

Seasonal variation in airway hyperresponsiveness and natural exposure to house dust mite allergens in patients with asthma

Sicco van der Heide, MS, Jan G. R. de Monchy, MD, Klaas de Vries, MD, Timca M. Bruggink, MD, and Henk F. Kauffman, PhD
Groningen, The Netherlands

Nonspecific airway hyperresponsiveness is a fundamental characteristic of patients with asthma and can be influenced by several stimuli. In nine patients with asthma and an isolated allergy to house dust mite, the variation of natural exposure to the house dust mite allergen Der p I and the corresponding changes in nonspecific airway hyperresponsiveness were followed up for 1 year. The concentration of Der p I in floor dust from living rooms and bedrooms (as a measure of exposure) reached maximum levels in late summer and the beginning of autumn (August to October), whereas the lowest levels were found during the months of March to May (Δ Der p I = +2.31 μ g/gm and -1.33 μ g/gm respectively, both compared with the year average). Airway hyperresponsiveness (as measured by the provocative concentration of histamine causing a 20% fall in forced expiratory volume in 1 second [PC_{20}] threshold) also showed a seasonal variation, with most severe hyperresponsiveness during the months of August to November, almost the same period in which the exposure to house dust mite allergens reached maximal levels (ΔPC_{20} histamine = -1.47 mg/ml in November vs +1.79 mg/ml in March, both compared with the year average). Our results support the view that seasonal changes of exposure to environmental allergens such as house dust mite allergens will have an effect on the level of airway hyperresponsiveness in patients with allergic asthma. (J ALLERGY CLIN IMMUNOL 1994;93:470-5.)

Key words: Asthma, airway hyperresponsiveness, environment, house dust mites, allergens, season

In Europe, allergens of the house dust mite *Dermatophagoides pteronyssinus* are probably the most significant inducers of allergic asthmatic reactions.¹⁻³ Next to bronchial obstruction, allergen exposure can also induce an increase in nonspecific bronchial hyperresponsiveness (BHR), which is a fundamental characteristic of patients with asthma. In the clinical laboratory,

Abbreviations used

BHR: Bronchial hyperresponsiveness
FEV₁: Forced expiratory volume in 1 second
HDMA: House dust mite allergens
PC₂₀: Provocative concentration causing a 20% fall in FEV₁

From the Department of Allergology, Clinic for Internal Medicine, University Hospital, Groningen, The Netherlands.

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Reprint requests: Sicco van der Heide, MS, Department of Allergology, Clinic for Internal Medicine, University Hospital Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands.

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asthmatic reactions induced by allergen inhalation challenges are often accompanied by an increase in BHR.⁴⁻⁶ However, the effects of natural exposure to allergens on BHR are less predictable. Seasonal exposure to pollen allergens may significantly increase BHR,^{7, 8} and occupational exposure to particular chemicals such as isocyanates may also cause a prolonged elevation of BHR.⁹ A significant reduction of exposure to house dust mite allergens (HDMA) (in mountainous areas or in a hospital) has been associated with dramatic

decreases in BHR.^{10, 11} The variation of the natural indoor exposure to HDMA is partly seasonal,¹²⁻¹⁴ although much less pronounced than exposure to pollen allergens.⁸ High humidity is a necessary condition for the survival of house dust mites, and it has been suggested that house dust mite-allergic patients with asthma in Western Europe may often show an increase of symptoms after the most humid months (autumn).

To study the influence of variation in natural exposure to HDMA on BHR, we measured the bronchial hyperreactivity and exposure to HDMA during 1 year in nine patients with asthma. To exclude interference of exposure to other aeroallergens, we only selected patients with an isolated allergy to house dust mites.

METHODS

Patients

Nine atopic patients with a history of asthma and nonspecific airway hyperreactivity (BHR) were selected for the study. All participants had an isolated allergy for house dust mite (*D. pteronyssinus*) as determined by intradermal skin testing, whereas skin test results to 18 other common inhalant allergens (grass pollen, tree pollen, animal dander, etc.) were negative. All patients had nonspecific airway hyperresponsiveness (BHR) as demonstrated by a histamine threshold of 32 mg/ml or less, with the use of the 30-second inhalation procedure.¹⁵ All patients showed reversible airway obstruction after inhalation of a bronchodilator. None of the patients were smokers. All patients gave informed consent, and the study was approved by the Medical Ethical Committee of the University Hospital Groningen.

Design of the study

Floor dust samples were collected from each patient's living room and bedroom every 2 weeks during the study period. During each visit the air temperature and relative air humidity were also recorded. Patients visited the outpatient department every month for spirometry, quantification of BHR, and skin testing with house dust mite extract. The eosinophil count in peripheral blood and in serum total and house dust mite specific IgE were also determined.

Skin testing and IgE measurements

Before the study, all patients underwent intracutaneous skin testing with a panel of 18 common aeroallergen extracts. The results are expressed as histamine equivalent wheal size, which was calculated by dividing the wheal area obtained with the allergen extract by the wheal area of a standard histamine solution. A skin test with a histamine equivalent wheal size of 0.7 or greater was regarded as positive. During the study a duplicate

skin test with a house dust mite extract was performed every month. The same batch of allergen extract (Diephuis Laboratories, Groningen, The Netherlands) was used throughout the study. Serum total IgE and house dust mite-specific IgE were measured by the Pharmacia IgE Enzyme Immuno Assay and Phadezym RAST, respectively (Pharmacia Diagnostics, Uppsala, Sweden).

Spirometry and measurement of airway hyperreactivity

Lung function (forced expiratory volume in 1 second [FEV₁] and vital capacity) was tested every month. Nonspecific airway hyperreactivity (BHR) was measured by stepwise inhalation of increasing concentrations of histamine solution during 30 seconds (Wiesbadener Doppelspray, 0.13 ml output; Wiesbadener Inhalator-Vertrieb, Wiesbaden, Germany) until a decrease in FEV₁ of 20% or more was observed.¹⁵ From the decline in FEV₁, the histamine provocative concentration causing a 20% fall in FEV₁ (PC₂₀) was calculated. All medication (except budesonide) was stopped before the tests: salbutamol and ipratropium bromide were stopped 12 hours before histamine challenge, and cromoglycate and terfenadine were stopped 72 hours before challenge.

Collection and extraction of house dust

The concentration of mite allergens in house dust samples was used as an indicator for exposure to airborne mite allergens. During each visit, the total floor surface of living room and bedroom were vacuumed with a 1100 W vacuum cleaner (Philips, Groningen, The Netherlands; type T560, with a double filtering system), and the dust from each room was collected in separate bags. The sampled floor area of each room was recorded. After sieving (0.35 mm), the amount of fine dust was weighed and a 10% (wt/vol) extraction in 0.01 mol/L NH₄SO₄ buffer was performed by overnight rotation at 4° C. The samples were centrifuged and the supernatants were stored at -18° C until HDMA concentration was measured.

Detection of HDMA

A monoclonal antibody (kindly provided by Prof. R. Aalberse, State University of Amsterdam, The Netherlands) directed against the allergen *Der p* I of the house dust mite *D. pteronyssinus* was coupled to CNBr-activated paper disks. The dust extracts (100 µl) were incubated at room temperature with an anti-*Der p* I disk for 3 hours with constant agitation. After washing three times with 2.5 ml of RAST buffer (Pharmacia Diagnostics), the disks were incubated for 3 hours with 50 µl of pooled serum, which was prepared from sera of 25 house dust mite-allergic patients (RAST class 4). The further steps were carried out according to the instructions for the Phadezym RAST kit. A reference house dust mite extract, which was calibrated for the content of *Der p* I by the Allergy Division of the Dutch

TABLE I. Patient characteristics at the start of the study

Patient No.	Sex	Age (yr)	FEV ₁ (% pred)*	Skin sensitivity†	Histamine PC ₂₀ (mg/ml)‡	Medication
1	M	33	71	1.4	4.95	CS
2	M	37	81	1.5	8.25	CBI
3	M	23	101	1.3	3.30	C
4	M	42	68	1.2	1.89	S
5	F	26	109	1.3	14.25	CS
6	F	37	89	1.2	5.35	CBI
7	M	31	89	1.4	4.70	—
8	M	32	66	1.4	2.42	CT
9	F	44	97	1.0	2.60	BS

C, Cromoglycate; S, salbutamol; B, budesonide; I, ipratropium bromide; T, terfenadine.

*FEV₁ corrected for sex, age, and height.

† Skin sensitivity to HDMA, expressed as histamine equivalent wheal size (see Methods section).

‡The concentration of histamine solution, which after inhalation, provokes a fall of 20% in FEV₁.

Central Laboratory of the Blood Transfusion Service (Amsterdam), was used in serial dilutions for calculation of the allergen content of the house dust samples.

Data analysis

Statistical analysis was performed with the SPSS package for personal computers (SPSS Inc., Chicago, Ill.). Results were expressed as means $\pm$ SEM. Because of large differences in histamine PC₂₀ values among individual patients, the seasonal (or monthly) change in histamine PC₂₀ of each patient was calculated by subtracting the measured histamine PC₂₀ value from the average histamine PC₂₀ value for that patient during the year. Afterward, with the individual change in histamine PC₂₀ values, the mean value ($\pm$ SEM) for the whole group was calculated. Comparison of the mean values of the change in histamine PC₂₀ was achieved by one-way analysis of variance. The same calculation procedure was used for the levels of the house dust mite allergen *Der p* I in dust samples and for the number of peripheral blood eosinophils. Differences with *p* values less than 0.05 were considered significant.

RESULTS

Patient characteristics

The clinical data of the nine patients are summarized in Table I.

Variation in airway hyperresponsiveness

In this group of nine patients with asthma and an isolated sensitization to house dust mites, a seasonal variation in BHR was observed. As shown in Fig. 1, A, the greatest hyperresponsiveness (lowest histamine PC₂₀ value) was found in autumn (September to November), whereas lowest BHR (higher histamine PC₂₀ value) was found during the months of March to May (Δ PC₂₀

histamine = -1.47 mg/ml in November vs $+1.79$ mg/ml in March, both compared with the year average; *p* < 0.05).

In addition to the change in BHR, the number of peripheral blood eosinophils also showed a seasonal variation, with the highest number of eosinophils found in autumn and limited numbers in spring, as is shown in Fig. 1, B. Lung function parameters, such as vital capacity and FEV₁, and also the levels of total serum IgE and house dust mite-specific IgE were not influenced by seasonal variation.

Variation in exposure to HDMA

The concentration of the HDMA *Der p* I in floor dust was followed by collection of dust samples every 2 weeks. The content of HDMA in floor dust varied greatly among the different houses (*Der p* I: range, 0.05 to 15.0 μ g/gm of fine dust).

Within houses, a relatively small but significant seasonal variation in *Der p* I levels in dust samples was found, with the highest levels in the period from late summer to the start of autumn, and lower levels during spring (Δ *Der p* I = $+2.31$ μ g/gm and -1.33 μ g/gm, respectively, both compared with the year average; *p* < 0.05). As shown in Fig. 2, A, for *Der p* I in floor dust from bedrooms, increased levels of HDMA were found in the period with more severe bronchial hyper-reactivity (lowest histamine PC₂₀ value). A comparable pattern of variation of *Der p* I levels in floor dust was found in living rooms. Furthermore, high levels of HDMA in floor dust from bedrooms were associated with high allergen levels in living rooms.

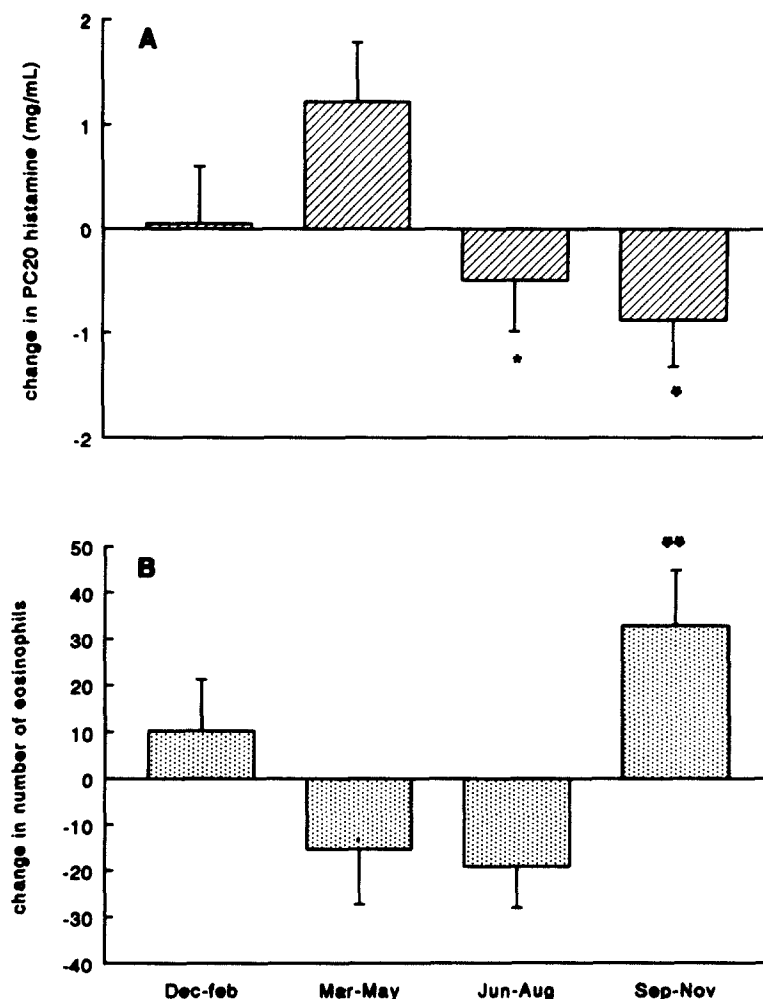


FIG. 1. Seasonal variation in airway hyperresponsiveness (histamine PC₂₀) (A) and number of blood eosinophils (B). Changes were calculated by comparison with the year average. ** $p < 0.05$ compared with March to August; * $p < 0.05$ compared with March to May.

The seasonal changes in levels of HDMA in dust samples corresponded with similar changes in air humidity, as demonstrated in Fig. 2, B. The highest absolute air humidity was found during the months of July to September, just before the increase in levels of HDMA in floor dust samples.

DISCUSSION

Airway hyperresponsiveness to various stimuli is a property that is present in most patients with asthma, and it has been observed that the severity of airway hyperresponsiveness is related to the frequency of complaints and the need for medications.^{16, 17} Although the pathogenesis of BHR must still be elucidated, it is well known that several factors can influence the degree of hyperresponsiveness. In patients with allergic

asthma exposure to aeroallergens is an important cause of increase in BHR, whereas a significant reduction of allergen exposure is accompanied by a sometimes marked decrease in BHR.^{7, 8, 11, 18, 19} The changes in seasonal exposure to pollen or exposure to HDMA after allergen reduction measures are much greater than the seasonal variations in natural exposure to HDMA as observed in our study.^{8, 11, 19, 20} Nevertheless, the results of our study suggest that even small changes in exposure to HDMA are associated with changes in airway hyperresponsiveness. Increased BHR was found in the months with maximal levels of HDMA in dust samples (Fig. 2, A). Because our group of patients with asthma was only sensitized to house dust mites, thereby excluding the interference of exposure to other airborne allergens, these results suggest a causal relationship

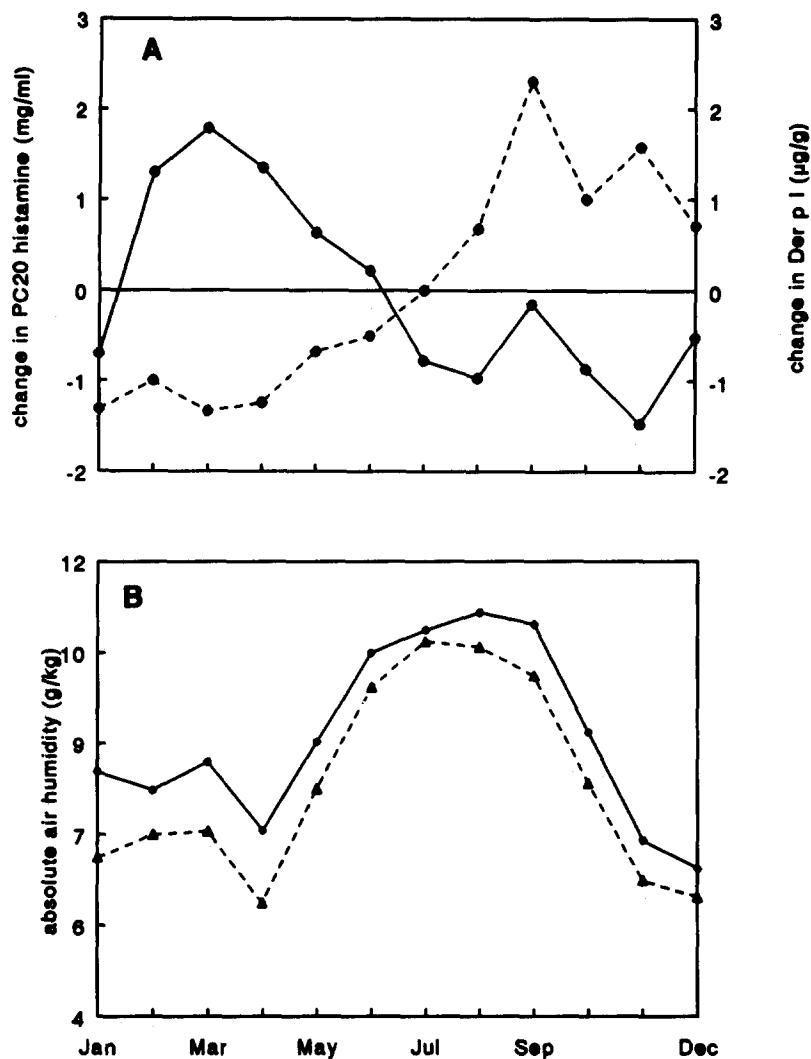


FIG. 2. A, Variation of histamine PC₂₀ threshold value (●—●) and of *Der p* I level (●---●) in floor dust from bedrooms, both calculated from the year average; B, variation of absolute air humidity in living rooms (●—●) and bedrooms (▲---▲).

between increased exposure to HDMA and enhanced BHR.

Because house dust mites appear to be strongly dependent on humidity for their growth, the increase of the HDMA *Der p* I during the late summer months is in accordance with the observed high levels of absolute air humidity during these months (Fig. 2, B).

In September a small improvement in BHR was found, followed by an increase in hyperresponsiveness in the next months. An explanation for this transient improvement may be that seven of the nine patients spent their holidays in August in camping areas in southern Europe where exposure to HDMA might be lower than at home.

Treatment of patients with asthma with antiin-

flammatory drugs, such as inhaled corticosteroids, causes a prolonged decrease in BHR,^{21, 22} a finding that supports the involvement of inflammation in the etiology of BHR. The number of peripheral blood eosinophils and especially the level of activation of these cells are known to be indicators for inflammation of lung tissue.^{22, 23} In our study the increase in BHR observed during the autumn months corresponds to the increase of peripheral blood eosinophil numbers seen during the same period (Fig. 1). This observation is in agreement with similar findings concerning changes of bronchial hyperreactivity and blood eosinophils during seasonal exposure to tree pollens.⁸

Exposure to indoor allergens is an important factor in the development of allergic asthmatic

reactions.^{1, 3} Our study demonstrates that even relatively small changes in allergen exposure may influence the degree of BHR. The corresponding changes in the number of peripheral blood eosinophils suggest the possibility that eosinophilic inflammation is involved in the observed changes in airway hyperresponsiveness.

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REFERENCES

1. Platts-Mills TAE, de Weck AL. Dust mite allergens and asthma. A worldwide problem. *J ALLERGY CLIN IMMUNOL* 1989;83:416-27.
2. Lau S, Falkenhurst G, Weber A, et al. High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. *J ALLERGY CLIN IMMUNOL* 1989;84:718-25.
3. Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house dust mite allergen (*Der p* I) and the development of asthma in childhood. *N Engl J Med* 1990;323:502-7.
4. Booi-Noord H, de Vries K, Sluiter HJ, Orie NGM. Late bronchial obstructive reaction to experimental inhalation of house dust extract. *Clin Allergy* 1972;2:43-61.
5. Cockcroft DW, Murdock KY. Comparative effects of inhaled salbutamol, sodium cromoglycate, and beclomethasone dipropionate on allergen-induced early asthmatic responses, late asthmatic responses and increased bronchial responsiveness to histamine. *J ALLERGY CLIN IMMUNOL* 1987;79:734-40.
6. Aalbers R, Kauffman HF, Koëter GH, Postma DS, de Vries K, de Monchy JGR. Dissimilarity in methacholine and adenosine 5'-monophosphate responsiveness 3 and 24 h after allergen challenge. *Am Rev Respir Dis* 1991;144:352-7.
7. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in non allergic bronchial responsiveness from seasonal pollen exposure. *J ALLERGY CLIN IMMUNOL* 1983;71:399-406.
8. Rak S, Löwhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. *J ALLERGY CLIN IMMUNOL* 1988;82:470-80.
9. Mapp CE, Di Giacomo GR, Omini C, Broseghini C, Fabbri LM. Late, but not early asthmatic reactions induced by toluene-diisocyanate are associated with increased airway responsiveness to methacholine. *Eur J Respir Dis* 1986;69:276-84.
10. Bonet AL, Niero E, Antonioni I, Valetta EA, Gaburro D. Pulmonary function and bronchial hyperreactivity in asthmatic children with house dust mite allergy during prolonged stay in the Italian Alps. *Ann Allergy* 1985;54:42-5.
11. Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkens SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982;2:675-8.
12. Platts-Mills TAE, Hayden ML, Chapman MD, Wilkens SR. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. *J ALLERGY CLIN IMMUNOL* 1987;79:781-91.
13. Hallas TE, Korsgaard J. Annual fluctuations of mites and fungi in Danish house dust: an example. *Allergol Immunopathol* 1983;11:195-200.
14. Murray AM, Zuk P. The seasonal variation in a population of house dust mites in a North American city. *J ALLERGY CLIN IMMUNOL* 1979;64:266-9.
15. de Vries K, Goei JT, Booi-Noord H, Orie NGM. Changes during 24 hours in lung function and histamine hyperreactivity of the bronchial tree in asthmatic and chronic bronchitic patients. *Int Arch Allergy Appl Immunol* 1962;20:93-101.
16. Juniper EF, Frith PA, Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax* 1981;36:575-9.
17. Vervloet D, Charpin D, Haddi E, et al. Medication requirements and house dust mite exposure in mite-sensitive asthmatics. *Allergy* 1991;46:554-8.
18. Kerrebijn KF. Endogenous factors in childhood CNSLD: methodological aspects in population studies. In: Orie NGM, Van der Lende R, eds. *Bronchitis III: Proceedings of the Third International Symposium on Bronchitis*, The Netherlands, 1969. Assen, The Netherlands: Royal Van Gorcum, 1970:38-48.
19. Ehner B, Lau-Schadendorf S, Weber A, Buettner P, Schou C, Wahn U. Reducing domestic exposure to dust mite allergen reduces bronchial hyperreactivity in sensitive children with asthma. *J ALLERGY CLIN IMMUNOL* 1992;90:135-8.
20. Owen S, Morganstern M, Hepworth J, Woodcock A. Control of house dust mite antigen in bedding. *Lancet* 1990;335:396-7.
21. Kraan J, Koëter GH, van der Mark TW, Sluiter HJ, de Vries K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with anti-asthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J ALLERGY CLIN IMMUNOL* 1985;76:628-36.
22. Laitinen LA, Laitinen A, Heino M, Haaktela L. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroids. *Am Rev Respir Dis* 1991;143:423-7.
23. De Monchy JGR, Kauffman HF, Venge P, et al. Bronchoalveolar eosinophils during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985;131:373-6.