

Abnormal spirometry in children with persistent allergic rhinitis due to mite sensitization: The benefit of nasal corticosteroids

Kessel A, Halloun H, Bamberger E, Kugelman A, Toubi E. Abnormal spirometry in children with persistent allergic rhinitis due to mite sensitization: The benefit of nasal corticosteroids.

Pediatr Allergy Immunol 2007.

© 2007 The Authors

Journal compilation © 2007 Blackwell Munksgaard

Inflammatory processes affecting nasal and bronchial mucosa are similar in nature. The purpose of this study was to examine whether children with perennial allergic rhinitis, without underlying asthma, have impaired pulmonary function. We also investigated whether nasal corticosteroids and loratadine would improve the pulmonary function tests of those children with impaired lung function. Fifty subjects with moderate/severe persistent allergic rhinitis due to exclusively dust mite sensitization and no past medical history suggestive of asthma were assessed. The control group consisted of 26 matched healthy subjects. Subjects with airway obstruction, as detected by forced expiratory volume/1 s (FEV1) or forced expiratory flow from 25% to 75% (FEF₂₅₋₇₅) values <80% of those predicted, were treated with loratadine, once a day for 10 days, and daily nasal budesonide for 3 months. We found that 11 of 50 patients (22%) with perennial allergic rhinitis had impaired pulmonary function (FEF₂₅₋₇₅ values <80%), compared to 1/26 (3.8%) of the control group ($p \leq 0.05$). Reversibility was observed in 9/11 (81.8%), mean $24.7\% \pm 10.3\%$. Within 3 months of treatment, 7/10 had FEF₂₅₋₇₅ > 80% of their predicted values as well as significant improvements in their FEV1 ($p = 0.04$), and FEV1/FVC ($p = 0.04$). We conclude that a substantial proportion of children with perennial allergic rhinitis have diminished FEF₂₅₋₇₅ values and reversible airway obstruction. Nasal corticosteroids improve the pulmonary function tests of these children with impaired lung function.

**Aharon Kessel¹, Hadeel Halloun¹,
Ellen Bamberger², Amir Kugelman³
and Elias Toubi¹**

¹Division of allergy and clinical Immunology, Department of Clinical Microbiology, ²Department of Neonatology, ³Bnai Zion Medical Center, Faculty of Medicine Technion, Haifa, Israel

Key words: allergic rhinitis; forced expiratory flow from 25% to 75%; nasal budesonide; pulmonary function

Dr Aharon Kessel, Division of allergy and clinical Immunology and Allergy Bnai-Zion Medical Center, 47 Golomb Street, PO Box 4940 Haifa 31048, Israel
Tel/Fax: 97248359659
E-mail: aharon.kessel@b-zion.org.il

Accepted 28 March 2007

Inflammatory processes affecting nasal and bronchial mucosa are similar in nature. Hence, their response to pharmacologic and immunologic interventions are similar (1). Epidemiologic data attest to the interrelationship between asthma and allergic rhinitis (AR). The majority of patients with asthma present seasonal or perennial allergic symptoms and up to 40% of patients with allergic rhinitis also have asthma (2). The impact of concomitant AR and asthma on the quality of life is noteworthy. Such patients frequently complain of sleep disturbances (79%

of children and adults), avoid participation in leisure activities and sports (75% of children and adults), and report poor concentration in school (73% of children) and disruptions in their social engagements (51% of children) (3). Additionally, flares of AR may precipitate additional asthma attacks and aggravate the underlying asthma symptoms. Allergic rhinitis is regarded as a risk factor for the development of asthma, especially in the presence of bronchial hyperresponsiveness (BHR) (4–7). Patients with underlying AR are three times more likely to develop asthma when

compared with normal subjects (8). Children who develop rhinitis within the first year of life are twice more likely to develop asthma than children who develop rhinitis later in life (2, 9). The presence of bronchial inflammation in non-asthmatic patients with seasonal allergic rhinitis is well-established (10, 11). Recently, Ciprandi et al. investigated the presence of bronchial hyperactivity and spirometric abnormalities in adults with perennial allergic rhinitis who were not diagnosed with asthma. They found that 48% of these individuals had reduced forced expiratory flow from 25% to 75% of pulmonary volume (FEF_{25-75}) values and that 5% of the patients demonstrated reduced values of forced expiratory volume/1 s (FEV_1). Additionally, 72% of the aforementioned patients had a positive methacholine challenge (12). To the best of our knowledge these findings have not been described in children. We therefore conducted a study to examine whether children with perennial allergic rhinitis without known underlying asthma have impaired lung function. We also investigated the effect of nasal corticosteroids and loratidine on pulmonary function tests (PFTs).

Subjects and methods

Fifty children with moderate/severe persistent AR and with no past medical history suggestive of asthma were recruited from our outpatient allergy clinic. Twenty-seven males and twenty-three females ages 6–17 yr (mean 12.0 ± 2.7 yr) were included in the study. A detailed clinical history and complete physical examination, including allergy evaluation, were performed. Individuals with a history of wheezing, dyspnoea, chest tightness, or those previously treated with anti-asthma medications were excluded from the study. Additional exclusion criteria included: previous or current treatment with immunotherapy, previous or current treatment with intranasal or oral corticosteroids within 4 wk, or prior use of leukotriene modifier. The diagnosis of moderate/severe persistent AR was made in accordance with the ARIA (allergic rhinitis and its impact on asthma) guidelines, referring to nasal symptoms more than 4 days a week for more than 4 wk and one or more of the following items present: 1. sleep disturbance 2. impairment of daily activities, leisure and/or sport 3. impairment of school or work 4. troublesome symptoms (13). Sensitization restricted to house dust mite was established by performing skin-prick reactivity to common inhaled allergens, in conjunction with positive and negative controls, 1 mg/ml histamine and 0.9% w/v saline, respectively (ALK

ABELLO Port, Washington, NY, USA). The panel consisted of house dust mite (dermatophagoides farine and pteronyssinus), mixed weeds (Pigweed, Lambs quarters, Sagebrush, Plaintain, Nettle, Wall pellitory, Cocklebur), mixed grass (Bermuda, Jhonson, Orchard, Timothy) mixed trees (Olive, Cypress, Pecan, Oak, Acacia, Cottonwood, Casuarina) mixed molds (Cladosporium, Alternaria, Aspergillus), dog, cat and cockroach extracts. Reactions to the allergens were read after 15 min. Mean diameters were calculated as the mean of the widest diameter and the perpendicular diameter measured at its midpoint. Wheals with a mean diameter ≥ 3 mm than those of the negative control were considered positive reactions (14). We chose patients with exclusive house-dust mite sensitizations since we wanted the cohort group to have a perennial antigen stimulation not significantly affected by change of seasons, vegetation and infectious etiologies. The control group consisted of 26 matched healthy subjects, without medical history suggestive of asthma or allergic diseases, 12 boys and 14 girls, ages 6–17 yr (mean age 11.4 ± 4 yr). Spirometry was performed by using a computer-assisted spirometer with an optoelectronic whirl flow meter as described by ERS (15). In subjects in whom an airway obstruction was present, as detected by FEV_1 or FEF_{25-75} values $< 80\%$ of those predicted, a bronchodilatation test was performed after 10–20 min with 400 μ g salbutamol metered dose inhaler via aerochamber. Bronchoconstriction was considered reversible in cases in which the FEV_1 or FEF_{25-75} increased by at least 12% from baseline after administering the bronchodilator. Patients with abnormal PFTs were treated with loratidine (Teva), 5–10 mg once a day for (a total) of 10 days, and daily nasal budesonide (Teva) 1 puff (100 μ g) in each nostril twice a day for 3 months. PFTs were assessed monthly during the study period. During the study period no other anti-asthmatic or anti-allergic medications were given. The study was approved by our Hospital's Ethics committee.

Statistical analysis

The comparison between the means values of pulmonary function of the difference groups were performed using paired *t*-test and within the groups by paired *t*-test. Chi-squared test was used to assess the difference in the prevalence of abnormal PFTs between patients with persistent rhinitis and the healthy control group. Differences were considered significant if *p*-values were ≤ 0.05 .

Results

There was a significantly higher percentage of subjects with abnormal lung function in the group of patients with persistent rhinitis when compared to the healthy control group (22% vs. 3.8%, $p \leq 0.05$, respectively). The demographics and PFTs of patients with persistent rhinitis vs. the healthy controls are displayed in Table 1. Patients with persistent rhinitis were divided into two groups on the basis of their PFTs: Group 1 consisted of 11 patients with impaired pulmonary function, FEF_{25-75} values $< 80\%$. One of the patients also had $FEV_1 < 80\%$. Group 2 was comprised of individuals with PFTs within the normal range. The demographic and PFTs of groups 1 and 2 are summarized in Table 2. All subjects in group 1 (rhinitis and impaired pulmonary function) were given $200 \mu\text{g}$ salbutamol. Reversibility was observed in 9/11 (81.8%), mean $24.7 \pm 10.3\%$ (Fig. 1). Ten of the eleven patients received loratadine, 5–10 mg once a day for a total of 10 days, and daily nasal budesonide 1 puff twice a day for 3 months. One patient was lost to follow-up. Subjects were evaluated every month in the outpatient clinic where spirometry was performed. Within 3 months, 7/10 had $FEF_{25-75} > 80\%$ of their predicted values

Table 1. Demographics and pulmonary function tests of children with allergic rhinitis vs. control group

Characteristic	Controls (n = 26)	Children allergic rhinitis (n = 50)	p-value
Mean age (yr)	11.4 $\pm$ 4.0	12.0 $\pm$ 2.7	N.S
Age range (yr)	6–17	6–17	
Female/male	14/12	23/27	N.S
FEV_1^*	93 $\pm$ 8	95 $\pm$ 9 N.S	
FVC*	96 $\pm$ 11	99 $\pm$ 11	N.S
FEF_{25-75}^*	105 $\pm$ 22	97 $\pm$ 18	0.06
FEF_{25-75}/FVC^*	1.11 $\pm$ 0.2	0.98 $\pm$ 0.2	0.02

*(% of predicted) mean $\pm$ s.d.

Table 2. Characteristics of children with allergic rhinitis with normal and abnormal pulmonary function tests (PFTs)

Characteristic	Children with normal PFT (n = 39)	Children with abnormal PFT (n = 11)	p-value
Mean age (yr)	11.9 $\pm$ 2.9	12.3 $\pm$ 2.4	N.S
Age range (yr)	6.3–17	7.6 $\pm$ 16.3	
Female/male	17/22	6/5	N.S
FEV_1^*	97.9 $\pm$ 9	87 $\pm$ 6	0.001
FVC*	99 $\pm$ 12	100 $\pm$ 7	N.S
FEF_{25-75}^*	104 $\pm$ 13	72 $\pm$ 2	<0.0005
FEF_{25-75}/FVC^*	1.0 $\pm$ 0.1	0.73 $\pm$ 0	<0.0005

*(% of predicted) mean $\pm$ s.d.

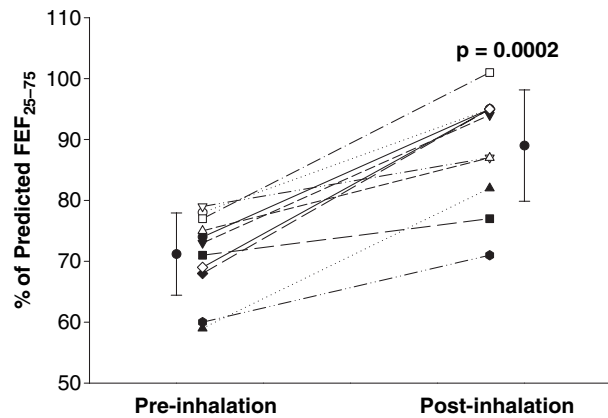


Fig. 1. Reversibility of airway obstruction of children with persistent allergic rhinitis and abnormal pulmonary function. FEF_{25-75} following salbutamol metered dose inhaler ($200 \mu\text{g}$).

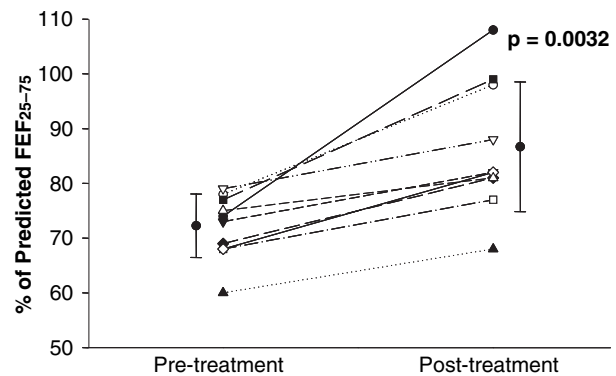


Fig. 2. FEF_{25-75} of children with persistent allergic rhinitis and abnormal pulmonary function at baseline and after treatment with daily nasal budesonide (3 months) and loratadine (10 days).

(Fig. 2) as well as significant improvements in their FEV_1 , and FEV_1/FVC (Fig. 3). In two of the three remaining patients, after the study period, the addition of montelukast (MSD) to the above pharmacologic regimen resulted in attaining an $FEF_{25-75} > 80\%$ of predicted values. Although a significant improvement in FEF_{25-75} was observed in all patients in group 1, their FEF_{25-75} was still lower than those of their counterparts with rhinitis and normal lung function 86.7 ± 11.8 vs. 105.5 ± 12.7 , $p = 0.0003$, respectively (Fig. 4).

Discussion

The notion that AR and allergic asthma are two manifestations of one syndrome affecting different regions of the respiratory tract is widely reported in the literature. As such the two

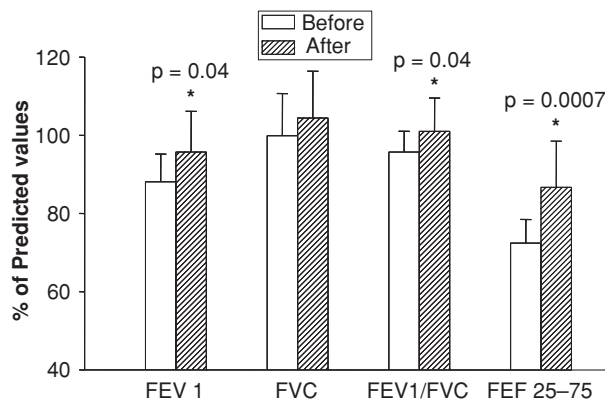


Fig. 3. Pulmonary function tests of children with persistent allergic rhinitis and abnormal pulmonary function at base line and after treatment with daily nasal budesonide (3 months) and loratidine (10 days).

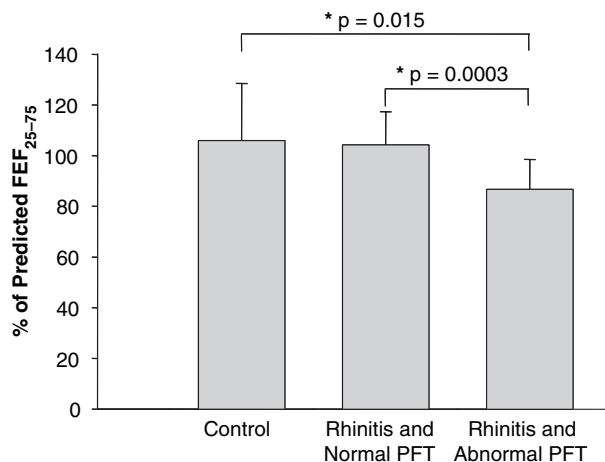


Fig. 4. Comparison of FEF₂₅₋₇₅ values among children with persistent allergic rhinitis and normal pulmonary function tests, healthy controls, and children with persistent allergic rhinitis and abnormal pulmonary function tests following treatment with daily nasal budesonide (3 months) and loratidine (10 days).

conditions share a common immunopathology and pathophysiology (1, 16, 17). Recently, investigators have found evidence in support of the bi-directional effects of the lower and upper airways. In patients with AR, the exposure of the nasal mucosa to an allergen may precipitate bronchial eosinophilia with up-regulation of various adhesion molecules (18). Similar findings were found in the nasal mucosa when allergen was directly administered to the lower airways through a bronchoscope (19). It appears that local inflammation in the nose or lungs triggers a systemic inflammation whereby T helper type 2 lymphocytes (which secrete interleukin (IL)-4, IL-5, IL-9 and IL-13) migrate to the bone marrow. Subsequently, these lymphocytes stimu-

late production and recruitment of inflammatory cells to the inflamed target tissues, which may exacerbate the inflammation in both upper and lower airways (20). These findings offer a plausible explanation for the high co-morbidity that exists between AR and allergic asthma. We found that 22% (11/50) of our patients had reduced values of FEF₂₅₋₇₅ and one of them had also reduced FEV₁. Our results are consistent with those observed in adult studies (12). FEF₂₅₋₇₅ is considered as a marker of small airway dysfunction and may be the only abnormal pulmonary finding among asthmatic patients with a normal FEV₁ (21–23). It should be emphasized that its measurement is independent of the subject's respiratory effort and as such is especially valuable in the evaluation of individuals who lack the necessary coordination for pulmonary testing (24). Although FEV₁ is considered the main parameter in the evaluation of bronchial obstruction, the underlying inflammation of the small airways, yet to be completely understood, also plays a role in the pathophysiology of asthma (25).

Previous studies in adults have demonstrated that in patients with allergic rhinitis there is good correlation between low values of FEF₂₅₋₇₅ and BHR, an important feature of asthma (12, 26, 27). Cuttitta et al. demonstrated that in children BHR is significantly associated with persistent allergic rhinitis and higher total IgE levels (28). It was found that patients with rhinitis and BHR are at a risk for the development of asthma (29, 30, 31). Additionally there is a significant association between FEF₂₅₋₇₅/FVC ratio and airway reactivity and sensitivity. Subjects with lower FEF₂₅₋₇₅/FVC ratio had higher airway reactivity and sensitivity to methacholine (32, 33). Notably, in our study, patients with AR had lower FEF₂₅₋₇₅/FVC ratio compared to the healthy controls ($p = 0.02$). Moreover among the patients with allergic rhinitis, those with abnormal PFTs compared to those with normal PFTs, attained significantly lower values of their FEF₂₅₋₇₅/FVC ($p < 0.0005$) (Table 2). Given the abnormal pulmonary function observed among patients with allergic rhinitis and airway reversibility, one may speculate that these individuals are at risk of developing asthma. It remains to be seen whether early anti-inflammatory intervention of such individuals will attain normal PFTs.

Among 7/10 patients with AR and impaired PFTs, the combined use of a corticosteroid nasal spray with a short course of antihistamine raised their FEF₂₅₋₇₅ values to normal values. After the study period, two other patients necessitated

additional intervention, namely the addition of montelukast to achieve normal FEF₂₅₋₇₅ values. Interestingly, although treatment achieved FEF₂₅₋₇₅ values >80% of predicated, these values still remained significantly lower than those with normal FEF₂₅₋₇₅ values ($p < 0.001$). The improvement in FEF₂₅₋₇₅ in conjunction with the patients decrease in allergic rhinitis symptoms may be explained by factors affecting lower airway dysfunction namely diminished postnasal drip, nasal bronchial reflex, oral breathing and most importantly decreased nasal inflammation. This decreased nasal inflammation might prevent the development of inflammation of the lower airways by reducing the systemic allergic reaction and by the direct effect on bronchial inflammatory cells secondary to systemic availability of nasal corticosteroids (34, 35). Additionally, previous clinical studies demonstrated that intranasal corticosteroids in patients with mild asthma and allergic rhinitis improved BHR to methacholine, exercise and clinical asthma symptoms (36–38). Treatment with antihistamines also improved asthma symptoms and PFTs (39). It was also found that allergic rhinitis and eczema is related to more severe asthma (40). These findings reinforce the importance of treating allergic rhinitis in patients with asthma.

Several limitations to our study should be mentioned. The number of subjects is limited, especially the subgroups receiving treatment (10 patients). There was no control group as all patients attending our outpatient clinical warranted pharmacologic treatment. Finally, we believe that these patients should have long-term follow-up to see whether or not they develop clinical asthma.

Our findings raise additional questions warranting further research. For example, to what degree are children with reduced FEF₂₅₋₇₅ values at increased risk of developing clinical asthma in the future? Additionally, is local nasal treatment sufficient to prevent the development of abnormal PFTs or might superior treatment outcome be achieved through a combination of preemptive corticosteroid, leukotriene receptor antagonists or allergen desensitization.

Conclusions

A substantial proportion of children with perennial allergic rhinitis have diminished FEF₂₅₋₇₅ values and reversible airway obstruction. Short-term nasal corticosteroid significantly improved the FEF₂₅₋₇₅ values among such patients. These findings might suggest that individuals with

perennial allergic rhinitis and diminished FEF₂₅₋₇₅ values have their PFTs checked periodically and should be encouraged to adhere to their prescribed treatment.

References

1. SIMONS FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol* 1999; 104: 534–40.
2. SETTIPANE RJ, HAGY GW, SETTIPANE GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994; 15: 21–5.
3. PAWANKAR R. Allergic rhinitis and asthma: the link, the new ARIA classification and global approaches to treatment. *Curr Opin Allergy Clin Immunol* 2004; 4: 1–4.
4. GUERRA S, SHERRILL DL, MARTINEZ FD, BARBEE RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109: 415–25.
5. RAMSDALE EH, MORRIS MM, ROBERTS RS, HARGREAVE FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985; 75: 573–7.
6. BRAMAN SS, BARROWS AA, DECOTIS BA, SETTIPANE GA, CORRAO WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest* 1987; 91: 671–4.
7. VAN BEVER HP, DESAGER KN, HAGENDORENS M. Critical evaluation of prognostic factors in childhood asthma. *Pediatr Allergy Immunol* 2002; 13: 77–83.
8. GUERRA S, SHERRILL DL, MARTINEZ FD, BARBEE RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002; 109: 419–25.
9. WRIGHT AL, HOLBERG CJ, MARTINEZ FD, HALONEN M, MORGAN W, TAUSSIG LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994; 94(6 Pt 1): 895–901.
10. KELLY EA, BUSSE WW, JARJOUR NN. A comparison of the airway response to segmental antigen bronchoprovocation in atopic asthma and allergic rhinitis. *J Allergy Clin Immunol* 2003; 111: 79–86.
11. CHAKIR J, LAVIOLETTE M, TURCOTTE H, BOUTET M, BOULET LP. Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis: influence of natural allergen exposure. *J Allergy Clin Immunol* 2000; 106: 904–10.
12. CIPRANDI G, CIRILLO I, ANGELA TOSCA M, VIZZACCARO A. Bronchial hyperreactivity and spirometric impairment in patients with perennial allergic rhinitis. *Int Arch Allergy Immunol* 2004; 133: 14–8.
13. BOUSQUET J, VAN CAUWEGNBERGE P, KHALTAEV N, ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (suppl. 5): S147–334.
14. PEPYS J. Skin tests for immediate, type I allergic reactions. *Proc R Soc Med* 1972; 65: 271–2.
15. QUANJER PH, TAMMELING GJ, COTES JE, PEDERSEN OF, PESLIN R, YERNAULT JC. Standardized lung function testing. *Eur Respir J* 1993; 6: 1–99.
16. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (suppl. 5): S147–334.
17. TOGIAS A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003; 111: 1171–84.

18. BRAUNSTAHL GJ, OVERBEEK S, KLEINJAN A, PRINS JB, HOKKENS W. Nasal allergen provocation induces adhesion molecules expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001; 107: 469–76.
19. BRAUNSTAHL GJ, KLEINJAN A, OVERBEEK S, PRINS JB, HOOGSTEDEN H, FOKKENS W. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000; 161: 2051–7.
20. PAWANKAR R. Allergic rhinitis and asthma: are they manifestations of one syndrome? *Clin Exp Allergy* 2006; 36: 1–4.
21. BJERMER L. History and future perspectives of treating asthma as a systemic and small airways disease. *Respir Med* 2001; 95: 703–19.
22. McFADDEN ER, LINDEN DA. A reduction in maximum mid-expiratory flow rate: a spirographic manifestation of small airway disease. *Am J Med* 1972; 52: 725–7.
23. LEBECQUE P, KIAKULANDA P, COATES AL. Spirometry in the asthmatic child: is FEF_{25–75} a more sensitive test than FEV₁/FVC? *Pediatr Pulmonol* 1993; 16: 19–22.
24. ACRES JC, KRYGER MH. Clinical significance of pulmonary function tests. Upper airway obstruction. *Chest* 1980; 80: 207–11.
25. HAMID Q, SONG Y, KOTSIMBOS TC, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997; 100: 44–51.
26. CIPRANDI G, CIRILLO I, TOSCA MA, VIZZACCARO A. Bronchial hyperreactivity and spirometric impairment in patients with seasonal allergic rhinitis. *Respir Med* 2004; 98: 826–31.
27. CIPRANDI G, CIRILLO I, TOSCA MA, VIZZACCARO A. Bronchial hyperreactivity and spirometric impairment in polysensitized patients with allergic rhinitis. *Clin Mol Allergy* 2004; 2: 3.
28. CUTTITTA G, CIBELLA F, LA GRUTTA S, et al. Non-specific bronchial hyper-responsiveness in children with allergic rhinitis: Relationship with atopic status. *Pediatr Allergy Immunol* 2003; 14: 458–63.
29. ZHONG NS, CHEN RC, YANG MO, WU ZY, ZHENG JP, LI YF. Is asymptomatic bronchial hyperresponsiveness an indication of potential asthma? A two-year follow-up of young students with bronchial hyperresponsiveness. *Chest* 1992; 102: 1104–9.
30. FERDOUSI HA, ZETTERSTROM O, DREBORG S. Bronchial hyper-responsiveness predicts the development of mild clinical asthma within 2 yr in school children with hay-fever. *Pediatr Allergy Immunol* 2005; 16: 478–86.
31. WARNER JO. Bronchial hyperresponsiveness, atopy, airway inflammation, and asthma. *Pediatr Allergy Immunol* 1998; 9: 56–60.
32. PARKER AL, ABU-HIJLEH M, MCCOOL FD. Ratio between forced expiratory flow between 25% and 75% of vital capacity and FVC is a determinant of airway reactivity and sensitivity to methacholine. *Chest* 2003; 124: 63–9.
33. LITONJUA AA, SPARROW D, WEISS ST. The FEF_{25–75}/FVC ratio is associated with methacholine airway responsiveness. The normative aging study. *Am J Respir Crit Care Med* 1999; 159(5 Pt 1): 1574–9.
34. SIMONS FER. What's in a name? The allergic rhinitis-asthma connection. *Clin Exp Allergy Rev* 2003; 3: 9–17.
35. WATSON WIA, BECKER AH, SIMONS FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993; 91: 97–101.
36. CORREN J, ADINO AD, BUCHMEIER AD, IRVIN CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992; 90: 250–6.
37. FORESI A, PELUCCI A, GHERSON G, MASTROPASQUA B, CHIAPPARINO A, TESTI R. Once-daily fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996; 98: 274–82.
38. HENRIKSEN JW, WENZEL A. Effect of an intranasally administered cortico-steroid (budesonide) on nasal obstruction, mouth breathing and asthma. *Am Rev Respir Dis* 1984; 130: 1013–8.
39. CORREN J, HARRIS A, AARONSON D, BEAUCHER W, BERKOWITZ R, BRONSKY E, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997; 100: 781–8.
40. SOLE D, CAMELO-NUNES IC, WANDALSEN GF, METO KC, NASPITZ CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? *Pediatr Allergy Immunol* 2005; 16: 121–5.