

# Exercise-Induced Bronchoconstriction

Seasonal Variation in Children with Asthma and in Those with Rhinitis

J. M. HENRIKSEN

Pediatric Department, University Hospital, Aarhus, Denmark

Standardized exercise challenge tests, symptom scores and whole-blood eosinophil and basophil counts were made before and during the pollen season in 32 children suffering from hay fever ( $n = 16$ ) or hay fever and asthma ( $n = 16$ ). All participants developed rhinitis symptoms during the season. The hay fever group showed in addition a significant seasonal increase in cough score (but in no other asthma symptom) and in circulating eosinophils ( $P < 0.01$ ); mean exercise-induced bronchoconstriction (EIB) did not change despite a slight increase in a few subjects. The asthma group showed seasonal increases in EIB ( $P < 0.001$ ), asthma symptom score ( $P < 0.002$ ), and total eosinophil count ( $P < 0.001$ ). The increase in the latter was significantly higher ( $P < 0.05$ ) than that in the hay fever group. The relative basophil count remained unchanged in both groups. In conclusion, the hay fever group and the asthma group could be clearly distinguished with respect to EIB during natural pollen exposure. The significantly higher increases in EIB and circulating eosinophils observed in the asthma group might possibly be due to greater pollen antigen sensitivity in the asthmatics.

*Key words:* basophils; bronchial asthma; children; eosinophils; exercise-induced; hay fever; seasonal variation.

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Airway hyperreactivity, which seems to be a fundamental feature of bronchial asthma, can be detected by physical exercise (3, 20) and by exposure to a wide spectrum of pharmacological and chemical agents (6), including histamine and methacholine.

Bronchial responsiveness to histamine is reported to be repeatable and reproducible (21, 22). On the other hand, there is evidence of increased bronchial reactivity to both histamine and methacholine after episodes of allergen-induced asthmatic responses (7, 8) and during natural pollen exposure (1, 5). These results make it reasonable to suggest a seasonal increase in exercise-induced bronchoconstriction (EIB) in pollen-sensitive asthmatics. The available data on this area (9, 25, 35) are sparse and conflicting. If sensitized asthmatics develop more EIB during the pollen season, what about hay fever subjects? Studies (31) have failed to

produce significant EIB in atopic rhinitis subjects. However, evidence of increased non-specific bronchial responsiveness in subjects with hay fever (13, 38), and the fact that it was difficult to distinguish between asthma and hay fever subjects on the basis of the bronchial response to inhaled pollen antigen (2, 11), indicate that airway hyperreactivity may be present in rhinitis subjects. Increased EIB in hay fever patients during the pollen season seems therefore to be a possibility which has not been evaluated previously.

The aim of the present investigation was to study the potential of seasonal variation of EIB in children with asthma and in those with rhinitis. For this purpose, the bronchial response to exercise challenge was evaluated in pollen-sensitive children before and during the pollen season. Additionally, whole-blood eosinophil and basophil counts were made simultaneously.

## MATERIAL AND METHODS

*Subjects*

Thirty-two children with a history of allergic rhinitis (16 subjects) or allergic rhinitis and asthma (16 subjects) during the pollen season were selected for the study. Informed consents were obtained. Subject characteristics are shown in Table 1. The diagnosis of pollen hypersensitivity was confirmed by history, a positive ( $\geq$  positive control = histamine chloride 1 mg/ml) skin prick test with 12 common allergens (allergen concentration: 1 HEP (Histamine Equivalent Prick), ALK, Copenhagen, Denmark) and a positive (class 3 or 4) RAST test. These criteria were considered as sufficient. Allergen challenge tests had only been performed in those children receiving immunotherapy.

All subjects were sensitive to grass and/or birch pollen. In addition, six asthmatic subjects were sensitive to animal dander and one to house dust mite. The rhinitis group showed no

other responses than to pollen. Nine subjects (6 rhinitis and 3 asthmatic subjects) had received immunotherapy for more than 1 year. Two asthmatics had received immunotherapy until 2 years before the study.

Presence or absence of EIB was not a selection criterion for the study. None of the hay fever subjects had previously complained of wheeze or asthma related symptoms. The medical treatment is given in Table 1. Corticosteroids had not been used the last 6 months, except in one subject who had used steroid aerosol intranasally until 1 week before the study. Four received antihistamines. All medication was withheld at least 16 h before exercise challenge.

*Study design*

The trial was carried out in January - July 1980-83. At least 1 month before the pollen season, which is in the middle of May for birch and in June for grass, the children were asked to record their daily asthma and hay fever symptoms. After 1-2 weeks they attended the clinic and performed a standardized exercise test. Immediately before exercise a blood sample was taken for analysis of circulating eosinophils and basophils. The same procedure (symptom recording for 1 week, exercise challenge, eosinophil and basophil counting) was repeated during the pollen season, i.e. 2-3 weeks after their hay fever and asthma symptoms had started.

*Diary recording*

The children and their parents recorded in a diary card the severity of asthma symptoms (dyspnoea, cough and wheeze) and hay fever symptoms (itching, sneezing, stuffy nose and runny nose/eyes). Symptoms were graded none (0), mild (1), moderate (2) or severe (3) giving a maximal weekly asthma score of 63 and rhinitis score of 84.

Pollen counts were analysed at the same time as the individual symptom recordings and expressed as the total weekly count per cubic meter air. The pollen grains were sampled daily by a Burkard volumetric pollen trap (37).

Table 1  
Subject characteristics

|                              | Asthma    | Rhinitis  |
|------------------------------|-----------|-----------|
| Boys/Girls, <i>n</i>         | 12/4      | 11/5      |
| Age, mean years              | 11        | 11        |
| (range)                      | (8-15)    | (8-16)    |
| IgE, mean                    | 455       | 249       |
| (range)                      | (73-1454) | 59-836)   |
| Height, mean cm              | 149       | 148       |
| $\pm$ SD                     | $\pm 9$   | $\pm 11$  |
| Weight, mean kg              | 39        | 39        |
| $\pm$ SD                     | $\pm 8$   | $\pm 10$  |
| Symptoms duration, mean year | 6         | 4         |
| $\pm$ SD                     | $\pm 2$   | $\pm 2$   |
| Allergen, subjects Nos.      |           |           |
| grass                        | 15        | 15        |
| birch                        | 1         | 3         |
| cat/dog                      | 4/3       | 0         |
| mite                         | 1         | 0         |
| Immunotherapy, number        | 3         | 6         |
| Treatment, subject Nos.      |           |           |
| SCG                          | 10        | 9 (nasal) |
| beta <sub>2</sub> -agonist   | 9         | 0         |
| antihistamine                | 2         | 2         |
| none                         | 1         | 5         |

SCG = Sodiumcromoglycate.

### Cell counts

Eosinophil and basophil counts were made on anticoagulated blood samples taken without stasis from a cubital vein immediately before exercise. The blood was stained with toluidine blue and light green and counted according to the method of Kimura et al. (23). This method permits also a count of the total white blood cells (WBC) which stain in a pale greyish-blue colour. All counts (Fuchs-Rosenthal counting chamber) were performed in duplicate and the mean of two counts was used for analysis. By this method the coefficient of variation for eosinophil, basophil and WBC counts was 6%, 14% and 4%, respectively.

### Exercise challenge

The exercise tests were performed on a treadmill (Quinton Instruments, Seattle, WA) and consisted of 5 to 6 min of continuous running with a constant work load adjusted individually to between 80% and 85% of the maximal working capacity. Heart rate was registered by radio-telemetry (Danica, Copenhagen, Denmark) during exercise. To eliminate the possible effect of impaired nasal air flow on EIA during the pollen season (12, 32) the children were provided with a nose clip during the exercise tasks.

Pulmonary function was evaluated by peak flow and spirometry performed immediately before exercise (baseline), at 2, 4 and 6 min of exercise (only peak flow), and 3, 5, 10 and 20 min after exercise. Peak expiratory flow (PEF) was measured by Wright's peak flow meter (Airmed Ltd., Harlow, UK). Forced expiratory flow in 1 s ( $FEV_1$ ), forced vital capacity (FVC) and forced expiratory flow in the middle half of FVC ( $FEF_{25-75}$ ) were calculated from spirometry obtained with a waterless spirometer (Vitalograph, Buckingham, UK). The best of three blowings was used for calculation. All the pulmonary data were transformed to percent predicted normal values (18, 19).

The pulmonary responses to exercise were expressed as the maximal *percentage fall from baseline* (baseline value - the lowest recorded value postexercise/ baseline value times 100%).

### Statistics

The respiratory data were analysed by *t* tests for paired comparisons. As the distribution of symptom scores, cell counts and IgE was skewed, these data were described by their median (geometric mean) and interquartile range (IQR) and analysed by non-parametric statistics (33). Correlations between variables were performed using Spearman's test. The 5% level, two-tailed, was considered as significant.

### RESULTS

As shown in Table 1, the two groups were comparable except in duration of symptoms ( $P < 0.01$ ), animal dander hypersensitivity, and use of  $\beta_2$ -agonists.

#### Symptom scores

Both groups showed highly significant ( $P < 0.002$ ) increases in total symptom scores, rhinitis symptom scores, and pollen counts (Table 2). There were no between group differences. Asthma scores increased in both the asthma group ( $P < 0.002$ ) and the rhinitis group ( $P < 0.02$ ) during the season. However, the only asthma symptom experienced by the rhinitis subjects ( $n = 11$ ) was cough. Five asthmatic subjects showed a very slight ( $< 10$ ) increase in the weekly asthma score. Judged by the pre-seasonal symptom scores and EIB the subjects in the asthma group were considered as mild asthmatics.

#### Pulmonary function

Table 3 displays the mean  $\pm$  SD values for PEF,  $FEV_1$ , FVC and  $FEF_{25-75}$  measured immediately before exercise. Between group comparisons showed that the asthma group had significantly lower  $FEV_1$  and  $FEF_{25-75}$  before the season. This difference had increased further during the season. Within group analysis showed a significant seasonal decrease in  $FEV_1$  and  $FEF_{25-75}$  in the asthmatics. No statistically significant changes in lung function were observed in the rhinitis group.

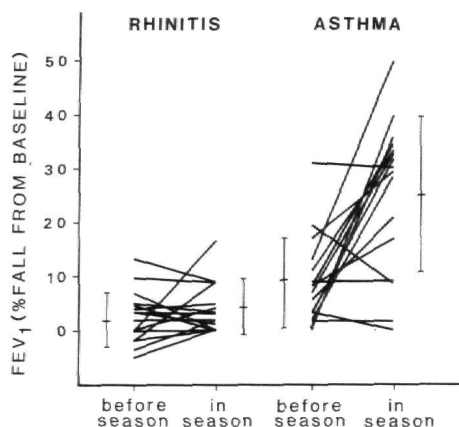


Fig. 1. The individual maximal percentage fall in  $FEV_1$  after treadmill exercise challenge before and during the pollen season, respectively. Results from 16 children with rhinitis and 16 children with asthma and rhinitis. Means  $\pm 1$  SD are shown.

### Exercise challenge

The individual exercise-induced changes in  $FEV_1$ , expressed as the maximal percentage fall from baseline, are given in the figure. Before the season, the mean ( $\pm$  SD) percentage falls in  $FEV_1$  in the rhinitis and in the asthma group were  $2 \pm 5\%$  and  $9 \pm 8\%$  ( $P < 0.02$ ), respectively. Only three subjects from the asthma group and none from the rhinitis group, had an EIB of more than 15%, before the season. During the pollen season, the asthma group showed a highly significant increase ( $P < 0.001$ ) in EIB. There was no significant increase in the rhinitis group. On an individual basis, five of 16 asthmatic subjects showed no increase in EIB during the season. Three of these five showed no increase in asthma symptom scores. One rhinitis subject increased in EIB from 0% to 17% during the season, whereas the rest had EIB  $< 10\%$ .

Based on group data, the exercise-induced changes in PEF and  $FEF_{25-75}$  were comparable

Table 2

Weekly symptom scores and pollen counts before and during the pollen season. Geometric means and IQR

|                                | Asthma score  |               | Rhinitis score |               | Total score   |               | Pollen counts |                  |
|--------------------------------|---------------|---------------|----------------|---------------|---------------|---------------|---------------|------------------|
|                                | Before season | In season     | Before season  | In season     | Before season | In season     | Before season | In season        |
| Asthma group<br>( $n = 16$ )   | 5<br>(2-7)    | 18<br>(14-29) | 6<br>(0-13)    | 31<br>(20-43) | 9<br>(6-16)   | 52<br>(42-60) | 0<br>(0-4)    | 230<br>(215-270) |
| Rhinitis group<br>( $n = 16$ ) | 0<br>(0-1)    | 6<br>(5-7)    | 6<br>(3-14)    | 40<br>(34-48) | 6<br>(3-15)   | 44<br>(38-51) | 0<br>(0-0)    | 225<br>(135-255) |

Table 3

Pulmonary function at rest. Mean  $\pm$  SD

|                          | PEF                         |                | $FEV_1$        |                  | FVC            |                 | $FEF_{25-75}$  |                  |
|--------------------------|-----------------------------|----------------|----------------|------------------|----------------|-----------------|----------------|------------------|
|                          | Before season               | In season      | Before season  | In season        | Before season  | In season       | Before season  | In season        |
| Asthma<br>( $n = 16$ )   | 86 <sup>§</sup><br>$\pm 14$ | 80<br>$\pm 13$ | 89<br>$\pm 11$ | 79**<br>$\pm 13$ | 99<br>$\pm 9$  | 94<br>$\pm 11$  | 76<br>$\pm 24$ | 57**<br>$\pm 25$ |
| Rhinitis<br>( $n = 16$ ) | 95<br>$\pm 7$               | 95<br>$\pm 13$ | 99<br>$\pm 10$ | 99<br>$\pm 12$   | 100<br>$\pm 9$ | 100<br>$\pm 10$ | 97<br>$\pm 19$ | 93<br>$\pm 23$   |
| P-value                  | NS                          | $< 0.02$       | $< 0.02$       | $< 0.002$        | NS             | NS              | $< 0.001$      | $< 0.001$        |

Abbreviations: see text. \*\*  $P < 0.01$  (paired *t*-tests. P-value: from between group comparisons (unpaired *t*-tests). <sup>§</sup> % predicted.

to those seen in FEV<sub>1</sub>. However, three rhinitis subjects had a 31%, 39% and 28% fall in FEF<sub>25-75</sub> during the season compared to -16%, 4% and 17%, respectively, before the season.

As mentioned above, baseline FEV<sub>1</sub> in the asthma group decreased significantly during the season. To evaluate a possible relationship between baseline airway function and EIB, the seasonal increase (in those with a significant increase) in EIB was compared between children with a small (< 5%) and a marked (> 10%) seasonal decrease in baseline FEV<sub>1</sub>. The results in the former group were ( $n = 6$ ; baseline (mean  $\pm$  SD):  $84 \pm 6\%$  to  $80 \pm 7\%$ ; EIB:  $7 \pm 5\%$  to  $31 \pm 12\%$ ) compared with the latter group ( $n = 5$ ; baseline:  $93 \pm 11\%$  to  $72 \pm 13\%$ ; EIB:  $7 \pm 6\%$  to  $33 \pm 4\%$ ).

Final heart rate (mean  $\pm$  SD) during exercise before and during the season, respectively, was  $177 \pm 8$  and  $175 \pm 8$  beats/min in the asthma group and  $180 \pm 7$  and  $181 \pm 8$  beats/min in the rhinitis group. The absolute humidity (gram water per kg dry air) in the laboratory was significantly higher during the season ( $8.7 \pm 1.9$  g versus  $10.7 \pm 1.4$  g in the asthma group ( $P < 0.01$ ) and  $9.7 \pm 1.3$  g versus  $10.9 \pm 1.9$  in the rhinitis group ( $P < 0.02$ )).

#### Cell counts

The median and IQR for circulating eosinophils, basophils and total WBC before and during the season are shown in Table 4. The table also gives the cell counts from 23 non-allergic

non-asthmatic children. The eosinophil count increased significantly in both study groups during the season, but the increase in eosinophils was significantly higher in the asthma group. The absolute basophil count increased in the asthma group during the season, but the median (IQR) basophil count expressed as percentage total WBC was 0.7 (0.4-0.9) % before and 0.7 (0.6-1.1) % during the pollen season (NS).

#### Correlations

The degree of EIB before the season did not correlate with the asthma symptom scores. However, the seasonal increases in these two parameters correlated positively ( $r_s = 0.60$ ,  $P < 0.02$ ). No interrelationship could be detected between the eosinophil count and EIB or between eosinophils and symptom scores.

#### DISCUSSION

In the present study, EIB and whole-blood eosinophils and basophils were evaluated before and during the pollen season in two groups of allergic children, one with hay fever and one with hay fever-associated asthma. The main results were: 1) a highly significant seasonal increase in EIB in the asthma group, 2) no seasonal change in EIB in the hay fever group, 3) a seasonal increase in circulating eosinophils (both groups but asthma group > hay fever group), and 4) a significant seasonal increase in

Table 4

Circulating eosinophils, basophils and total WBC before and during the pollen season. Median and IQR ( $\times 10^9/l$ )

|              | Eosinophils   |           | Basophils     |           | WBC           |             |
|--------------|---------------|-----------|---------------|-----------|---------------|-------------|
|              | Before season | In season | Before season | In season | Before season | In season   |
| Rhinitis     | 246           | 532**     | 28            | 31        | 6190          | 6560        |
| ( $n = 16$ ) | (180-343)     | (288-676) | (22-43)       | (21-47)   | (4430-7360)   | (5240-7240) |
| Asthma       | 286           | 730**     | 38            | 47*       | 5910          | 6420        |
| ( $n = 16$ ) | (214-377)     | (499-937) | (25-45)       | (36-69)   | (4630-7430)   | (4960-7750) |
| P-value      | NS            | < 0.05    | NS            | < 0.05    | NS            | NS          |
| Controls     |               | 136       |               | 34        |               | 5160        |
| ( $n = 23$ ) |               | (99-242)  |               | (22-47)   |               | (4420-6360) |

\*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$  (Wilcoxon matched-pairs signed-ranks test). P-values (Mann-Whitney U test).

the absolute basophil count (asthma group) but not in the relative basophil count (both groups). The results suggest greater allergic responsiveness and thereby (?) heightened bronchial responsiveness in the asthma group.

The diagnosis pollen allergy was not confirmed by challenge tests in this study, except in those children who had received immunotherapy. It can therefore not be stated with certainty that the allergic symptoms in fact had been caused by pollen antigens in all subjects or that all subjects were pollen allergic. However, the increase in symptom scores, circulating eosinophils, and pollen counts at the same time, together with the demonstration of a positive correlation between the increase in asthma symptom score and EIB, strongly suggest a direct relationship between pollen exposure, pollen allergic symptoms, and increased EIB. Moreover, I find it unlikely that the increase in EIB might have been caused by other environmental conditions. The treadmill work load was similar on the two exercise challenges and there is good evidence (10, 14, 15) that the mean EIB in a group of asthmatics remains unchanged, even during long periods (15, 34), if the exercise stress is reproduced. The absolute humidity in the laboratory was significantly higher during the season, but that is in favour of *less* EIB (4, 36). Finally, the present results confirm the seasonal increase in EIB reported by Eggleston (9).

It might be argued that the seasonal increase in EIB was a result of the decrease in baseline airway function (Table 3). The finding that baseline FEV<sub>1</sub> decreased during the season in the asthma group, but remained unchanged in the hay fever group which did not increase in EIB, seems to support this view. However, the fact that two events (decreased baseline, increased EIB) occur at the same time does not prove a direct interrelationship between them. Furthermore, considerable evidence argues against such a relationship. First of all, evidence of a direct relationship between baseline airway level and EIB expressed as percentage fall from baseline has never been documented. On the contrary, several studies (10, 15, 34) have failed to show it, and the finding of large differences in non-specific

bronchial responsiveness in the same subjects when baseline airway levels were similar (30) seems to argue against it indirectly. Moreover, the present results showed that the increase in EIB(PEF) was equal to that in EIB(FEV<sub>1</sub>) although the seasonal decrease in baseline PEF was small and insignificant and no difference in the seasonal increase in EIB could be found between children with a negligible and children with a marked seasonal decrease in baseline FEV<sub>1</sub>. Thus, it seems that bronchial *calibre* and bronchial *reactivity* are two independent features which may or may not be changing at the same time in asthmatic subjects.

Few studies have been designed to evaluate EIB in subjects with hay fever. Abnormal pulmonary responses to exercise have been demonstrated in about 40% (20, 26), but the responses in these studies were expressed as lability index, which takes into account both the increase in lung function during exercise and the decrease in lung function after exercise (% rise + % decrease). Analysis of their data show that several of their patients were characterised by abnormal bronchodilatation during exercise rather than by bronchoconstriction after exercise. The present finding of EIB < 15% in all the hay fever patients at the pre-season challenge, together with the results from Scofield et al. (31), who were unable to distinguish EIB (% fall) in hay fever patients from that in normal controls, suggest that the incidence of significant (> 15%) EIB is quite low in individuals with hay fever. On the other hand, the present study also showed that EIB may increase in a few hay fever subjects following heightened antigen exposure. This finding is in agreement with the observation (38) of some overlap between hay fever and asthma subjects in their response to non-allergic stimuli. Furthermore, pollen challenge has been shown to induce bronchoconstriction in subjects with hay fever (11). The question is whether it is the same fraction of hay fever patients who react to non-specific as well as specific stimuli and whether it is this fraction who will develop asthma later in life.

The total eosinophil count reflects disease activity in both atopic (27) and non-atopic (17)

asthmatic individuals and has been shown to increase during the pollen season in subjects with hay fever (39). In the present study, the eosinophil count was significantly elevated during the pollen season in both the rhinitis and the asthma group, indicating a higher antigen load. Moreover, the asthma group produced a significantly higher eosinophil response than did the hay fever group. This finding might be explained by 1) the asthmatics had been exposed to higher pollen levels. The pollen counts gave no evidence of that, but the possibility can not be excluded as there may have been great variations in the local pollen concentrations. 2) The asthmatics react with a greater mucosa surface and therefore produce a more intense allergic response, and/or 3) the asthmatics are more sensitive to pollen antigen. The finding that hay fever subjects required eight times more pollen antigen than did asthmatic subjects before a 20% fall in lung function was reached (11) supports this hypothesis.

Few clinical studies have been designed to evaluate the role of circulating basophils in allergic disease. The number has been found to elevate prior to an episode of asthma (24) and in hay fever patients during the pollen season (16). The present study can not confirm these observations, although there was a significant increase in the absolute basophil count in the asthma group. The relative basophil count (= number basophils/total WBC), which I think is more important in this context, was completely unchanged. The hay fever group showed no change in either the absolute or the relative basophil count. Based on these results, it appears that circulating basophils are changing passively with total WBC in contrast to circulating eosinophils which seem to be a specific answer on allergic activity.

The interrelationship between allergic rhinitis and asthma is incompletely understood, and it is largely unknown why some develop rhinitis, others asthma, and others again both asthma and rhinitis. A survey in Danish general practice (28) showed no general trend: among patients with both asthma and rhinitis, 40% developed rhinitis first, 35% asthma first, while 25% developed both within the same year. The

present study showed some overlap between asthma and hay fever patients with respect to EIB. If the hay fever patients with EIB are those who will develop asthma later on, the result of exercise challenge may be of prognostic value. Prospective, longitudinal studies are needed to investigate this.

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## Address

Jørn M. Henriksen, M.D.  
 Dr. Margrethesvej 6  
 8200 Aarhus N  
 Denmark

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