The great expectations of small airways

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Editorial Board PNEUMON

"Take nothing on its looks; take everything on evidence. There's no better rule."
Charles Dickens, Great Expectations

INTRODUCTION

The pathophysiology of asthma has traditionally been attributed to an inflammatory process occurring predominantly in the large airways.[1] Studies have clearly shown that asthma involves structural changes in the airways, including hypertrophy and hyperplasia of the smooth muscle, thickening of the basement membrane, mucus hypersecretion and oedema in the airway wall.[1] Autopsy studies and, to a greater extent, fiberoptic bronchoscopy have enabled scientists to identify the involvement of the large airways in the pathogenesis of asthma.[2,3] The possible involvement of small airways inflammation and/or remodelling in the pathophysiology and clinical manifestations of asthma has recently been re-emphasized.[4-6] Small airways disease has not been thoroughly investigated in asthma due to the difficulties of *in vivo* sampling and the lack of specificity of the physiological measurements for this site.

It was not until the 1960s that the issue of airways resistance was highlighted and the distinction was drawn between the large and small airways.[7] Small airways are defined as airways of less than 2 mm internal diameter, without cartilage, that correspond to generations 12-23 in Weibel's model of lung architecture.[8,9] Due to the extensive branching pattern of the tracheobronchial tree, the total volume and the surface area of the small airways are much greater than those of the large airways.[8] The small airways are considered traditionally to be pathways of little resistance, contributing less than 10% of the total airflow resistance in the lung.[10-12] Accordingly, extensive damage of small airways may occur before the appearance of any symptoms or the results of any of the conventional lung function tests become abnormal. For that reason, in the 1970s the small airways were described as the "quiet zone" of the lung.[10] More recently, it has been shown that in mild asthma with normal spirometric values, peripheral airway resistance may be increased up to 7-fold compared to that in control subjects, and these measurements are correlated with responsiveness to methacholine.[13]

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PATHOLOGICAL EVIDENCE

The main questions regarding the small airways in asthma are: 1) whether the inflammation that is characteristically present in the large airways is also present in the small airways; 2) what is the extent of this inflammation; and 3) whether this inflammation induces structural changes.

Studies on surgically resected lung tissue, autopsy lung specimens and transbronchial biopsies (TBB) have indicated that inflammatory and structural changes do occur in the small airways and lung parenchyma of patients with asthma.[4,14-20] Histological examination of autopsy lung material from cases of asthma often demonstrates luminal changes of mucus plugging in small airways which are devoid of mucus-secreting glands,[21] and epithelial damage is also seen in these airways.[22] Autopsy studies have demonstrated increased numbers of lymphocytes and eosinophils uniformly distributed throughout the large and small airways in lung tissue from both fatal cases of asthma and subjects with mild and severe asthma who died of other causes, compared to control subjects with no history of asthma.[4,15] In addition, increases in T cells ($CD3^+$), total eosinophils, major basic protein (MBP^+) and activated eosinophils ($EG2^+$) were found in both small and large airways of resected lung specimens from patients with asthma who underwent thoracic surgery compared with specimens from asthma-free patients.[4] Greater numbers of activated eosinophils were seen in small than in large airways, indicating a more severe inflammatory process in the peripheral airways.[23] Increased numbers of interleukin-4 (IL-4) and IL-5 mRNA-positive cells were found in the small airways of patients with mild-to-moderate asthma compared with control subjects, and the expression of IL-5 mRNA was higher in the small than in the large airways.[19]

Haley and co-workers demonstrated that the density of the inflammatory cells was different in the inner and outer walls of conducting airways[24]; specifically, in asthma the majority of inflammatory cells, such as eosinophils and $CD45^+$ leukocytes, in the small airways were located in the "outer" airway wall region (i.e., between the smooth muscle and the alveolar attachments)[24]; while most of the eosinophils in the large airways were found in the "inner" airway wall region (i.e., between the basement membrane and the smooth muscle).[24] The authors were able to show that these differences in the distribution of cells between the large and small airways are disease-specific, as they were not observed in cystic fibrosis (CF).[24]

In patients with nocturnal asthma, Kraft and co-workers showed significant alveolar inflammation, which they suggested may also be important in the pathogenesis of asthma.[17] They evaluated proximal endobronchial biopsies and TBB in patients with asthma, at 4:00 a.m. and at 4:00 p.m. Patients with nocturnal asthma had increased numbers of eosinophils in the lung parenchyma at 4:00 a.m. compared with those without nocturnal asthma[17], and a greater number of eosinophils and macrophages in alveolar tissue at 4:00 a.m. than at 4:00 p.m.[17]

Bronchoalveolar lavage (BAL) can help in the characterization of inflammatory events occurring in the peripheral airways, but BAL findings may be different from the changes in the airway wall, and BAL does not provide information on changes in airway structure. Endobronchial biopsies obtained from lobar, segmental and subsegmental bronchi have been used to elucidate the pathophysiology of asthma, but the most appropriate means of retrieving information about the structure of the peripheral airways and lung parenchyma is by TBB.[17,18,25] Balzar and co-workers sampled small airways by TBB and found a greater density of inflammatory cells in the small than in the medium or large airways.[25] Only a limited number of small airways can be obtained by TBB, however,[25] and the possible significant complications, including pneumothorax or significant bleeding, should always be considered.[26,27]

Bronchial myofibroblasts are observed in the large airways and are thought to be responsible for the fibrotic process and the subepithelial collagen deposition. It appears that there is a continuous population of such cells throughout the airways, but their contribution to the formation and remodelling of the small conducting airways is not known.[22] Changes in the extracellular matrix, such as decreased decorin expression in the airway wall, have been described in the small airways of patients with fatal asthma, possibly contributing to fibrosis via TGF-β regulation.[28] Surfactant may also play a role in fatal asthma, because its loss may enhance small airways closure.

In conclusion, the majority of histological studies have shown that the distribution of inflammatory cells between large and small airways differs for lymphocytes, macrophages, eosinophils and mast cells. However, certain limitations should always be considered; important factors for the accurate determination of the true number of cells within a volume of tissue include the size of cells relative to section thickness, the orientation of sections, the randomness of the tissue sample and the orientation of cells within the section. The relative amounts of connec-

tive tissue, blood vessel and smooth muscle in the airway wall are very different in membranous and cartilaginous airways, and this should be considered when comparing findings from samples of small and large airways. In addition, the relative contribution of the bronchial and pulmonary circulations to airway wall perfusion are different in the large and small airways, which may affect the traffic of inflammatory cells in the two sites. Finally it should be pointed out that autopsy findings in patients with fatal asthma, which probably represents an acute exacerbation of the disease, cannot necessarily be extrapolated to patients with chronic severe asthma.

PHYSIOLOGICAL EVIDENCE

Assessment of the small airways continues to be complex, and includes a variety of techniques, such as gas washout tests, frequency dependence of compliance, forced oscillation technique (FOT) and, more recently, novel imaging techniques.[29-34]

The physiological tests of the small airways are based on non-uniformity of ventilation and airway closure.[11] The best known physiological measurement of the small airways is flow rate at low lung volumes ($MEF_{25\%}$), a test which is technically difficult to perform and which exhibits marked variability and may be affected by changes in the large airways and lung volumes.[35-37] Low flow rates during the last part of the volume may be considered to express the small airways only if the elastic recoil of the lung is normal, there is no narrowing of the large airways and there is no difference between breaths of maximal and submaximal expiratory effort. Data originating from the database of the Severe Asthma Research Program of the US National Heart Lung and Blood Institute showed that $FEF_{25-75\%}$ presented poor correlation with other markers of air trapping, such as RV/TLC and FVC, thus questioning the ability of this technique to detect small airways obstruction.[38] The RV/TLC ratio may represent the most interesting marker of small airways closure for use in clinical practice and large multicentre trials, because it is widely available and more reproducible than the MEF25%.[39]

The measurement of closing volume (CV) offers more sensitive assessment and probably earlier identification of small airways dysfunction, but it is more complex and available only in research centres.[40,41] When the slope of phase III or the CV in the single breath nitrogen washout test is increased, the small airways are likely to be involved.[42] The CV correlates well with RV/TLC,[43] but its clinical application is limited due to its wide within-subject and inter-reader variability.[44]

Multiple-breath nitrogen washout is based on ventilation heterogeneity in the intra-acinar airway zone and the peripheral conducting zone,[31] while FOT measures the distensibility of the airways.[45] Both techniques have been used in the evaluation of small airways function, but their use is currently limited to research purposes.

The exhaled nitric oxide (NO) concentration may discriminate between the bronchial and the alveolar contribution, using a mathematical model,[46] and this method has shown good reproducibility.[47] Van Veen and co-workers have shown that alveolar NO is associated with air trapping, as measured by the RV/TLC ratio, which is a marker of premature airway closure.[48]

As far as imaging techniques are concerned, currently available high resolution computed tomography (HRCT) scanning does not permit visualization of airways <2-2.5 mm in diameter. The HRCT appearance of small airways disease consists of patchy areas of high and low attenuation of the lung parenchyma – called mosaic perfusion – which is thought to be the consequence of reflex vasoconstriction in under-ventilated areas of the lung. This is accentuated in scans obtained at the end of expiration, consistent with air trapping, and may distinguish the heterogeneity seen on inspiratory CT scans from those mosaic patterns seen occasionally in thromboembolic or other vascular disease.[49] In a study of patients with asthma, HRCT scans were acquired before and after methacholine challenge testing, then repeated after a 4-week course of treatment with either montelukast or placebo, revealing a beneficial effect of montelukast on small airways patency.[33] This study raised the concept that oral anti-inflammatory medication might improve small airway function, but the reduction in gas trapping was not correlated with airway hyperresponsiveness (AHR) or CV measured by single-breath nitrogen washout. None of the physiological measures of small airways disease (FEF25-75, RV, RV/TLC, FRC, or CV/VC) showed significant changes from baseline after montelukast treatment.[33]

A major problem in the wider application of HRCT is radiation exposure. Unless resolution can be greatly increased without concomitant increase in radiation exposure, direct visualization of the small airways with HRCT will remain limited. Micro-CT is similar in principle to CT but uses a micro-focused X-ray source and achieves a better resolution of bronchiolar and alveolar structures.[50,51]

Despite continuing progress in imaging and functional assessment of the respiratory system, no single test is currently available for the diagnosis and monitoring of small

airway disease in clinical practice. The future in assessment of the small airways is probably the evaluation of large numbers of patients with well-characterized asthma by the use of a combination of multiple techniques.

TREATMENT TARGETING THE SMALL AIRWAYS IN ASTHMA

The main questions are whether the currently available anti-inflammatory asthma therapies target the small airways, and whether such targeting is important for the optimal clinical response. One of the most important current therapeutic challenges is to develop better inhalation technologies in order to improve the delivery of anti-inflammatory agents to the distal airways and lung parenchyma. The aim of treatment is to reverse the damage or to prevent its progression to a stage when it becomes irreversible.

A few studies on bronchodilators have attempted to address these issues; for these drugs, lung function testing provides a rapid measure of response, but data on inhaled anti-inflammatory therapy are not widely available, mainly due to difficulties in determining the optimal measure of response.[52-54] Studies assessing the optimal particle size have provided conflicting results. In one study of patients with chronic stable severe asthma, technetium-labelled salbutamol produced a similar deposition pattern and similar bronchodilator effect for both 1.4 μm and 5.5μm particles.[52] In a study using nebulized terbutaline, the effect of a particle size of 1.8μm was superior to both 4.6 μm and 10.3μm.[55] Aerosol characteristics that may influence the effectiveness of airway deposition include the size (diameter), shape, electric charge, hygroscopic characteristics, density and mass of the particles being generated.[56-58] The use of appropriate oral agents may benefit patients with predominantly small airways disease, as the systemic route is more likely to reach the area of the small airways.[59]

To overcome the limited drug delivery to the airways, the mean particle size of the inhaled drug should be in the range of 1.5-3 μm, in order to reach peripheral airways. Small-particle aerosols, such as hydrofluoroalkane-134a (HFA) beclomethasone and ciclesonide, with particle sizes around 1μm, have recently become available, and such formulations have been shown to achieve greater deposition in lung periphery.[60] Treatment with inhaled ciclesonide for 5 weeks improved alveolar exhaled NO, AHR and spirometry results, but not CV.[29] The use of a small-particle beclomethasone formulation resulted in similar improvements in symptoms and lung function at half the delivered dose of standard formulations.[61] HFA-beclomethasone produced results superior to fluticasone in improvement in airway closure, measured by single-breath nitrogen washout.[62] Improvement in ventilation inhomogeneity was demonstrated in 30 patients with asthma after treatment with inhaled HFA-beclomethasone, compared to the same dose of budesonide.[47] In a recent 12-week study, inhaled treatment with HFA-beclomethasone/formoterol extra-fine combination resulted in a trend towards improvement of single breath nitrogen washout closing capacity, providing evidence for efficacy of small particle combinations in both the large and small airways.[63] Finally, in a recent real-life study, patients who received step-up inhalation therapy with small-particle HFA-beclomethasone were more likely to achieve asthma control than those treated with CFC-beclomethasone.[64]

Comparison between fine-particle HFA-beclomethasone and larger particle aerosol treatment demonstrated less regional gas trapping on HRCT with the fine-particle aerosol.[65] In another study, however, no difference was found on HRCT between patients treated with either HFA-beclomethasone or a dry-powder inhaled steroid.[66] Despite the discordant findings reported by different groups using various techniques, it is possible that patients with specific asthma phenotypes, especially those with evident small airways disease, may benefit more from treatment with extra-fine particle aerosols.

CONCLUSIONS

Review of the current literature confirms that our knowledge on the role of the small airways in asthma is still limited. Many of the studies described here have come under criticism regarding both the selection of patients and the sampling techniques, and there are certain limitations to the ways in which pathologists, physiologists, radiologists and molecular biologists approach study of the small airways. In the future, integrated approaches, including local cellular phenotyping at the RNA level, proteomic or metabolomic approaches in the study of exhaled air, sophisticated imaging modalities, or even modified pulmonary function techniques, may provide better evidence in the evaluation of the role of small airways in asthma.

On the other hand, there is already a considerable amount of documentation to show that small airway inflammation contributes to the clinical expression of asthma, especially difficult to treat and nocturnal asthma,

and also that small-particle aerosols may improve small airway function and inflammation. It is still not known whether all subjects with asthma have small airways involvement or if a "small airways phenotype" exists. Whatever the case, the small airways currently represent the area of the lungs which gives rise to great expectations for future improvements. Ongoing research can be expected to provide the answers.

REFERENCES

1. Curschmann H. Exudative bronchiolitis and its relationship with asthma nervosa [in German]. Dtsch Arch Klin Med 1882:1-34.
2. Bentley AM, Meng Q, Robinson DS, Hamid Q, Kay AB, Durham SR. Increases in activated T lymphocytes, eosinophils, and cytokine mRNA expression for interleukin-5 and granulocyte/macrophage colony-stimulating factor in bronchial biopsies after allergen inhalation challenge in atopic asthmatics. Am J Respir Cell Mol Biol 1993;8:35-42.
3. Djukanovic R, Wilson JW, Lai CK, Holgate ST, Howarth PH. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. Am Rev Respir Dis 1991;143:772-7.
4. Hamid Q, Song Y, Kotsimbos TC, et al. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997;100:44-51.
5. Martin RJ. Therapeutic significance of distal airway inflammation in asthma. J Allergy Clin Immunol 2002;109:S447-60.
6. Shaw RJ, Djukanovic R, Tashkin DP, Millar AB, du Bois RM, Orr PA. The role of small airways in lung disease. Respir Med 2002;96:67-80.
7. Evans DJ, Green M. Small airways: a time to revisit? Thorax 1998;53:629-30.
8. Weibel ER. Principles and methods for the morphometric study of the lung and other organs. Lab Invest 1963;12:131-55.
9. Ranga V, Kleinerman J. Structure and function of small airways in health and disease. Arch Pathol Lab Med 1978;102:609-17.
10. Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. J Appl Physiol 1967;22:395-401.
11. Brown R, Woolcock AJ, Vincent NJ, Macklem PT. Physiological effects of experimental airway obstruction with beads. J Appl Physiol 1969;27:328-35.
12. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278:1355-60.
13. Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. Am Rev Respir Dis 1990;141:584-8.
14. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. Eur Respir J 1996;9:709-15.
15. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. Eur Respir J 1997;10:292-300.
16. Christodoulopoulos P, Leung DY, Elliott MW, et al. Increased number of glucocorticoid receptor-beta-expressing cells in the airways in fatal asthma. J Allergy Clin Immunol 2000;106:479-84.
17. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996;154:1505-10.
18. Kraft M, Martin RJ, Wilson S, Djukanovic R, Holgate ST. Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. Am J Respir Crit Care Med 1999;159:228-34.
19. Minshall EM, Hogg JC, Hamid QA. Cytokine mRNA expression in asthma is not restricted to the large airways. J Allergy Clin Immunol 1998;101:386-90.
20. Rovina N, Baraldo S, Saetta M. Severe asthma: inflammation. Pneumon 2011; 24: 306-313
21. Saetta M, Di Stefano A, Rosina C, Thiene G, Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. Am Rev Respir Dis 1991;143:138-43.
22. Roche WR. Inflammatory and structural changes in the small airways in bronchial asthma. Am J Respir Crit Care Med 1998;157:S191-4.
23. Hamid QA. Peripheral inflammation is more important than central inflammation. Respir Med 1997;91 Suppl A:11-2.
24. Haley KJ, Sunday ME, Wiggs BR, et al. Inflammatory cell distribution within and along asthmatic airways. Am J Respir Crit Care Med 1998;158:565-72.
25. Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. Eur Respir J 2002;20:254-9.
26. Bolliger CT, Mathur PN, Beamis JF, et al. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J 2002;19:356-73.
27. Hernandez Blasco L, Sanchez Hernandez IM, Villena Garrido V, de Miguel Poch E, Nunez Delgado M, Alfaro Abreu J. Safety of the transbronchial biopsy in outpatients. Chest 1991;99:562-5.
28. de Medeiros Matsushita M, da Silva LF, dos Santos MA, et al. Airway proteoglycans are differentially altered in fatal asthma. J Pathol 2005;207:102-10.
29. 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;31:1213-20.
30. 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;161:1902-6.
31. Downie SR, Salome CM, Verbanck S, Thompson B, Berend N, King GG. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. Thorax 2007;62:684-9.
32. Tgavalekos NT, Musch G, Harris RS, et al. Relationship between airway narrowing, patchy ventilation and lung mechanics in asthmatics. Eur Respir J 2007;29:1174-81.
33. Zeidler MR, Kleerup EC, Goldin JG, et al. Montelukast improves regional air-trapping due to small airways obstruction in asthma. Eur Respir J 2006;27:307-15.
34. Kaminsky DA, Irvin CG, Lundblad LK, et al. Heterogeneity of

bronchoconstriction does not distinguish mild asthmatic subjects from healthy controls when supine. J Appl Physiol 2008;104:10-9.
35. Sherter CB, Connolly JJ, Schilder DP. The significance of volume-adjusting the maximal midexpiratory flow in assessing the response to a bronchodilator drug. Chest 1978;73:568-71.
36. Macklem PT. Obstruction in small airways--a challenge to medicine. Am J Med 1972;52:721-4.
37. Solomon DA. Are small airways tests helpful in the detection of early airflow obstruction? Chest 1978;74:567-9.
38. 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.
39. Burgel PR. The role of small airways in obstructive airway diseases. Eur Respir Rev 2011;20:23-33.
40. Gelb AF, Zamel N. Simplified diagnosis of small-airway obstruction. N Engl J Med 1973;288:395-8.
41. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. J Clin Invest 1969;48:1097-106.
42. Stanescu D, Teculescu D, Pacuraru R. Reproducibility and normal values of the single breath nitrogen test. Scand J Respir Dis 1968;49:322-30.
43. McFadden ER, Jr., Kiker R, Holmes B, DeGroot WJ. Small airway disease. An assessment of the tests of peripheral airway function. Am J Med 1974;57:171-82.
44. McFadden ER, Jr., holmes B, Kiker R. Variability of closing volume measurements in normal man. Am Rev Respir Dis 1975;111:135-40.
45. Brown NJ, Salome CM, Berend N, Thorpe CW, King GG. Airway distensibility in adults with asthma and healthy adults, measured by forced oscillation technique. Am J Respir Crit Care Med 2007;176:129-37.
46. Tsoukias NM, George SC. A two-compartment model of pulmonary nitric oxide exchange dynamics. J Appl Physiol 1998;85:653-66.
47. Verbanck S, Schuermans D, Paiva M, Vincken W. The functional benefit of anti-inflammatory aerosols in the lung periphery. J Allergy Clin Immunol 2006;118:340-6.
48. 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;27:951-6.
49. Desai SR, Hansell DM. Small airways disease: expiratory computed tomography comes of age. Clin Radiol 1997;52:332-7.
50. Watz H, Breithecker A, Rau WS, Kriete A. Micro-CT of the human lung: imaging of alveoli and virtual endoscopy of an alveolar duct in a normal lung and in a lung with centrilobular emphysema--initial observations. Radiology 2005;236:1053-8.
51. Donough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine 2011;365:1567-75.
52. Mitchell DM, Solomon MA, Tolfree SE, Short M, Spiro SG. Effect of particle size of bronchodilator aerosols on lung distribution and pulmonary function in patients with chronic asthma. Thorax 1987;42:457-61.
53. Zainudin BM, Biddiscombe M, Tolfree SE, Short M, Spiro SG. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution. Thorax 1990;45:469-73.
54. Zainudin BM, Tolfree SE, Short M, Spiro SG. Influence of breathing pattern on lung deposition and bronchodilator response to nebulised salbutamol in patients with stable asthma. Thorax 1988;43:987-91.
55. Clay MM, Pavia D, Clarke SW. Effect of aerosol particle size on bronchodilatation with nebulised terbutaline in asthmatic subjects. Thorax 1986;41:364-8.
56. Ariyananda PL, Agnew JE, Clarke SW. Aerosol delivery systems for bronchial asthma. Postgrad Med J 1996;72:151-6.
57. Ferron GA. Aerosol properties and lung deposition. Eur Respir J 1994;7:1392-4.
58. Vincent JH, Johnston AM, Jones AD, Bolton RE, Addison J. Kinetics of deposition and clearance of inhaled mineral dusts during chronic exposure. Br J Ind Med 1985;42:707-15.
59. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med 1997;337:1412-8.
60. Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. Respir Med 2006;100:375-84.
61. Vanden Burgt JA, Busse WW, Martin RJ, Szefler 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;106:1209-26.
62. 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;42:257-63.
63. Scichilone N, Battaglia S, Sorino C, et al. Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma. Allergy 2010;65:897-902.
64. Barnes N, Price D, Colice G, et al. Asthma control with extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle chlorofluorocarbon-beclometasone: a real-world observational study. Clin Exp Allergy 2011.
65. Goldin JG, Tashkin DP, Kleerup EC, et al. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography. J Allergy Clin Immunol 1999;104:S258-67.
66. Tunon-de-Lara JM, Laurent F, Giraud V, et al. Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. J Allergy Clin Immunol 2007;119:583-90.