

Prevalence and characteristics of exercise-induced asthma in children

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We have evaluated the prevalence and the characteristics of exercise-induced asthma (EIA) in a group of 71 patients with a prior history of mild, moderate or severe asthma (42 males and 29 females), aged 6–16 years-old. Measurements of the forced expiratory volume in 1 second (FEV₁) were obtained before and at regular intervals up to 8 hours following exercise. As a control, the same patients were evaluated at similar time intervals on another day when they had not been submitted to an exercise challenge. Using pre-exercise FEV₁ values as the reference, 32 patients (45.1%) had a positive exercise challenge, defined as a fall in FEV₁ value equal to or greater than 15% from baseline following exercise. Among the patients with a positive exercise challenge, the majority (23/32, 71.8%) had an immediate response alone, with no significant changes in FEV₁ within the 8-hour follow-up. However, a subgroup of patients (9/32, 28.1%) had both an immediate and a late-phase response to exercise. During the control day, no significant fall in FEV₁ were observed. In keeping with previous investigations, no correlation was found between a history of EIA and a positive exercise challenge in the present study. Positive exercise challenges were found more frequently among patients with moderate and severe asthma than patients with mild asthma.

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The possibility that exercise can cause both an immediate and a late-phase asthmatic response, similar to the response observed after antigen challenge, was initially proposed by Bierman et al. (1, 2). These authors reported the development of dual asthmatic responses in eight out of nine adults challenged by exercise on a treadmill. Subsequently, it was reported that late phase asthmatic responses occurring 3 to 6 hours after exercise were associated with an increase in serum neutrophil chemotactic activity (3). No significant differences in asthma severity, circadian variations of FEV₁, or reactivity to acetylcholine, have been observed between patients with both immediate and late-phase responses and patients with immediate response alone. However, it has been reported that in patients with dual response, there is a significant correlation between the magnitude of the immediate response and the development of a late-phase response, suggesting that the late-phase response to exercise could be dependent on the preceding immediate asthmatic response. In addition, the rate of spontaneous recovery from the immediate response is lower among patients who presented a late-phase response, as compared to patients who do not present it (4).

Although several studies have reported the occurrence of a late-phase response to exercise (1, 4–10), its existence is still questioned by some investigators (11–13). The major criticism has been the lack of an appropriate control day on which the patient would have time-matched spirometric measurements taken without performing any exercise, for comparison with the exercise challenge day. Other proposed models for performing control day measurements have included time-matched, non-specific bronchial challenge with metacholine and exercise challenge breathing hot and humid air, which can inhibit mediator release and bronchoconstriction in EIA patients (14). The control day would rule out the possible influence of spontaneous variation of bronchial caliber or of daily medication withdrawal prior to the exercise challenge. The results of a number of studies using a control day (2, 4, 5, 8) have been criticized for reasons which include the long time interval between medication withdrawal and the challenge; the magnitude of the variation of spirometric values being within normal circadian limits; the fact that exercise may be solely a trigger factor for asthma symptoms (11, 15). To the best of our knowledge, this is the first report of late-phase asthmatic reac-

tions following exercise challenges in children breathing cold and dry air.

Patients and methods

Patients

Seventy-one asthmatic patients (42 males and 29 females), aged 6 to 16 years old, seen at the Pediatric Allergy Clinic at Paulista School of Medicine, Federal University of São Paulo (UNIFESP-EPM), Brazil, were enrolled in the present study. Patients with a prior history of mild, moderate or severe asthma (16) were treated and when the asthma was well-controlled were randomly selected for the present study if they had not taken sodium cromoglycate, Nedocromil, inhaled or oral steroids for at least one month prior to enrollment, regardless of the clinical history of EIA.

Exercise Challenge Protocol

Exercise challenges were performed using an ergometric bicycle, with patients breathing dry air cooled to 5°C through a facial mask. Bronchodilators (beta-agonists and theophyllines) were withdrawn 24 hours prior to challenge, and basal FEV₁ measures were greater than 75% of predicted values for age and height (17). The exercise load was calculated to cause patients to reach 80 to 90% of the maximal heart rate predicted for their ages (18–20), based on the following equation: $Kp = 0.035 \times \text{weight}$ (in kilograms), where Kp equals kilopounds. After this workload was achieved, exercise was maintained for six minutes at a speed of 50 to 60 cycles per minute. FEV₁ measures were taken before exercise (baseline) and at 0, 5, 10, 15, 30, 60, 120, 180, 360 and 480 minutes following exercise, according to the American Thoracic Society 1987 Guidelines (21). Post-exercise spirometric measurements were performed at room air and ambient temperature. A fall of FEV₁ equal to or greater than 15% of the pre-exercise value following exercise was considered a positive challenge.

Spirometry was also performed on a control day, when patients had not done any exercise, were not subjected to any other stimuli which could cause bronchospasm, and when bronchodilators had been withdrawn for the last 24 hours. The control day was before the challenge day, which was performed within the same week. Spirometric measurements were time-matched with those taken on the exercise challenge day.

Statistical analysis

The following statistical tests were applied: Wilcoxon test, to compare variables of the control day with

Table 1. Correlation between history of exercise-induced asthma (EIA) and positive exercise challenge with cold and dry air.

History of EIA	Exercise challenge			
	Positive	Negative	Total	%
Positive	9	14	23	32
Negative	23	25	48	68
Total	32	39	71	100

P = 0.0939; Fisher's exact test.

the exercise challenge day; Friedman's analysis of variance, to compare FEV₁ variations in the control and challenge days; chi-square test, to compare the proportion of positive challenges among groups with mild, moderate and severe asthma; Fisher's exact test to compare challenge results between groups with positive and negative history of EIA (22).

Results

In the group of 71 patients studied, 32 (45.1%) showed a positive exercise challenge, or EIA; twenty three of those (71.8%) presented with an immediate response alone, and nine (28.1%) presented with both immediate and late-phase responses. Thirty nine patients (54.9%) had a negative exercise challenge. Tables 1 and 2 show the percent changes in FEV₁ in relation to baseline in patients who had an immediate response and patients who had both immediate and late-phase responses to exercise challenge with cold and dry air, respectively. Mean values for measurements obtained on the challenge and control days, in patients with only an immediate response and with dual responses are shown in Figures 1 and 2, respectively.

Among the patients who developed an immediate asthmatic response, significant differences from baseline were observed at 0, 10, 15 and 30 minutes following exercise (Fig. 1). Likewise, significant differences in relation to control day values were

Table 2. Correlation between asthma severity and positive exercise challenge with cold and dry air

Asthma Severity	Exercise Challenge			
	Positive	Negative	Total	%
Mild	7	29	36	50.7
Moderate	14	8	22	31.0
Severe	11	2	13	18.3
Total	32	39	71	100

Chi-square test; X^2 calculated = 20.82*; X^2 critic = 5.99; mild < moderate and severe

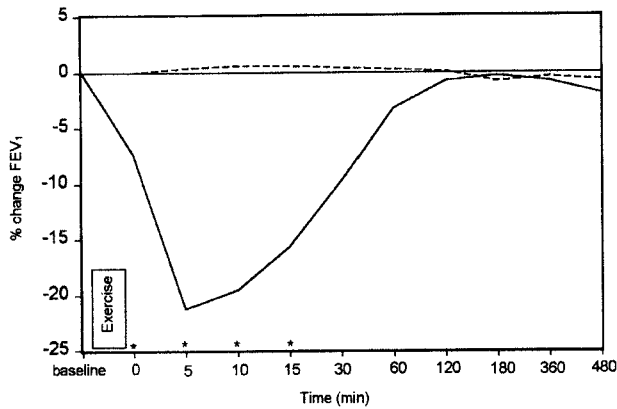


Fig. 1. Mean values of forced expiratory volume in 1 second (FEV_1), expressed as % change from baseline, among patients who had only an immediate response to exercise challenge, on the challenge day (—) and on the control day (---). Significant differences from the baseline are indicated (*).

found at 0, 5, 10, 15 and 30 minutes following exercise. Baseline FEV_1 values on challenge and control days showed no significant differences, with mean values 89.1% and 89.3% of the predicted values, respectively.

Among the patients with dual responses, significant differences in relation to baseline values were found at 0, 5, 10, 15 and 30 minutes following exercise (immediate EIA), and also at 480 minutes after exercise, comprising the late-phase EIA (Fig. 2). Analysis of FEV_1 values between challenge and control days showed significant differences from time 0 to 60 minutes after exercise, going back to normal values at 120 minutes. At 180 minutes following exercise, there was a significant difference in the FEV_1 values obtained on the challenge day as compared to the control day, and this difference persisted until 480 minutes (Fig. 2). Baseline FEV_1 values were 92.7% and 89.1% of the predicted values

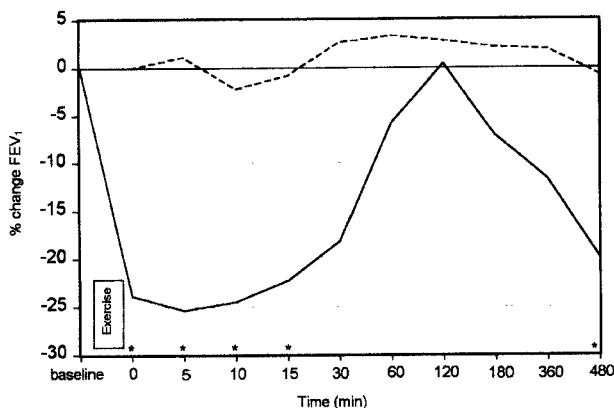


Fig. 2. Mean values of forced expiratory volume in 1 second (FEV_1), expressed as % change from baseline, among patients who had both an immediate and a late-phase response to exercise challenge day (—) and on the control day (---). Significant differences from baseline are indicated (*).

among children on challenge and control days, respectively, and this difference was not significant.

A positive exercise challenge was found in only nine of the 23 patients with a clinical history of EIA. Among the 48 patients with a negative history of EIA, 23 had a positive exercise challenge. There was no correlation between history of EIA and a positive exercise challenge (Table 1).

Positive exercise challenges were observed more frequently among patients with moderate and severe asthma, as compared to mild asthma (Table 2). In the subgroup of nine patients with both an immediate and a late-phase asthmatic response to exercise, zero, four, and five, patients had mild, moderate and severe asthma, respectively.

Discussion

We have demonstrated the existence of a late-phase response in EIA in a subset of asthmatic patients by comparing the FEV_1 fall following an exercise challenge in both baseline FEV_1 levels on the day of the challenge and levels obtained on a control day. The control day was designed to provide information on the individual circadian patterns of FEV_1 variations and to allow more accurate comparisons. In this study, we have identified 9/71 patients (12.6%) who showed a dual asthmatic response to an exercise challenge with cold and dry air. These nine patients comprised 28.1% of the 32 patients with a positive exercise challenge.

Analysis of the FEV_1 variations following exercise challenge in the patients with dual responses revealed that there was a significant fall in FEV_1 values immediately after exercise (at time 0). This fall remained significant for up to 30 minutes, but was no longer significant at 60 minutes and thereafter. However, the FEV_1 fall was again significant as compared to baseline at 480 minutes. All patients had a fall in FEV_1 of 15% or greater at 360 or 480 minutes following the exercise challenge. On the control day, there was no significant fall in FEV_1 compared to baseline values.

Compared to control day measurements, significant differences in FEV_1 could be found at 0 to 60 minutes and then no significant differences at 120 minutes. These results are in keeping with a previous study showing that patients with a dual response to an exercise challenge have long-lasting spirometric changes starting immediately after exercise (4). In these cases, return to baseline values may take 60 minutes or more. At 180 minutes, significant changes compared to FEV_1 values obtained on the control day could already be observed, which persisted for up to 480 minutes.

The rate of recovery from the immediate response was lower among patients who had a dual response,

as compared to the patients with an immediate response alone. Some of the patients who had a late-phase response showed no complete recovery from the immediate response. These results suggest that a slow rate of recovery from the initial bronchospasm may be predictive of the late-phase reaction in EIA.

Patients with a dual response did not show bronchodilation during the first minutes after exercise, which has often been reported in asthmatics who undergo exercise challenges while breathing ambient air. This difference in lung function has been previously appreciated (23) and has been attributed to the increased water loss and consequent increase in the osmolarity of the airways when patients breath dry air during exercise-induced hyperventilation. The role of osmotic changes occurring in the respiratory mucosa in the pathophysiology of EIA has been studied for over twenty years (24–27). Previous investigations among asthmatic patients have determined the amount of water exchanged at the level of the respiratory mucosa as a result of hyperventilation during exercise, showing that there is a negative balance (28–29). It has also been suggested that re-hydration of the mucosa lining the airways dehydrated by the exercise-induced hyperpnea, occurs more slowly in asthmatics than in normal children, as a result of the chronic underlying inflammation (30). In addition, the cooling of the airway mucosa has been suggested to play a causative role in EIA (31, 32). In the present study, we have not measured the intrathoracic airway temperature; we have instead used dry air cooled to 5°C. At this temperature, it has been previously demonstrated that cooling of the airways occurs (33). Under the conditions used in our model of exercise challenge, an increased intensity of bronchospasm following exercise is obtained (34), and an increase in bronchial reactivity to metacholine has been previously reported (12).

Very recently, Carlsen, *et al.*, (35) have demonstrated that children with bronchial asthma are substantially more sensitive to cold air than children with chronic lung disease; exercise-induced bronchoconstriction (EIB) is markedly increased by cold air inhalation in asthmatic children, maintaining the specificity of the EIB test and increasing the sensitivity.

It has been reported that, in patients with well-controlled mild and/or moderate asthma, bronchoconstriction following exercise occurs predominantly in the large airways. On the other hand, patients with unstable asthma and a high level of bronchial hyperreactivity with an underlying airway inflammation show more intense responses to exercise challenges, and bronchoconstriction occurs in both large and small airways (36–38). This might be the reason for our finding a higher prevalence and intensity of EIA among patients with a prior history of more severe asthma.

The mechanisms underlying the late-phase responses in EIA are not well understood. Lee, *et al.* have reported an increase in neutrophil chemotactic activity in serum of patients with EIA (39, 40). It is possible that other inflammatory mediators similar to those described during the immediate response may be involved (41). If the late-phase reaction in EIA represents an inflammatory component, management of EIA may need to be reviewed. The use of cromones (sodium cromoglycate and Nedocromil) for the prevention of EIA may be preferred, since these drugs have been shown to inhibit the immediate response (42) and to have an anti-inflammatory action which prevents the late-phase reaction.

In keeping with a previous study (43), we could not demonstrate a significant correlation between clinical history of EIA and EIA diagnosed by a positive challenge. Kawabori, *et al.*, (44), studying 135 asthmatic children, have reported a positive correlation between clinical history of EIA and positive challenge in 63% of their patients.

In conclusion, we have demonstrated the existence of a late-phase asthmatic response to an exercise challenge with cold dry air in a subset of patients with asthma. By using comparisons of FEV₁ changes between the challenge day and a control day, when patients did not have any exercise but had FEV₁ measurements taken at time-matched intervals, we believe we have minimized the influence of factors which might interfere with the diagnosis of a true late-phase asthmatic response. In our patients, late-phase reactions were preceded by an immediate response of a longer duration, sometimes not accompanied by a return to baseline between the two reactions, suggesting that late-phase responses could be predicted by analyzing the characteristics of the immediate response. Further studies addressing the mechanisms by which late-phase reactions occur and the role of inflammation in these reactions will be important for establishing the best management strategies for EIA.

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