

# The occurrence of late asthmatic response to exercise after allergen challenge

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**Background:** The determinants of late asthmatic responses to exercise remain unknown. It has been reported that they may develop in some adult subjects with asthma following a late asthmatic response to allergen.

**Objective:** We intended to corroborate this finding in children with asthma and to investigate which aspect of airway responses to allergen is associated with late asthmatic responses to exercise.

**Methods:** We studied 17 children with allergic asthma, who showed late asthmatic responses to inhaled allergen (*Dermatophagoides pteronyssinus*). Each underwent an exercise challenge test two days before (pre-allergen) and two days after (postallergen) an allergen inhalation challenge. FEV<sub>1</sub> was measured at regular intervals up to ten hours after each challenge. Methacholine PC<sub>20</sub> was measured before the allergen challenge and before the postallergen exercise challenge.

**Results:** After the pre-allergen exercise test, all the subjects showed isolated early asthmatic responses. After the postallergen exercise test, seven showed dual responses (early and late asthmatic responses) (group I) and the remaining ten showed isolated early asthmatic responses (group II). Bronchial responses to pre-allergen exercise or inhaled allergen and the severity of early asthmatic responses to postallergen exercise were similar in groups I and II. Neither before allergen inhalation nor before the postallergen exercise was methacholine PC<sub>20</sub> different between the two groups. Methacholine dose shift caused by allergen challenge, however, was significantly greater in group I than in group II ( $-2.00 \pm 0.39$  versus  $-1.36 \pm 0.53$  doubling doses;  $P < .05$ ). There was significant correlation between the dose shift and the magnitude of late response to the postallergen exercise in the whole group ( $r = 0.51$ ,  $P < .05$ ).

**Conclusion:** Late asthmatic responses to exercise may develop in some children with asthma following a late asthmatic response to allergen. This phenomenon was related neither to the baseline nor to postallergen methacholine PC<sub>20</sub> but to the extent of increased sensitivity to methacholine caused by allergen challenge.

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## INTRODUCTION

It is well established that when patients with atopic asthma are exposed to specific antigens, the immediate obstructive response that develops can be followed by a secondary wave of bronchoconstriction three to ten hours lat-

er.<sup>1,2</sup> When this response exceeds a predetermined value, ie, a fall in FEV<sub>1</sub> (forced expiratory volume in one second) of more than 20% of baseline, it is called a late asthmatic response.<sup>3</sup>

Exercise may also produce phasic changes in lung function. Several studies have shown that a late asthmatic response may occur after strenuous exercise,<sup>4,5</sup> although the prevalence of this seems to be somewhat lower than allergen-induced late asthmatic response.<sup>4,6</sup> It has been reported that the response pattern is very similar to the pattern observed after exposure to an allergen, and the release of mediators

has been shown to be the same during a late asthmatic response to exercise<sup>7</sup> as in allergen-induced asthma. Although data on the clinical significance or consequences of exercise-induced late asthmatic responses are tenuous, it has been reported to prolong asthmatic symptoms<sup>8</sup> and to increase airway responses to other stimuli such as allergens,<sup>9</sup> especially in children.

The determinants of a late asthmatic response to exercise remain unknown. Zawadzki et al<sup>10</sup> have reported that the late bronchoconstriction induced by exercise may occur as a manifestation of diurnal fluctuations in expiratory flow. We<sup>9</sup> have observed, however, that many subjects with little or no spontaneous fall in expiratory flow during the daytime had late asthmatic responses after exercise. Many investigators have attempted to determine whether the baseline level of nonspecific bronchial responsiveness is a predictor of who will develop a late asthmatic response following exercise. Most studies<sup>11,12</sup> however, have been unable to demonstrate any differences, in terms of the baseline level of nonspecific bronchial responsiveness. On the other hand, Crimi et al<sup>13</sup> showed that subjects with late asthmatic responses after exercise had more pronounced airway inflammation, as demonstrated by bronchoalveolar lavage.

Boulet et al<sup>14</sup> have reported that late asthmatic responses to exercise may develop in some adult subjects with asthma following late asthmatic responses to allergen. Since this is associated with an influx of inflammatory cells and the subsequent enhancement of nonspecific bronchial responsiveness,<sup>15</sup> one may assume that these are responsible for the development of a late asthmatic response to exercise.

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Boulet et al<sup>14</sup> noted, however, that the degree of nonspecific bronchial responsiveness after an allergen challenge could not help predict the occurrence of a late asthmatic response to exercise.

Our intention was to determine whether a preceding late asthmatic response to allergen could change the pattern of airway response to exercise and lead to the development of late asthmatic responses in children with asthma. We performed an exercise test two days before (pre-allergen) and two days after (postallergen) an allergen inhalation test. If late asthmatic responses to exercise were to develop,

we intended also to investigate which aspect of airway responses to allergen is associated with such responses. Since the inflammatory process developing after allergen challenge has been considered responsible for changes in nonspecific bronchial responsiveness,<sup>16,17</sup> we hypothesized that in a given subject, the occurrence of a late asthmatic response to exercise might be associated with the degree of increase in nonspecific bronchial responsiveness, rather than with its heightened level. To test this hypothesis, we measured methacholine PC<sub>20</sub> (provocative concentration which caused a 20% fall in FEV<sub>1</sub> from baseline) before

allergen challenge and two days after this, before the postallergen exercise challenge; we then compared the levels of methacholine PC<sub>20</sub> and their changes, between the subjects who developed late asthmatic responses to exercise and those who did not.

## MATERIALS AND METHODS

### Patients

Seventeen children with asthma (ten boys and seven girls), aged 7.4 to 14.8 (mean  $\pm$  SD: 11.1  $\pm$  2.3) years, completed this study (Table 1). All were suffering from atopic asthma and had positive prick test results to house dust

Table 1. Demographic and Bronchoprovocation Data of Subjects Studied

| Subject No. | Sex (M/F) | Age (years) | Pre-Allergen Exercise |                  | Baseline MCH PC <sub>20</sub> ‡ (mg/mL) | Allergen Bronchoprovocation |                  | Post-Allergen MCH PC <sub>20</sub> ‡ (mg/mL) | Post-Allergen Exercise |                  |
|-------------|-----------|-------------|-----------------------|------------------|-----------------------------------------|-----------------------------|------------------|----------------------------------------------|------------------------|------------------|
|             |           |             | Early phase*          | Late phase†      |                                         | Early phase§                | Late phase†      |                                              | Early phase*           | Late phase†      |
|             |           |             | FEV <sub>1</sub>      | FEV <sub>1</sub> |                                         | FEV <sub>1</sub>            | FEV <sub>1</sub> |                                              | FEV <sub>1</sub>       | FEV <sub>1</sub> |
|             |           |             | (%Baseline)           | (%Baseline)      |                                         | (%Baseline)                 | (%Baseline)      |                                              | (%Baseline)            | (%Baseline)      |
| Group I     |           |             |                       |                  |                                         |                             |                  |                                              |                        |                  |
| 1           | M         | 9.3         | 76.7                  | 99.2             | 1.38                                    | 72.9                        | 71.1             | 0.47                                         | 65.3                   | 74.0             |
| 2           | F         | 11.5        | 63.8                  | 93.0             | 2.77                                    | 66.7                        | 58.9             | 0.55                                         | 59.1                   | 68.7             |
| 3           | F         | 11.3        | 68.7                  | 101.4            | 3.16                                    | 74.3                        | 60.4             | 0.77                                         | 60.2                   | 72.2             |
| 4           | M         | 13.5        | 64.2                  | 91.0             | 0.97                                    | 75.1                        | 56.8             | 0.31                                         | 58.4                   | 69.6             |
| 5           | M         | 10.7        | 73.3                  | 95.8             | 2.44                                    | 67.1                        | 64.6             | 0.38                                         | 56.6                   | 73.5             |
| 6           | M         | 14.7        | 67.5                  | 97.7             | 4.66                                    | 66.0                        | 73.8             | 1.32                                         | 69.0                   | 75.3             |
| 7           | M         | 7.9         | 65.6                  | 98.9             | 2.89                                    | 73.5                        | 68.7             | 0.76                                         | 63.6                   | 68.3             |
| Mean        | 5M/       | 11.3        | 68.5                  | 96.7             | 2.34¶                                   | 70.8                        | 64.9             | 0.59¶                                        | 61.7                   | 71.7             |
| SD          | 2F        | 2.3         | 4.8                   | 3.7              | 1.35–4.07#                              | 4.0                         | 6.5              | 0.36–0.95#                                   | 4.4                    | 2.8              |
| Group II    |           |             |                       |                  |                                         |                             |                  |                                              |                        |                  |
| 1           | F         | 7.4         | 66.1                  | 99.4             | 0.85                                    | 74.4                        | 69.2             | 0.36                                         | 52.5                   | 76.4**           |
| 2           | M         | 10.0        | 61.7                  | 95.3             | 2.08                                    | 78.7                        | 72.4             | 0.95                                         | 67.4                   | 84.3             |
| 3           | F         | 13.7        | 52.6                  | 92.5             | 1.23                                    | 70.6                        | 77.0             | 0.67                                         | 56.9                   | 95.5             |
| 4           | F         | 8.3         | 72.9                  | 99.8             | 3.41                                    | 71.3                        | 74.3             | 1.37                                         | 64.9                   | 93.5             |
| 5           | M         | 9.2         | 74.0                  | 100.6            | 0.52                                    | 68.1                        | 54.0             | 0.35                                         | 62.1                   | 88.7             |
| 6           | M         | 9.9         | 75.0                  | 92.8             | 2.03                                    | 77.5                        | 62.6             | 0.54                                         | 61.9                   | 85.8             |
| 7           | M         | 14.8        | 76.2                  | 93.6             | 2.50                                    | 72.6                        | 70.0             | 1.01                                         | 67.1                   | 94.0             |
| 8           | F         | 11.8        | 69.4                  | 94.3             | 1.82                                    | 75.0                        | 67.5             | 0.90                                         | 64.2                   | 94.8             |
| 9           | F         | 12.4        | 79.5                  | 96.5             | 5.43                                    | 76.3                        | 77.8             | 2.30                                         | 71.2                   | 93.0             |
| 10          | M         | 12.9        | 46.4                  | 97.6             | 3.38                                    | 72.7                        | 63.5             | 0.92                                         | 44.3                   | 89.8             |
| Mean        | 5M/       | 11.0        | 67.4                  | 96.2             | 1.91¶                                   | 73.7                        | 68.8             | 0.81¶                                        | 61.3                   | 89.6             |
| SD          | 5F        | 2.4         | 10.8                  | 3.0              | 0.95–3.80#                              | 3.3                         | 7.3              | 0.46–1.45#                                   | 8.0                    | 6.0              |
| Total       |           |             |                       |                  |                                         |                             |                  |                                              |                        |                  |
| Mean        | 10M/      | 11.1        | 67.9                  | 96.4             | 2.09¶                                   | 72.5                        | 67.2             | 0.71¶                                        | 61.5                   | 82.2             |
| SD          | 7F        | 2.3         | 8.7                   | 3.2              | 1.12–3.89#                              | 3.8                         | 7.1              | 0.41–1.23#                                   | 6.6                    | 10.3             |

\* Time of maximal response during the first hour after exercise challenge.

† Time of maximal response between three and ten hours after exercise or allergen challenge.

‡ Provocative concentration of methacholine that caused a 20% fall in FEV<sub>1</sub> from the baseline.

§ Ten minutes after inhalation of the last concentration of allergen.

¶ Geometric mean.

# Range of 1 SD.

\*\* Did not meet the criteria of late asthmatic response to exercise.<sup>20</sup>

mite (*Dermatophagoides pteronyssinus*: Der P) among 20 common airborne allergens. Their records showed that in the preliminary exercise tests, asthma was induced with falls in FEV<sub>1</sub>  $\geq 20\%$  within one hour of exercise and no subsequent falls  $\geq 5\%$  during the following nine hours. Twenty-seven subjects initially took part in the study, but ten were eliminated: in two, FEV<sub>1</sub> fell by less than 20% in the pre-allergen exercise test (two days before the allergen challenge); five did not show late asthmatic responses after the allergen challenge; two had severe late asthmatic responses to allergen that required medication; one subject could not undergo the postallergen exercise test (two days after the allergen challenge) because of a delayed recovery of the airway caliber after the allergen challenge. At the time of the study, all patients had been free of symptoms of acute respiratory infections for 4 weeks. Asthma was mild to moderate, stable, and controlled by  $\beta_2$ -agonist alone on an as-needed basis ( $n = 7$ ), or with inhaled cromolyn sodium ( $n = 6$ ) or corticosteroids ( $n = 4$ ). Beta<sub>2</sub>-agonists or other medications were withdrawn from all patients 24 hours prior to the study, oral theophylline 48 hours prior, and inhaled cromolyn sodium or corticosteroids 7 days prior.

The parents of the patients gave informed consent for the study and the protocol was approved by the hospital ethics committee.

### Study Design

The subjects attended the laboratory on four separate days, of which the last three days were consecutive. On each of the test days, lung function was measured with a computerized spirometer (Microspiro-HI 298, Chest, Japan) after a rest of 30 minutes, and the study was continued only if baseline FEV<sub>1</sub> before each test was at least 70% of predicted value.<sup>18</sup> The largest value of triplicate FEV<sub>1</sub> on each occasion was used for analysis. All tests started between 8:00 and 9:00 AM; subjects stayed in the laboratory all day and did not take any medication or caffeine. On the first day, a pre-allergen exer-

cise test was performed, and FEV<sub>1</sub> was measured at graduated intervals for 60 minutes, and then hourly for a further nine hours. Only subjects with definite early asthmatic responses to exercise went on to the second day, two days later. They underwent methacholine challenge tests to determine baseline levels of nonspecific bronchial responsiveness. Two hours later, once airway caliber had recovered to more than 95% of FEV<sub>1</sub> at the start of that day, they underwent allergen challenge tests. FEV<sub>1</sub> was measured every hour for ten hours, and only subjects with definite late asthmatic responses to allergen were selected. If, after this challenge, symptoms during the late phase were too troublesome, corticosteroids were administered orally and the cases were excluded. On the third day (control day), FEV<sub>1</sub> was measured regularly over a 10-hour period to evaluate spontaneous fluctuations of expiratory flows. On the fourth day, methacholine responsiveness was remeasured to determine postallergen level of nonspecific bronchial responsiveness, and a postallergen exercise test was then performed. FEV<sub>1</sub> was measured according to the procedure followed on the first day. Exercise or methacholine bronchoprovocation tests were performed such that each stimulus was given at a fixed time of the day.

### Exercise Challenge Test

Exercise tests consisted of eight minutes' use of a cycle ergometer, set at a fixed load, in such a way as to achieve approximately 80% of maximal heart rate.<sup>19</sup> Tests were performed in an air conditioned laboratory. Throughout the series of experiments, there was no significant variation in environmental temperature or humidity. FEV<sub>1</sub> was measured at 5, 8, 11, 15, 20, 30, and 60 minutes, then every hour until 10 hours after exercise. The response was calculated as maximal  $\Delta$ FEV<sub>1</sub> (percentage fall in FEV<sub>1</sub>, from baseline) occurring in the first hour (magnitude of early response) and maximal  $\Delta$ FEV<sub>1</sub> occurring between three and ten hours after exercise (magnitude of late response). A late asthmatic response was

defined as occurring when  $\Delta$ FEV<sub>1</sub> was  $\geq 20\%$  at three consecutive time points<sup>20</sup> between three and ten hours after the test.

### Methacholine Inhalation Test

Methacholine bronchial challenges were carried out using the method described by Chai et al,<sup>21</sup> but with modifications. Concentrations (0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, 25 mg/mL) of methacholine (Sigma Chemical, St. Louis, USA) were prepared through dilution with buffered saline (pH 7.4). A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, USA) triggered by a solenoid valve set to remain open for 0.6 seconds, was used to deliver the aerosol generated from a DeVilbiss 646 nebulizer with pressurized air at 20 psi. Each subject inhaled five inspiratory capacity breaths of buffered saline with increasing concentrations of methacholine until FEV<sub>1</sub> had fallen by  $>20\%$  of the postsaline value. FEV<sub>1</sub> was measured at one and one-half minutes after each inhalation. The methacholine PC<sub>20</sub> was obtained from the log concentration-percent fall in FEV<sub>1</sub> curve by linear interpolation of the last two points.

### Allergen Challenge Test

Allergen challenge tests used the method described by Chai et al<sup>21</sup> but with simple modifications. Der P extracts were obtained from Bencard, UK. Serial alternative 5-fold and 2-fold dilutions were prepared using buffer phosphate ( $10^{-3}$ ,  $2 \times 10^{-4}$ ,  $10^{-4}$ ,  $2 \times 10^{-5}$ ,  $10^{-5}$  wt/vol concentrations). Allergen concentrations were inhaled after a control inhalation of buffer phosphate, starting with the dilution producing a 2-mm wheal reaction in the skin prick test. Baseline values were the FEV<sub>1</sub> obtained after inhaling buffer solutions just before the allergen exposure. Aerosols were generated in the same way as during the methacholine challenge test, and FEV<sub>1</sub> was measured ten minutes after the inhalation of five inspiratory capacity breaths of each concentration. Inhalations were continued at 15-

minute intervals until there was a fall of 20% or more from baseline FEV<sub>1</sub>; if the fall in FEV<sub>1</sub> was between 15% and 20%, the next increment was given at half the usual concentration. After administration of the last concentration, FEV<sub>1</sub> was measured every hour for ten hours. Changes in FEV<sub>1</sub> after allergen inhalation were expressed as a percentage of baseline value. The responses were calculated as  $\Delta$ FEV<sub>1</sub> measured ten minutes after the last inhalation of allergen concentration (magnitude of early response) and maximal  $\Delta$ FEV<sub>1</sub> occurring between three and ten hours after the allergen inhalation (magnitude of late response). An early or late asthmatic response was defined as occurring when the magnitude of early or late response exceeded 20%.

#### Statistical Analysis

Values for methacholine PC<sub>20</sub> were logarithmically transformed before analysis and were expressed as a geometric mean (range of 1 SD). Other values were presented as mean  $\pm$  1 SD. Changes in methacholine responsiveness after the allergen challenge were expressed as dose shift (in doubling doses) in the following formula:

$$\Delta \log_{10} \text{PC}_{20} [\log_{10}(\text{PC}_{20} \text{ before the postallergen exercise challenge}) - \log_{10}(\text{PC}_{20} \text{ before the allergen challenge})] / \log_{10} 2^{22}$$

Appropriate parametric or nonparametric statistical procedures were used to compare the paired data. Values between the groups were compared using the Wilcoxon rank sum test. In each case, statistical significance was accepted when  $P < .05$ .

#### RESULTS

In all subjects, baseline FEV<sub>1</sub> was  $>70\%$  of the predicted<sup>18</sup> before each challenge test. Bronchial responses to a pre-allergen exercise challenge, an allergen challenge, and a postallergen exercise challenge, and values of methacholine PC<sub>20</sub> before the latter two challenges are shown in Table 1.

Mean ( $\pm$ SD) baseline FEV<sub>1</sub> for the pre-allergen exercise challenge was  $92.9 \pm 5.5\%$  of the predicted (range: 84.7% to 103.8%) (not shown). After this exercise, all the subjects showed an early asthmatic response (range of  $\Delta$ FEV<sub>1</sub>: 20.5% to 53.6%) at five or eight minutes, but no late asthmatic response was observed. Baseline methacholine PC<sub>20</sub> varied from 0.52 to 5.43 mg/mL (geometric mean: 2.09). Mean baseline FEV<sub>1</sub> for the allergen challenge was  $92.5\% \pm 6.2\%$  of the predicted (range: 82.8% to 106.3%) (not shown). In all subjects, allergen inhalation induced dual responses (early and late asthmatic responses). Mean  $\Delta$ FEV<sub>1</sub> in the early phase was  $27.5\% \pm 3.8\%$ . These initial falls were reversed (FEV<sub>1</sub>  $> 90\%$  of the baseline value) within two hours and were followed by late asthmatic responses which peaked between five and ten hours after the challenge, with a mean  $\Delta$ FEV<sub>1</sub> of  $32.8 \pm 7.1\%$ . On a control day, the day following the allergen challenge, spontaneous fluctuations of FEV<sub>1</sub> were observed. The maximum fall in FEV<sub>1</sub> during the ten hours varied from  $-1.5\%$  to  $8.3\%$ , with a mean of  $4.4\% \pm 2.8\%$  (not shown). The geometric mean of the postallergen methacholine PC<sub>20</sub> was 0.71 mg/mL (range: 0.31 to 2.30). When compared with its baseline value, postallergen PC<sub>20</sub> fell by a factor ranging from 1.5-fold to 6.4-fold. Mean baseline FEV<sub>1</sub> for the postallergen exercise challenge was  $89.5 \pm 5.9\%$  of the predicted (range: 79.6% to 103.8%) (not shown). In no subject did the individual value of baseline FEV<sub>1</sub> of this challenge change by more than 10% from that of the pre-allergen exercise test. After the exercise, early asthmatic responses developed in all subjects, with a mean  $\Delta$ FEV<sub>1</sub> of  $38.5 \pm 6.6\%$ . This was significantly higher ( $P < .01$ ) than that ( $32.1 \pm 8.7\%$ ) after the pre-allergen exercise challenge. Seven subjects developed late asthmatic responses to the postallergen exercise, as previously defined,<sup>20</sup> and were listed as group I. The remaining ten subjects were nonresponders by this criterion and listed as group II. One subject in this group

had a late response of 23.6% but did not meet the criteria.<sup>20</sup>

When we compare group I with group II, airway responses to the pre-allergen exercise test were similar (early phase  $\Delta$ FEV<sub>1</sub>:  $31.5\% \pm 4.8\%$  versus  $32.6 \pm 10.8\%$ ; late phase  $\Delta$ FEV<sub>1</sub>:  $3.3 \pm 3.7\%$  versus  $3.8 \pm 3.0\%$ ). The severity of early or late asthmatic response after the allergen challenge appeared to be higher in group I than in group II (early phase  $\Delta$ FEV<sub>1</sub>:  $29.2\% \pm 4.0\%$  versus  $26.3\% \pm 3.3\%$ ; late phase  $\Delta$ FEV<sub>1</sub>:  $35.1\% \pm 6.5\%$  versus  $31.2\% \pm 7.3\%$ ), but these differences were not statistically significant ( $P > .05$ ). On a control day, there was no significant difference in spontaneous fluctuation of FEV<sub>1</sub> (maximal fall:  $4.4\% \pm 3.2\%$  versus  $4.5\% \pm 2.7\%$ ) (not shown). Neither was the severity of early asthmatic response to postallergen exercise significantly different ( $38.3\% \pm 4.4\%$  versus  $38.7\% \pm 8.0\%$ ). The comparison of baseline PC<sub>20</sub> or postallergen PC<sub>20</sub> between the two groups showed no significant difference in either value [baseline PC<sub>20</sub>: 2.34 (1.35-4.07) versus 1.91 (0.95-3.80); postallergen PC<sub>20</sub>: 0.59 (0.36-0.95) versus 0.81 (0.46-1.45)]. The dose shift of methacholine PC<sub>20</sub> produced by the allergen challenge, however, was significantly greater ( $P < .05$ ) in group I ( $-2.00 \pm 0.39$  doubling doses) than in group II ( $-1.36 \pm 0.53$  doubling doses) (Fig 1).

To substantiate the occurrence of late asthmatic responses to exercise according to the degree of nonspecific bronchial responsiveness or its change, we calculated the correlation of baseline methacholine PC<sub>20</sub>, postallergen methacholine PC<sub>20</sub>, and its dose shift produced by the allergen challenge, respectively, with the magnitude of late response to the postallergen exercise in the two groups combined. There was no correlation between baseline PC<sub>20</sub> or postallergen PC<sub>20</sub> and the magnitude of late response to exercise (not shown). There was, however, a significant correlation between the dose shift and the magnitude of late response to exercise ( $r = 0.51$ ,  $P < .05$ ) (Fig 2).

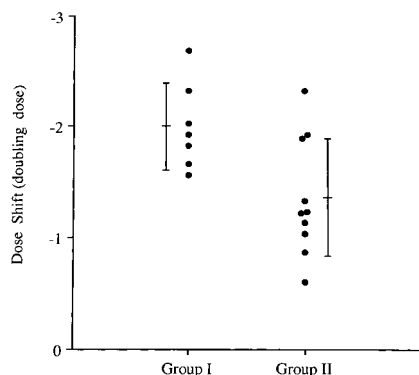


Figure 1. A comparison of the dose shift of methacholine  $PC_{20}$  produced by the allergen challenge between groups I and II. Mean and 1 SD of each group are indicated with horizontal bars. It was significantly higher in group I than in group II ( $P < .05$ ).

## DISCUSSION

The enhancing effect of exposure to allergens in the environment<sup>23</sup> or bronchoprovocation<sup>24</sup> on exercise-induced early asthmatic responses has been known for many years. Our finding that this response is increased after allergen provocation is compatible with the results of a previous study.<sup>24</sup> On the other hand, the effects of allergen exposure on late responses to exercise have not been extensively studied. Boulet et al<sup>14</sup> reported that late asthmatic responses to exercise developed in two adult subjects with asthma following a late asthmatic response to

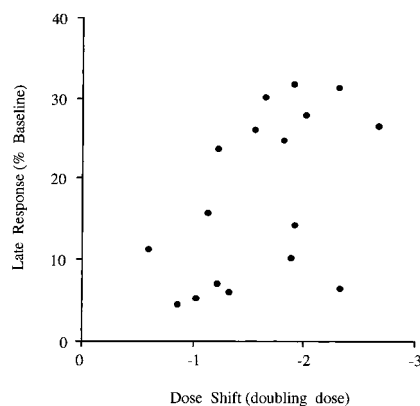


Figure 2. The magnitude of late response to the post-allergen exercise according to the dose shift of methacholine  $PC_{20}$  produced by the allergen challenge. There was significant correlation ( $r = 0.51$ ,  $P < .05$ ).

allergen. Our results corroborate this finding in children with asthma. We attempted to determine which aspect of airway responses to allergen might be associated with the occurrence of late asthmatic responses to exercise. These responses were not related to the severity of late asthmatic response to allergen or the subsequently heightened level of nonspecific bronchial responsiveness, but to the degree of increase in this produced by the preceding allergen challenge.

The exercise challenge was performed in an air conditioned laboratory under constant environmental conditions. The difference of airway responses to exercise between the two conditions (pre-allergen and postallergen) could not, therefore, be accounted for by different experimental environments, although we did not measure the respiratory water loss during exercise. The occurrence of late asthmatic responses to exercise does not seem to be due to an increase in the severity of early asthmatic response, because in groups I and II the increment of this reaction was similar. Another report<sup>11</sup> also suggested that the degree of early asthmatic response did not influence the development of a late asthmatic response to exercise. All patients first performed the control exercise challenge, which raises the possibility that the results seen were due to an "order effect". It is not, however, pertinent to randomize the order in which the tests are performed, because an allergen challenge may have a long-lasting effect on airway responses to exercise challenge.<sup>24</sup> Forty-eight hours after the allergen challenge was the time interval chosen for the second exercise challenge because it represents an appropriate time point that allows airway caliber to return to the baseline<sup>25</sup> and helps to compare the airway responses between the two exercise challenges while minimizing their possible diurnal variation.<sup>26</sup> Mean baseline  $FEV_1$  on the postallergen exercise day was still 3.4% predicted lower than that on the pre-allergen exercise day. Although this could theoretically affect the measurements of airway responses to stim-

uli such as allergen,<sup>27</sup> the strength of this effect has not been tested on the late response to exercise. Some investigators have reported that baseline  $FEV_1$  was not different between the isolated immediate responders and dual responders after the exercise challenge.<sup>11,28</sup> We therefore believe that such a baseline effect would not account for the increased late response to exercise.

Because of diurnal variation of pulmonary function, some studies<sup>5,20</sup> have advocated the use of a clock-time comparison on a control day without exercise instead of a pre-exercise baseline comparison. Our previous observations on a control day,<sup>9</sup> however, revealed no significant change or even a tendency for  $FEV_1$  to increase from its baseline value at the time corresponding to a late asthmatic response. In the present study, we did not—for ethical reasons—have an exact control day, which should have been surveyed two days after the allergen challenge. Instead, on the day following the allergen challenge, we assessed spontaneous fluctuation of  $FEV_1$ , which showed minimal changes. Although we cannot exclude that diurnal variation of  $FEV_1$  could have been more marked on the second day after the challenge, it is unlikely, these fluctuations decreasing usually after the first day.<sup>29</sup> A reanalysis of the data by comparison to  $FEV_1$  of the corresponding time for defining a late asthmatic response to exercise did not change the figure of the present study (not shown). We realize that the degree of continual exposure to Der P in the environment may have changed throughout the study period; this potential variability, however, would not exert an important effect since this study was performed between December and February, the period when Der P levels in Korea have been found to be at their lowest, and almost constant.<sup>30</sup>

How can the appearance of late asthmatic responses to exercise after antigenic exposure be explained? The severity of early or late asthmatic response after the allergen challenge was not significantly different between

groups I and II. Neither before the allergen challenge nor before the postallergen exercise challenge was methacholine PC<sub>20</sub> different between the two groups. This confirms the finding of Boulet et al<sup>14</sup> that the degree of baseline or postallergen methacholine sensitivity was not a useful predictor of the occurrence of a late asthmatic response to exercise. Methacholine dose shift caused by the allergen challenge, however, was significantly greater in group I than in group II. This is a novel finding, but reanalysis of the data of Boulet et al<sup>14</sup> reveals that one of their two subjects had the highest elevation of nonspecific bronchial responsiveness after the allergen challenge. It can be seen that the range of late responses to exercise forms a continuum from virtually no response to a maximal response of 31.7%. The division of subjects into isolated immediate responders and dual responders may therefore be arbitrary. When treating them as a single group with varying degrees of late response to exercise, the degree of methacholine dose shift correlated significantly with the magnitude of late response (Fig 2). Since airway hyperresponsiveness is thought to be a consequence of underlying airway inflammation,<sup>31</sup> we speculate that the development of late asthmatic responses to exercise following a late asthmatic response to allergen might be related to a quantitative change in airway inflammation in a given patient rather than to the degree of preexisting or allergen-provoked airway inflammation.

Bronchoalveolar lavage data from human as well as animal studies suggest that airway inflammation with eosinophils and possibly other cells is important for the production of both a late asthmatic response and increases in nonspecific bronchial responsiveness.<sup>32,33</sup> Because the same inflammatory cells can be demonstrated by bronchoalveolar lavage in patients with asthma,<sup>34</sup> these responses are considered to be the experimental equivalent of clinical asthma. There is some evidence, however, that an allergen challenge modifies the pattern of infil-

trative cells or the release of mediators involved in preexisting airway inflammation. For example, the histamine-containing, IgE-bearing cells in the bronchoalveolar lavage fluid obtained during a late asthmatic response are predominantly basophils,<sup>35</sup> whereas the cells with the same characteristics in patients with stable asthma are mostly mast cells.<sup>34</sup> Although further studies are needed, we speculate that changes in the pattern of response to exercise might also result from this qualitative change in airway inflammation provoked by the allergen challenge.

Little is known about the clinical significance or consequences of late asthmatic responses after exercise. Iikura et al<sup>8</sup> reported a notable increase in children's asthmatic symptoms for several days after the development of exercise-induced late asthmatic responses, although other investigators<sup>11</sup> have been unable to confirm this finding. We noted that when late asthmatic responses to exercise developed, airway responsiveness to allergen increased 24 hours after the exercise challenge.<sup>9</sup> These observations suggest that late asthmatic responses after exercise may contribute to prolongation and augmentation of asthmatic symptoms.

It is unlikely that airways would be exposed to a dose of allergen as high as the dose used for this allergen challenge. Such challenges, therefore, do not precisely represent naturally occurring exposure. Nonetheless, the phenomena observed in this study may have provided added insights into the mechanism involved in the symptomatology provoked by allergen and exercise in atopic asthma. It is well known that patients with atopic asthma experience more trouble from their asthma during seasons of natural allergen exposure.<sup>2</sup> We have previously observed patients with seasonal asthma, whose nocturnal symptoms worsened after strenuous daytime exercise at the end of a period of natural allergen exposure. This phenomenon was not seen during the rest of year. Our results suggest that if exposed to a relevant

allergen, a patient's response to exercise may be biphasic rather than isolated immediate.

In conclusion, late asthmatic responses to exercise may develop in some children with asthma following a late asthmatic response to an allergen. This phenomenon was related not to the baseline or postallergen methacholine PC<sub>20</sub> but to the degree of increase in methacholine sensitivity. We hypothesize that in an individual subject, changes in the pattern of response to exercise may result from quantitative or qualitative changes in airway inflammation provoked by the allergen challenge.

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