICS formulations, achieving a much better deposition within the peripheral airways [41[¶]]. Currently, there are three small particle ICS formulations available: hydrofluoroalkane (HFA)-beclomethasone dipropionate, HFA-flunisolide, and HFA-ciclesonide. All these compounds have been shown to improve small airway function, either by reducing air trapping or by improving small airway physiological and inflammatory parameters, compared with standard inhaled strategies, mostly chlorofluorocarbon (CFC)-driven metered dose inhalers [41[¶]]. Clearly, small particle size ICS represent a new treatment option for small airway disease in both asthma and chronic obstructive pulmonary disease. Unfortunately, there is still lack of large studies including long-term outcome parameters to provide evidence that small particle ICS treatment, rather than standard ICS treatment, is disease-modifying, that is, can change the natural course of the disease.

Another reason for poor small airway control could be that some inflammatory mechanisms in the peripheral airways are more or less steroid-resistant. In our study, uncontrolled asthma appeared related to an increased number of IgE-positive mast cells within the peripheral airways [29[¶]]. This is in

line with other observations [42] and calls upon strategies to control mast cell-induced or mast cell-associated inflammation. This is of special interest, as mast cells seem to have a crucial role also in the process of airway remodeling [43[¶]]. The majority of mast cells express leukotriene C4-synthase, a key enzyme in leukotriene synthesis [44], while the affinity and the number of cysteinyl leukotriene receptors are actually higher within peripheral than in central airways [45]. In addition, leukotriene modifiers have been shown to improve distal airway function as measured by IOS in children [46] or as reflected by decreased air trapping on HRCT [47]. Therefore, future developments should identify novel therapeutic targets, including effective anti-mast cell drugs.

CONCLUSION

Small airway involvement is thus a prerequisite for asthma development, while the degree of inflammation is related to the severity of the disease. Small airway dysfunction increases the risk of uncontrolled disease and predicts increased risk of asthma exacerbations, and is associated with important clinical entities such as nocturnal asthma and asthma related to exercise-induced signs and symptoms. **In order to adequately control asthma and possibly to be able to interfere with the long-term course of the disease, it is important to have a strategy including treatment of small airway inflammation/remodeling.** This includes both targeting the small airways by the inhaled route using ultrafine particles, but also finding new strategies to treat steroid-resistant mechanisms that may have a central role in (small) airway remodeling, predicting the course of asthma.

For the future I believe it is of utmost importance that small airways come more into play. This will require a different thinking, away from the

traditional outcome parameters mainly being related to central airway function. We already at present have good physiological tools to measure small airway function, and, hopefully, we will have even better instruments in the near future that will help us to improve disease management. We will also need larger long-term studies to see whether a better control of small airway inflammation can prevent some degree of airway remodeling and thus have a positive impact on the natural course of the disease.

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Conflicts of interest

The author has delivered lectures for the following companies during the past 5 years: Almirall, AstraZeneca, Airsonette, Andre Pharma-Chiesi, Boehringer, Glaxo-SmithKline, Meda, Merck, Mundipharma, Niigard Pharma, Novartis, Pfizer, Takeda/Nycomed, Teva, and UCB. He also participated on the Advisory Board, nationally or internationally, arranged by the following companies: Almirall, AstraZeneca, Airsonette, Boehringer, Genentech, GlaxoSmithKline, Merck, Mundipharma, Niigard Pharma, Novartis, and Takeda/Nycomed.

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. Bjerner L. History and future perspectives of treating asthma as a systemic and small airways disease. *Respir Med* 2001; 95:703–719.
 2. Hamid Q, Song Y, Kotsimbos TC, *et al.* Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997; 100:44–51.
 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. Leynaert B, Neukirch C, Kony S, *et al.* Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004; 113:86–93.
 5. Alvarez MJ, Olagübel JM, Garcia BE, *et al.* Airway inflammation in asthma and perennial allergic rhinitis. Relationship with nonspecific bronchial responsiveness and maximal airway narrowing. *Allergy* 2000; 55:355–362.
 6. Settipane GA, Greisner WA 3rd, Settipane RJ. Natural history of asthma: a 23-year followup of college students. *Ann Allergy Asthma Immunol* 2000; 84:499–503.
 7. Aronsson D, Tufvesson E, Bjerner L. Allergic rhinitis with or without concomitant asthma: difference in perception of dyspnoea and levels of fractional exhaled nitric oxide. *Clin Exp Allergy* 2005; 35:1457–1461.
 8. Aronsson D, Tufvesson E, Ankerst J, Bjerner L. Allergic rhinitis with hyper-responsiveness differs from asthma in degree of peripheral obstruction during metacholine challenge test. *Clin Physiol Funct Imaging* 2008; 28:81–85.
 9. Tufvesson E, Aronsson D, Ankerst J, *et al.* Peripheral nitric oxide is increased in rhinitic patients with asthma compared to bronchial hyperresponsiveness. *Respir Med* 2007; 101:2321–2326.
 10. Andersson CK, Tufvesson E, Aronsson D, *et al.* Alveolar mast cells shift to an ■ FcεpsilonRI-expressing phenotype in mild atopic asthma: a novel feature in allergic asthma pathology. *Allergy* 2011; 66:1590–1597.
- The article clearly shows the difference between patients with rhinitis and bronchial hyperresponsiveness versus those with symptomatic asthma. The latter have on average a six-fold increase of IgE-receptor-positive mast cells in the peripheral alveolar tissue.
11. 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.
 12. Nihlberg K, Larsen K, Hultgardh-Nilsson A, *et al.* Tissue fibrocytes in patients with mild asthma: a possible link to thickness of reticular basement membrane? *Respir Res* 2006; 7:50.
 13. Bai TR, Vonk JM, Postma DS, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J* 2007; 30:452–456.
 14. Miller MK, Lee JH, Miller DP, *et al.* Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007; 101:481–489.
 15. 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.
 16. Bourdin A, Paquin F, Prefaut C, *et al.* Nitrogen washout slope in poorly controlled asthma. *Allergy* 2006; 61:85–89.
 17. Brown RH, Scichilone N, Mudge B, *et al.* High-resolution computed tomographic evaluation of airway distensibility and the effects of lung inflation on airway caliber in healthy subjects and individuals with asthma. *Am J Respir Crit Care Med* 2001; 163:994–1001.
 18. Lee YM, Park JS, Hwang JH, *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.
 19. Frey U, Suki B. Complexity of chronic asthma and chronic obstructive pulmonary disease: implications for risk assessment, disease progression and control. *Lancet* 2008; 372:1088–1099.
 20. Lehtimäki L, Kankaanranta H, Saarelainen S, *et al.* Increased alveolar nitric oxide concentration in asthmatic patients with nocturnal symptoms. *Eur Respir J* 2002; 20:841–845.
 21. Georges G, Bartelson BB, Martin RJ, Silkoff PE. Circadian variation in exhaled nitric oxide in nocturnal asthma. *J Asthma* 1999; 36:467–473.
 22. Durrington HJ, Farrow SN, Loudon AS, Ray DW. The circadian clock and asthma. *Thorax* 2013. [Epub ahead of print]
 23. Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol* 2005; 116:1179–1186.
 24. Kraft M, Djukanovic R, Wilson S, *et al.* Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996; 154:1505–1510.
 25. Kraft M, Pak J, Martin RJ, *et al.* Distal lung dysfunction at night in nocturnal asthma. *Am J Respir Crit Care Med* 2001; 163:1551–1556.
 26. Kraft M, Djukanovic R, Torvik J, *et al.* Evaluation of airway inflammation by endobronchial and transbronchial biopsy in nocturnal and nonnocturnal asthma. *Chest* 1995; 107 (3 Suppl):162S.
 27. Olagübel JM, Quirce S, Julia B, *et al.* Measurement of asthma control according to Global Initiative for Asthma guidelines: a comparison with the Asthma Control Questionnaire. *Respir Res* 2012; 13:50.
 28. Bateman ED, Jacques L, Goldfrad C, *et al.* Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol* 2006; 117:563–570.
 29. Andersson CK, Berqqvist A, Mori M, *et al.* Mast cell-associated alveolar ■ inflammation in patients with atopic uncontrolled asthma. *J Allergy Clin Immunol* 2011; 127:905–912.
- In contrast to bronchial biopsy findings in the central airways, patients with uncontrolled asthma show a profound increase of IgE-receptor-positive mast cells in the alveolar tissue.
30. Berry M, Harqadon 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.
 31. Carlsen KH, Anderson SD, Bjerner L, *et al.* Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008; 63:387–403.
 32. Parsons JP, Kaeding C, Phillips G, *et al.* Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. *Med Sci Sports Exerc* 2007; 39:1487–1492.
 33. Sue-Chu M, Larsson L, Bjerner L. Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden. *Respir Med* 1996; 90:99–105.
 34. Chimenti L, Morici G, Paterno A, *et al.* Endurance training damages small airway epithelium in mice. *Am J Respir Crit Care Med* 2007; 175:442–449.
 35. Davis MS, Freed AN. Repetitive hyperpnoea causes peripheral airway obstruction and eosinophilia. *Eur Respir J* 1999; 14:57–62.
 36. Romberg K, Bjerner L, Tufvesson E. Exercise but not mannitol provocation increases urinary Clara cell protein (CC16) in elite swimmers. *Respir Med* 2011; 105:31–36.
 37. Kosmas EN, Milic-Emili J, Polychronaki A, *et al.* Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. *Eur Respir J* 2004; 24:378–384.
 38. Strunk RC, Sternberg AL, Szeffer SJ, *et al.* Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr* 2009; 154:682–687.
 39. Guilbert TW, Morgan WJ, Zeiger RS, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985–1997.

40. Van Muylem A, Kerckx Y, Michils A. Acinar effect of inhaled steroids evidenced by exhaled nitric oxide. *J Allergy Clin Immunol* 2010; 126:730–735.
41. van den Berge M, ten Hacken NH, Cohen J, *et al.* Small airway disease in ■ asthma and COPD: clinical implications. *Chest* 2011; 139:412–423. Updated review on the importance of small airways in both asthma and chronic obstructive pulmonary disease.
42. Balzar S, Chu HW, Strand M, Wenzel S. Relationship of small airway chymase-positive mast cells and lung function in severe asthma. *Am J Respir Crit Care Med* 2005; 171:431–439.
43. Alkhouri H, Holins F, Moir LM, *et al.* Human lung mast cells modulate the functions of airway smooth muscle cells in asthma. *Allergy* 2011; 66:1231–1241. ■ The article highlights the important role by mast cells in lower airway inflammation and remodeling.
44. Cai Y, Bjermer L, Halstensen TS. Bronchial mast cells are the dominating LTC4S-expressing cells in aspirin-tolerant asthma. *Am J Respir Cell Mol Biol* 2003; 29:683–693.
45. Mechiche H, Candenas L, Pinto FM, *et al.* Characterization of cysteinyl leukotriene receptors on human saphenous veins: antagonist activity of montelukast and its metabolites. *J Cardiovasc Pharmacol* 2004; 43:113–120.
46. Nieto A, Pamier R, Oliver F, *et al.* Montelukast improves pulmonary function measured by impulse oscillometry in children with asthma (Mio study). *Respir Med* 2006; 100:1180–1185.
47. Zeidler MR, Kleerup EC, Goldin JG, *et al.* Montelukast improves regional air-trapping due to small airways obstruction in asthma. *Eur Respir J* 2006; 27:307–315.