

Seasonal variability of exercise-induced asthma especially outdoors. Effect of birch pollen allergy

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Summary

A study was made to determine whether natural allergenic exposure modulates exercise-induced asthma. Eighteen asthmatic men, ten non-allergic and eight allergic to birch pollen, underwent heart rate-monitored outdoor exercise tests during both the cold winter season and in the spring, the birch pollen season. The mean fall in FEV₁ after the outdoor exercise test increased in the allergic group from 17±3% in the winter to 27±6% in the spring, while it decreased in the non-allergic group from 31±6% to 22±4%, respectively ($P < 0.01$). Initial FEV₁ and FVC values remained unchanged in both groups. The non-specific airway responsiveness to histamine did not change significantly in birch pollen allergic or non-allergic subjects during the spring, when compared with the winter values. We conclude that the exercise-induced asthma is aggravated in the birch pollen allergic asthmatics during the pollen season, when compared to the non-birch pollen allergic asthmatics, in whom the exercise-induced bronchoconstriction is attenuated as expected, because of the warmer and more humid weather in the spring.

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Introduction

Experimental studies in the laboratory have shown that the main factor in the development of exercise-induced asthma (EIA) is the loss of heat and water from the airways mucosa [1–3]. However, it is our experience [4], and that of the others [5], that while the temperature and humidity of the inspired air mostly explain the magnitude of EIA in experimental circumstances in a particular individual, these factors only partially explain the variability of EIA occurring in real life outdoor situations.

The atmospheric pollution and its interaction with the barometric pressure and wind speed have been linked to the increased incidence of acute asthma-attacks [6,7]. Aero-allergens, like pollens and fungal spores, may worsen asthma in persons sensitive to these factors. It is not known if naturally occurring aero-allergens partly explain the variability in real life EIA based on the increase in the basic airways reactivity in sensitive subjects. Therefore we studied EIA under two very

different climatic conditions (the cold winter season and the warm birch pollen season) in non-allergic and birch pollen sensitive asthmatic subjects.

Subjects and methods

The 18 subjects were young men, army conscripts, aged 20±0.3 yr, who had mild asthma. Their medications were withheld for at least 24 hr before any study day. All had previously been studied at the Central Military Hospital and had demonstrated EIA (>10% fall in peak expiratory flow values after the exercise, from the pre-exercise level) in a standardized outdoor running test during autumn or winter. None of the subjects was found to be a late responder after the exercise challenge. All subjects underwent spirometry (Bodyscreen II, Erich Jaeger GmbH & Co. KG, Wurzburg, FRG), skin-prick tests with 15 common antigens, serum IgE immunoglobulin level determinations (Phadezym IgE PRIST, Pharmacia Diagnostics, Sweden) and radio-allergosorbent tests (Phadebas RAST, Pharmacia Diagnostics, Sweden) for specific IgE antibodies against birch pollen (a scoring system of semi-quantitative grading from 0 to 4, where 0 = negative, 1 = uncertain, and 2–4 = positive). Maximal

heart rate was measured for each subject using a treadmill exercise test in a separate session. The subjects were hospitalized during the study periods. Informed consent was obtained from each subject.

Study protocol

The subjects underwent a histamine inhalation challenge test and an outdoor heart rate-monitored exercise test on consecutive days, in random order in both the cold winter and the warm spring (the birch pollen season). In the spring the tests did not take place until the pollen season had lasted at least 1 week. The mean interval between winter and spring exercise tests was 80 (range 30–140) days. In each subject, the change from winter to spring in the magnitude of EIA (maximal fall in forced expiratory volume during 1 sec (FEV₁) taking place from 2 to 20 min after the exercise) was related to the changes in climatic conditions: temperature, water content of the inspired air, and atmospheric birch pollen counts. The results in those asthmatics who proved to be allergic (RAST score 2–4) were compared with the asthmatics who proved to be non-allergic (RAST score 0–1) to birch pollen.

Exercise test

The outdoor exercise tests were carried out in the immediate vicinity of the hospital on a 150 m circular track, surrounded by birch trees. The ventilation during the exercise tests was standardized by monitoring the subjects' heart rate, since the direct measurement of ventilation would have required a mask which would have interfered with the experiment. During the 2-min warming up period the subjects raised their heart rate up to 85% of the previously measured individual maximal heart rate. This heart rate was maintained for the remaining 6 min of the test. The heart rate was monitored during the running by the subject himself with a Sport Tester TM PE 3000 heart rate meter (Polar Electro Ky, Kempele, Finland), which displayed the heart rate on a wristwatch-like recorder by averaging it from 16 consecutive beats. Heart rate values were further collected at 15-sec intervals into the memory of the heart rate meter and analysed later. Two FEV₁ values were measured immediately before and at 2, 5, 10 and 20 min after the test. The maximal fall in FEV₁ from the mean of two pre-exercise values was taken as the measure of exercise-induced bronchoconstriction. In order to detect the possible late reactions, FEV₁ values were also measured at 3 and 7 hr after the exercise test.

Histamine provocation

Histamine diphosphate was administered by four calibrated DeVilbiss nebulizers, No. 40 (DeVilbiss Co,

Somerset, U.K.), with a constant air flow of 5 l/min. After three control inhalations of saline, increasing doses of histamine diphosphate were slowly inhaled, without prior inspiration, from the functional residual capacity to the total lung capacity within 2 sec. The subject then held his breath for 3 sec. Doses of histamine diphosphate were used in the following order: 0.03% one breath (0.06 µmol); 0.03% one breath (0.06 µmol); 0.06% one breath (0.07 µmol); 0.06% two breaths (0.14 µmol); 2.5% one breath (0.35 µmol); 2.5% two breaths (0.69 µmol); 5.0% one breath (0.84 µmol); 5.0% two breaths (1.68 µmol). Histamine was delivered at 2-min intervals. The response was measured 1 min after the inhalation and two reproducible FEV₁ values were required (Bodyscreen II, Erich Jaeger GmbH & Co. KG, Wurzburg, FRG). The percentage change from the post-saline values of the

Table 1. The baseline studies and the results of histamine inhalation provocations

				Histamine PD ₁₅ (μmol)	
	RAST score to birch pollen	Number of positive prick tests	IgE (kU/l)	Winter	Spring (pollen season)
Non-birch pollen allergic subjects					
1	0	1	85	3.61	2.87
2	0	4	125	0.88	0.22
3	0	6	30	2.06	2.28
4	0	5	125	1.53	2.77
5	0	6	300	1.30	1.00
6	0	2	210	0.07	0.07
7	0	4	2700	1.81	1.59
8	1	7	370	0.16	0.34
9	1	2	1050	3.85	1.44
10	0	3	50	0.82	0.91
Mean	0.2	4	504	1.0*	0.9*
s.e.m.	±0.1	±1	±262	±0.4	±0.3
Birch pollen allergic subjects					
11	2	9	290	1.64	1.64
12	4	9	200	4.00	4.00
13	3	5	195	2.68	2.13
14	4	11	115	0.20	1.64
15	4	7	260	2.60	0.91
16	4	7	475	4.00	2.96
17	4	8	180	1.24	0.20
18	4	8	250	2.85	0.92
Mean	3.6	8	246	1.3*	1.1*
s.e.m.	±0.2	±0.6	±38	±0.5	±0.4

* Geometric mean.

Table 2. Results and climatic conditions of outdoor exercise tests in winter and spring

	Winter				Spring				
	Temperature (°C)	Water content (g/m ³)	Initial FEV ₁ (litre)	Change in the FEV ₁ (%)	Temperature (°C)	Water content (g/m ³)	Initial FEV ₁ (litre)	Change in the FEV ₁ (%)	Birch pollen (grains/m ³)
Non birch pollen allergic subjects									
1	-7	2.3	3.3	12	17	11.3	3.0	10	79
2	-20	0.8	4.7	15	8	6.0	4.5	29	0
3	-18	0.7	4.9	35	14	5.3	4.7	11	237
4	-4	3.6	4.7	13	5	3.2	4.6	13	7331
5	-6	2.9	5.1	50	17	11.3	5.0	14	79
6	3	5.7	3.8	45	14	9.3	3.7	35	1201
7	-8	2.0	5.4	21	14	5.3	5.0	20	253
8	5	4.7	4.0	70	11	4.4	4.4	54	1059
9	5	5.7	3.2	16	12	8.4	3.3	12	3555
10	4	3.6	3.7	37	16	6.3	3.8	15	16
Mean	-4.6	3.2	4.3	31	13	7.1	4.2	22	1381
s.e.m.	±2.9	±0.6	±0.3	±6	±1	±0.9	±0.2	±4	±745
Birch pollen allergic subjects									
11	0	4.8	4.3	16	6	5.5	4.2	21	0
12	2	3.7	4.1	10	11	5.6	4.2	14	1738
13	-18	0.7	3.9	27	14	5.3	3.9	11	237
14	5	5.9	3.8	16	14	9.4	3.9	49	2180
15	-8	2.0	4.6	10	14	5.2	4.7	34	253
16	4	3.6	5.2	10	16	6.3	5.0	12	16
17	5	3.8	4.7	34	13	9.7	4.7	58	158
18	-4	3.5	4.9	16	12	10.5	5.1	20	174
Mean	-1.9	3.5	4.4	17	13	7.2	4.5	27.4	595
s.e.m.	±2.9	±0.5	±0.2	±3	±1	±0.8	±0.2	±6	±302

FEV₁ was calculated as a function of the administered dose of histamine on a cumulative log dose scale. The result was obtained by linear interpolation from this cumulative dose-response curve as the provocation dose of histamine producing a 15% fall in FEV₁ (PD₁₅ FEV₁) [8]. No PD₁₅ FEV₁ value exceeding 4 µmol was given.

Aero-allergens were sampled with a Hirst-Burkard collector, and pollen counts were analysed at the Department of Botany, University of Helsinki. The sampling site was situated in the wooded terrain similar to the area of the outdoor exercise test, 900 m from the exercise track. The water content of the air (g/m³) was calculated from standard tables [9] on the basis of the relative humidity and the temperature of the air.

Statistical analysis

The analysis of variance for a repeated measures design with one between-subjects (allergic and non-allergic

subjects) and one within-subjects factor (exercise or histamine tests during winter and spring) was used (BMDP2V, [10]). The results were expressed as mean ± s.e.m. and a *P* value of ≤0.05 was regarded as significant. In the absence of interactions between the group and the test, the ANOVA gave the significance of the differences between the groups directly. In this case, the Newman-Keuls test was used to establish the significance of differences between the tests [11]. If the interaction between the group and the test was significant, the significance of differences between the tests was tested separately for the allergic and non-allergic group with the Newman-Keuls test.

Results

Eight of the 18 subjects were RAST-positive to birch pollen; they also had a positive skin-prick test for birch pollen. In ten RAST-negative individuals the skin tests

for birch pollen were negative. The eight allergic subjects also had more positive skin-prick tests against other inhaled allergens ($P < 0.001$, ANOVA). All subjects were treated with sympathomimetic aerosols. In addition, one birch pollen allergic subject used steroid inhalations and Theophylline, one non-allergic subject used sodium cromoglycate and another non-allergic subject Theophylline. The baseline FEV₁ values from predicted were $87 \pm 3\%$ in the non-allergic group and $91 \pm 4\%$ in the allergic group, the difference was not significant. Table 1 shows the results of the baseline studies including the individual RAST scores. Serum IgE concentrations did not differ significantly between the allergic and non-allergic groups ($P > 0.10$, ANOVA).

Table 2 shows the mean daily birch pollen levels during the exercise days, and the temperature and water content of the inspired air during the outdoor exercise tests. The initial forced vital capacity (FVC) and FEV₁ remained unchanged during seasonal experiments in both groups (P for group = 0.49, P for exercise test = 0.55, and P for interaction = 0.26, ANOVA).

When all 18 subjects were analysed together, there was no significant correlation between the change in the post-exercise FEV₁ fall, in the two seasons, and between the

change in the temperature or water content of the inspired air during the outdoor running tests (Table 2). The 18 subjects' post-exercise fall in the FEV₁ averaged $25 \pm 3\%$ in the winter and $24 \pm 4\%$ in the spring (P for exercise test = 0.97, ANOVA).

The changes in FEV₁ after exercise in allergic and non-allergic subjects to birch are presented separately in Fig. 1. The average of the winter and pollen season post-exercise fall of the ventilatory function was equal in the allergic and non-allergic subjects ($22 \pm 4\%$ and $26 \pm 4\%$, respectively, P for group = 0.53, ANOVA). In the allergic group, all but one subject had a greater fall in FEV₁ during the pollen season ($27 \pm 6\%$) than in the winter ($17 \pm 3\%$, $P > 0.10$, Newman-Keuls), even though the inspired air was more humid and warmer in the spring (Table 2). The non-allergic group had the opposite result ($31 \pm 6\%$ in the winter and $22 \pm 4\%$ in the spring, $P < 0.05$, Newman-Keuls). Only one non-allergic subject had an aggravated EIA-response in the spring. When the seasonal change in the post-exercise FEV₁ fall in the allergic group was compared with the respective change in the non-allergic group, the difference was significant (P for interaction between the groups and the exercise tests = 0.01, ANOVA). In the allergic group, there was no correlation between the aggravated EIA-responses in the spring and the air birch pollen counts on the exercise days.

During all exercise tests the subjects managed to maintain a heart rate in the range of $85 \pm 0.5\%$ of the previously measured individual maximal heart rate. None of the subjects had a late reaction after the exercise test in the winter or in the spring.

The basal airways reactivity measured by the histamine inhalation tests did not change significantly from the winter to the spring pollen season in either of the groups, although in birch pollen allergic asthmatics there was a tendency to greater responsiveness to inhaled histamine in the pollen season (P for group = 0.25, P for histamine challenge = 0.08, and P for interaction = 0.48, ANOVA, Table 1).

Discussion

The present study shows that asthmatic subjects who are allergic to birch pollen have aggravated EIA-responses during the pollen season when compared with the response of non-birch pollen allergic asthmatic individuals. The increased responsiveness of pollen allergic asthmatics to exercise is not due to changes in airway calibre, as the initial lung volumes (FVC, FEV₁) remained unchanged. The response to outdoor exercise in non-allergic asthmatics was as expected on the basis of laboratory studies: EIA attenuates in the warmer and more humid spring weather compared with the cold and dry winter weather.

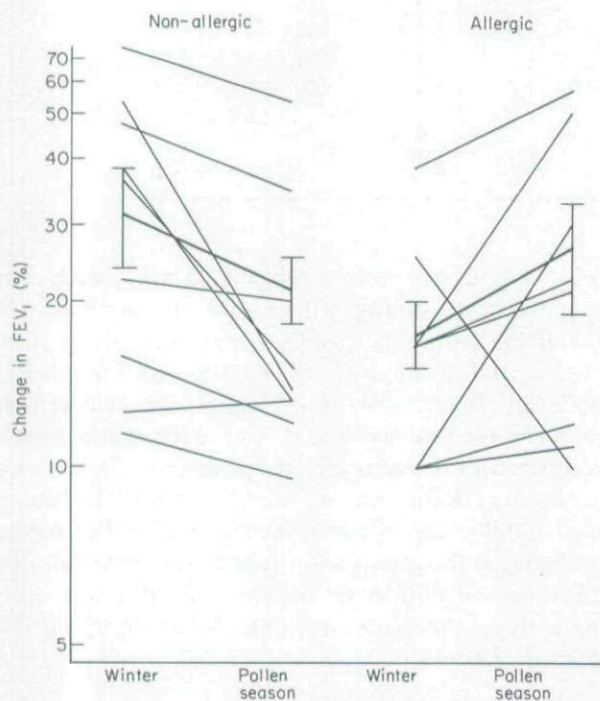


Fig. 1. Maximal post-exercise FEV₁ falls after an outdoor exercise test in the winter and spring (the birch pollen season) in ten non-allergic asthmatics (RAST 0–1 to birch pollen) and in eight allergic subjects (RAST 2–4). Thick lines represent mean $\pm$ s.e.m.

It has been suggested [5] that the variability of EIA may well be due to variations in the intrinsic bronchial reactivity resulting from the allergenic stimulation. Our results support this suggestion. Earlier studies have demonstrated an increased reactivity to histamine [12] and metacholine [13] after allergen challenge and an increase in the severity of EIA during the week following an antigen challenge [14]. In the present study the increase in the bronchial responsiveness to histamine in the pollen season remained insignificant in the allergic subjects. The changes in the bronchial epithelium induced by the allergen exposition during the spring may not affect the histamine permeability and thus, does not change the histamine responsiveness [15]. Our results are in agreement with the study of Mussaffi *et al.* [14], who found that allergen challenge increased bronchial responsiveness more to exercise than to histamine. They actually found the increment of histamine responsiveness only in those asthmatics who also had a late reaction after antigen challenge. We did not perform allergen challenge in the laboratory to our subjects in order to verify the possible late reaction after allergen exposure. However, the fact that the baseline pulmonary function tests also remained unchanged in the birch pollen allergic asthmatics during pollen season, suggests that there are no significant late reactions in these subjects. The pathophysiology of histamine-induced asthma and exercise-induced asthma is obviously different. Exercise-induced bronchoconstriction is inhibited by prophylactic sodium cromoglycate and it is followed by a refractory period, however, sodium cromoglycate does not inhibit histamine-induced bronchoconstriction, which is not followed by a refractory period [16,17].

Pollinosis due to birch pollen is common in Northern Europe, and is the main cause of allergic symptoms in the spring in Finland. Birch pollen counts in the air may reach very high levels, $>10\,000/\text{m}^3$. It seems that the altered basic airways reactivity in allergic asthmatics resulting from the natural allergenic stimulation in the proceeding weeks was the major factor explaining the seasonal variability of EIA (i.e. the variability which is not explained on the basis of the changes in temperature and water content of the inspired air), while the direct effect of pollen antigens inhaled during the exercise test was probably insignificant. The worsening of EIA in the spring did not correlate with the actual pollen counts during the exercise test day, however, because of the small number of allergic subjects, definitive conclusions cannot be drawn. It is generally believed, that there is no substantial penetration of pollen-sized (e.i. $15\text{ }\mu\text{m}$) aerosols beyond the airway carina. Thus, birch pollen grains measuring $25\text{--}30\text{ }\mu\text{m}$ would be captured by the upper airways [18,19].

There are numerous arguments in favour of the theory that EIA, like antigen-induced asthma, is triggered by the liberation of mediators by inflammatory cells [20]. The stimulus for this may be water-loss and/or a cooling of the airways. This response is greatly modified by the antigenic stimulus, leading to variations in the intrinsic bronchial reactivity.

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