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Original Article

Heterogeneity of bronchial response to exercise among children with asthma

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ABSTRACT

Background: Exercise-induced broncho-obstruction (EIB) is common among asthmatic children with a prevalence rate of 40–90. It is one of the leading causes of the deterioration of the general condition of asthmatics and the limitation of physical activity. Therefore, early recognition and provision of adequate therapy is necessary. However, it is not possible to achieve this without first having information about the features of the bronchial response. The aim of the present study was to determine the bronchial response to exercise and to establish a connection between bronchial response and the clinical features of the disease in asthmatic children.

Methods: One hundred and three clinically stable children with different clinical severities of asthma were studied with a standardized step-up exercise test. The airway response to exercise was investigated by peak flowmetry to measure the peak expiratory flow rate (PEFR). Bronchial permeability was determined before and after exercise at 0, 5, 10, 15, 30 and 60 min and then hourly for the next 11 h. These determinations were repeated at the same time points on a non-exercise (control) day.

Results: The test resulted in four types of response to exercise: (i) non-obstructive; (ii) isolated early airway response (EAR); (iii) dual-waved; and (iv) prolonged EAR. The frequency of these responses in the study population was 33.0, 39.81, 26.21 and 0.97%, respectively. No significant difference in clinical features, such as severity and duration of disease, baseline values for PEFR, atopic status, age and gender, was observed with different forms of response to exercise. However, children with moderate and severe asthma had significantly more frequent EIB-positive type responses than children with a mild form of asthma.

Conclusions: Responses to exercise in asthmatic children are heterogeneous and, quite possibly, are particular to each individual patient.

Key words: asthma, children, exercise-induced broncho-obstruction, types of response.

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INTRODUCTION

Exercise-induced broncho-obstruction (EIB) has been described as a phenomenon in which vigorous physical activity causes airflow limitation in subjects with increased airway responsiveness. Exercise-induced broncho-obstruction is common among asthmatics and the frequency of its occurrence in this group has been reported to vary from 40 to 90%.[1–6] This condition is seen more frequently in children and teenagers with asthma. Because exercise is one of the leading causes of the deterioration of general condition and limitation of physical activity in asthmatic children, early recognition of EIB and provision of adequate therapy is necessary. However, this is not possible without first having information about the features of the response to exercise and the effects of the clinical features of asthma on these responses.

Many factors that contribute to the appearance and severity of EIB have been determined and include the type of exercise, fluctuations in temperature and relative humidity, effects of viruses and pollutants, the severity of airway hyperresponsiveness to pharmacological agents and the type and duration of therapy.[7–9] At the same time, answers to the question regarding the type of response to exercise and its connection with the clinical features of asthma are unclear.

The purpose of present study was to determine the types of bronchial response to exercise in asthmatic children and to establish a connection between the type of response and the clinical features of the disease.

METHODS

Subjects

The selection criteria for the study subjects were: (i) documented wheezing in the previous 1 year; (ii) values of peak expiratory flow rate (PEFR) predicted > 70%; (iii) no inhaled or systemic corticosteroids and nedocromil sodium or sodium cromoglycate therapy regularly for the past 2 weeks; (iv) no history of acute respiratory infection and acute asthma exacerbation during the past 4 weeks; (v) ability to properly use the peak flow meter; (vi) parental consent for children to participate in the study.

According to the selection criteria, 103 children with a clinical diagnosis of mild, moderate or severe asthma were included in the present study. In all patients, the diagnosis of asthma was based on the International Consensus Report on Diagnosis and Treatment of Asthma.[10] Patient characteristics are given in Table 1.

All children were treated with inhaled short-acting β_2-adrenoceptor agonists on demand; 31 receiving non-regular inhaled nedocromil sodium or sodium cromoglycate, five receiving short-acting methylxanthines and nine being treated with antihistamines. None of the children received long-acting β_2-adrenoceptor agonists or methylxanthines.

Study design

The study took 2 days to complete, with an interval of 1–2 days between the study periods. On the first (control) day, bronchial permeability without exercise challenge was determined at 0, 5, 10, 15, 30 and 60 min and then hourly for the next 11 h. On the second (exercise) day, pre-exercise (baseline) values for bronchial permeability were established and each child went through an exercise test. After exercise, bronchial permeability was determined again at the same time intervals as on the control day. Children withheld using β_2-adrenoceptor agonists and methylxanthines for 8 h, sodium cromoglycate or nedocromil sodium for 1 day, antihistamines for 2 days and any exercise for 1 day prior to the study. The study protocol was approved by the local Ethics Committee.

Exercise challenge

The exercise test and determination of bronchial permeability was undertaken in a temperature-controlled

Table 1 Clinical features of the patients

Clinical features	Asthma severity			Total
	Mild (*n* = 55)	Moderate (*n* = 40)	Severe (*n* = 8)	
Gender (male/female)	32/23	34/6	6/2	72/31
Age (years)				
Range	6–15	7–15	9–13	6–15
Mean ± SD	9.9 ± 2.7	12.5 ± 3.0	11.3 ± 2.1	11.0 ± 2.8
Duration of disease (years)				
Range	1–10	1–12	4–9	1–12
Mean ± SD	3.6 ± 2.7	6.5 ± 3.0	6.0 ± 2.1	4.9 ± 3.1
No. atopic*	35	38	8	81
Baseline PEFR on control day (% predicted)				
Range	74–116	76–112	72–96	72–116
Mean ± SD	97.0 ± 9.7	94.5 ± 9.7	80.9 ± 10.4	94.4 ± 10.1
Baseline PEFR of the study day (% predicted)				
Range	76–119	75–121	72–100	72–121
Mean ± SD	90.5 ± 20.5	96.3 ± 13.5	75.0 ± 11.4	94.4 ± 12.2

*Atopic, positive skin test to one or more allergens, including house dust mite, pollen, animal dander, microfungi.
PEFR, peak expiratory flow rate.

(20–22°C) room with relative humidity between 45 and 50%. After donning a nose clip, each child did a series of step-ups (on and off a bench; range of bench height 0.2–0.35 m; actual bench height for each individual patient determined by Hettinger's nomogram according to the length of the patients' legs) for 6 min. The intensity of the test was designed to ensure a pulse rate of up to 170–180 b.p.m. for at least 4 min. The rhythm of the exercise was provided by a metronome. Pulmonary function was monitored with a low- and middle-range peak-flow meter (Clement Clarke International, Edinburgh, UK) and PEFR was measured. At least three acceptable and reproducible PEFR values were obtained and the highest value was selected for subsequent analysis. Predicted normal values were obtained from Knudson *et al.*[11]

Assessment of response

Bronchial responses to exercise are expressed as maximum percentage fall in PEFR from the pre-exercise (baseline) values according to the following formula:

$$((\text{baseline values} - \text{postexercise values})/\text{baseline values}) \times 100\%$$

The percentage fall in PEFR was calculated for different time points after exercise for all children.

We considered the first fall in PEFR $\geq$ 10% than the pre-exercise value to be an early asthmatic reaction (EAR). The late asthmatic reaction (LAR) was defined as the second fall in PEFR $\geq$ 10% in comparison with levels obtained on the control day, after EAR had been restored.

The severity of broncho-obstruction (for both LAR and EAR) was considered as mild in cases in which the fall in PEFR was 10–20%, moderate in cases where the fall was 21–30%, severe when the fall in PEFR was 31–40% and very severe when the fall was greater than 41% baseline PEFR values.

Statistical analysis

Study data were analyzed by the calculation of the mean $\pm$ SD, 95% confidence intervals (CI), Student's *t*-test, Yates's corrected χ^2-test and Pearson's product–moment correlation coefficient. $P < 0.05$ was considered significant.

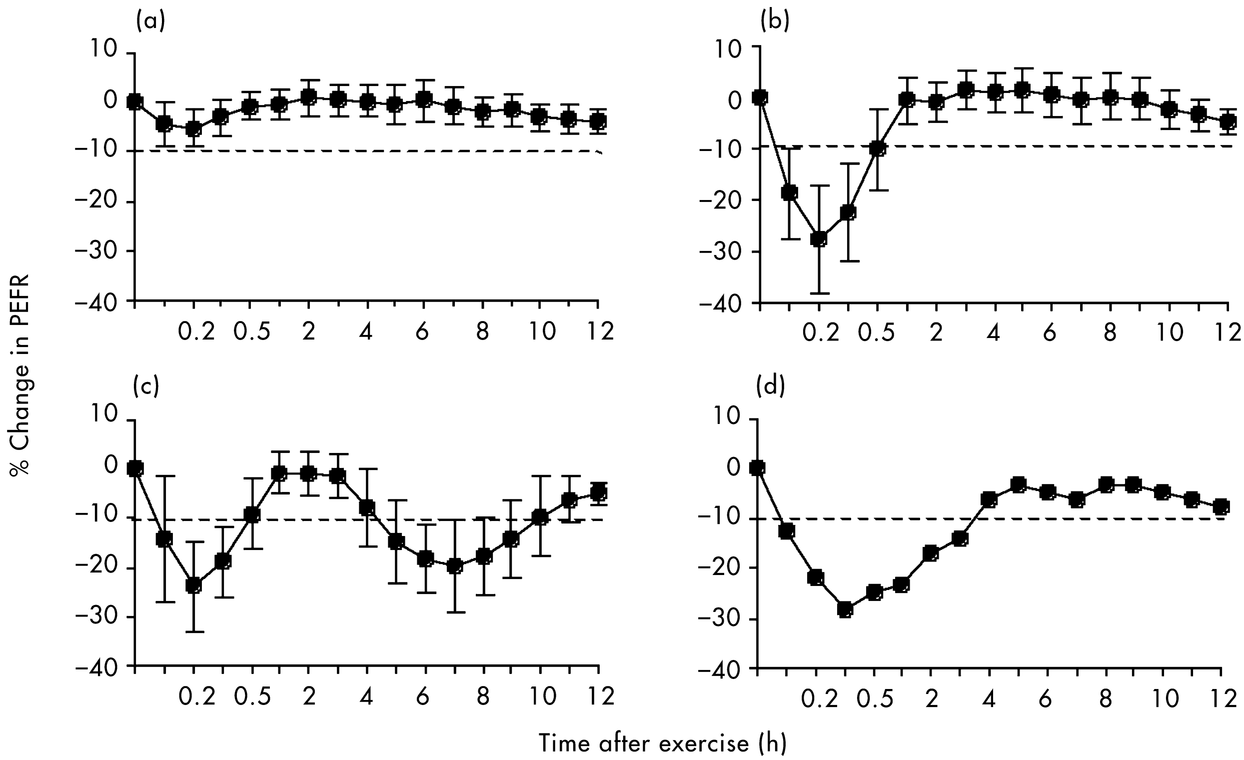

Fig. 1 Types of bronchial response to exercise among children with asthma, namely (a) the non-obstructive response, (b) the isolated early airway response (EAR), (c) the dual-waved airway response and (d) prolonged EAR. (--------), 10% fall in peak expiratory flow rate (PEFR).

RESULTS

The exercise challenge was easy to perform and all children were able to complete the test without any complications, even patients with severe asthma. No significant difference in mean ± SD baseline PEFR values between the control and study days was observed ($t = 0.166$; $P = 0.434$).

Types of responses

There were four types of responses to exercise challenge observed in asthmatic children. The first was observed in 34 patients (33.0%) and was characterized by an absence of any disturbance of bronchial permeability after exercise challenge (non-obstructive response; Fig. 1a). Forty-one children (39.81%) had a response in the form of an isolated EAR (Fig. 1b), whereas in 27 patients (26.2%) the bronchial response had dual-waved character and included the EAR followed by a LAR (Fig. 1c). The last type of response to exercise challenge, namely prolonged EAR, was observed only in one child (0.97%) with moderate asthma (Fig. 1d).

No significant difference in terms of clinical features was observed among the children with different types of responses to exercise (Table 2).

According to the data, all patients could be divided into one of two groups, namely children with either EIB-negative responses (non-obstructive type) or EIB-positive responses (isolated EAR, dual-waved and prolonged EAR types).

A significant prevalence of EIB-positive responses was observed among children with moderate and severe clinical asthma (Table 3).

For further analysis, we chose the group of children with EIB-positive responses.

Early asthmatic reaction

An EAR was typical for all three types of EIB-positive responses (Fig. 1b–d) and was present in 69 children (67.0%) with asthma. We did not observe any significant differences in the parameters of EAR between children with either isolated EAR or dual-waved types of bronchial response (Table 4).

Table 3 Prevalence of exercise-induced broncho-obstruction-positive types of responses according to clinical severity among asthmatic children

EIB	Asthma severity			Total
	Mild	Moderate	Severe	
No. children (%)				
Positive	32 (58.2)	29 (72.5)	8 (100)	69
Negative	23	11	0	34
Total	55	40	8	103

$\chi^2 = 6.422$; d.f. = 2; $P < 0.05$.
EIB, exercise-induced broncho-obstruction.

Table 2 Clinical features of patients according to type of response

Clinical features	Type of response			
	Non-obstructive ($n = 34$)	Isolated EAR ($n = 41$)	Dual-waved ($n = 27$)	Prolonged EAR ($n = 1$)
Age (years)				
Range	6–15	6–15	6–15	15
Mean ± SD	10.1 ± 2.7	10.9 ± 2.7	10.9 ± 2.9	
95% CI	8.4–11.8	10.0–13.2	9.1–12.7	
Gender (males/females)	23/11	30/11	18/9	1/0
Asthma severity (mild/moderate/severe)	23/11/0	19/17/5	13/11/3	0/1/0
No. atopic	25	32	23	1
Duration of disease (years)				
Range	1–11	1–12	1–8	12
Mean ± SD	4.5 ± 3.3	5.3 ± 3.2	4.4 ± 2.4	
95% CI	1.3–7.7	2.5–8.1	2.0–6.8	
Baseline PEFR (% predicted)				
Range	76–115	77–119	73–119	119
Mean ± SD	93.5 ± 10.2	95.3 ± 10.8	93.1 ± 15.6	
95% CI	91.4–95.6	93.1–97.5	89.9–96.3	

There were no significant differences observed.
PEFR, peak-expiratory flow rate; EAR, early asthmatic reaction; CI, confidence interval.

The prevalence of different degrees of EAR severity according to the severity of clinical asthma is shown in Fig. 2.

Interdependence of the degree of severity of EAR with the severity of asthma ($\chi^2 = 11.181$; d.f. = 6; $P > 0.05$) was not recorded.

There was no correlation between baseline values of PEFR and the greatest fall in PEFR (Fig. 3).

Late asthmatic reaction

A LAR was observed in 27 EIB-positive asthmatic children (26.21%) and was the reason for the dual-waved response to the exercise challenge.

The mean (± SD) maximum fall in PEFR for the control day was 5.6 ± 2.2% and this was significantly less in comparison with the maximum fall in PEFR for the same time-point on the day of exercise ($t = 12.203$; $p < 0.0001$). The characteristics of the LAR are given in Table 5.

Table 4 Comparative characteristics of the early asthmatic reaction in asthmatic children according to type of response

Parameters	Types of bronchial responses			d.f	*t*	*P**
	Isolated EAR	Dual-waved	Prolonged EAR			
Baseline PEFR (% predicted)						
Range	77–119	73–119	119			
Mean ± SD	95.3 ± 10.8	93.1 ± 15.6		66	0.69	0.2
95% CI	93.1–97.5	89.9–96.3				
Maximum fall in PEFR (%)						
Range	13–49	13–47	28			
Mean ± SD	29.1 ± 10.1	25.9 ± 9.1		60	–1.35	0.09
95% CI	25.4–32.8	22.3–29.5				
Time taken for maximum fall in PEFR (min)						
Range	5–15	5–15	15			
Mean ± SD	9.9 ± 2.6	10.2 ± 3.5		44	–0.39	0.35
95% CI	8.2–11.6	8.0–12.4				
Duration (min)						
Range	10–55	10–55	~ 4 h			
Mean ± SD	37.7 ± 18.4	37.2 ± 16.3		60	0.108	0.46
95% CI	31.8–43.6	31.9–42.5				

*Isolated early asthmatic reaction (EAR) compared with the dual-waved response.
PEFR, peak-expiratory flow rate; CI, confidence interval.

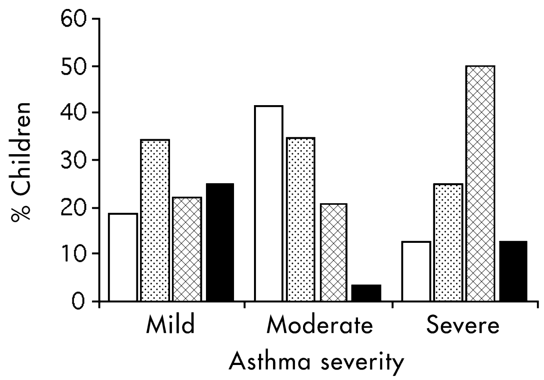

Fig. 2 Prevalence of different severity forms of early airway response (EAR) according to the severity of asthma among exercise-induced broncho-obstruction (EIB)-positive asthmatic children. (□), mild EAR; (▒), moderate EAR; (⊠), severe EAR; (■), very severe EAR. There were 32 children with mild asthma, 29 with moderate asthma and eight with severe asthma.

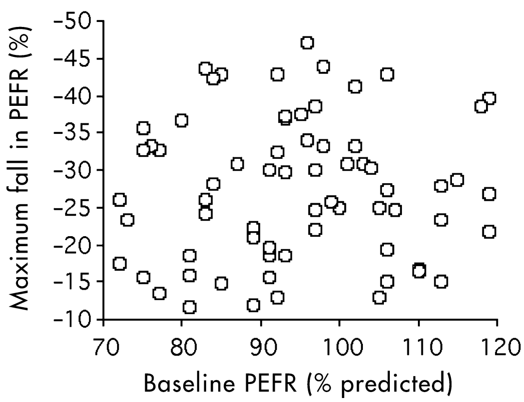

Fig. 3 Relationship between baseline peak expiratory flow rate (PEFR) values and maximum fall in PEFR during the early airway response (EAR) in asthmatic children with exercise-induced broncho-obstruction (EIB)-positive responses. ($r = –0.111$; $P > 0.05$)

Table 5 Characteristic of the late asthmatic reaction (LAR) in asthmatic children with a dual-waved response

Parameters	Values
Onset time (h)	
Range	1–6
Mean ± SD	4.7 ± 1.6
95% CI	3.1–6.3
Duration (h)	
Range	3–8
Mean ± SD	5.1 ± 1.2
95% CI	4.4–5.9
Maximum fall in PEFR (%)	
Range	16–49
Mean ± SD	25.6 ± 8.5
95% CI	22.3–28.9
Time for maximum fall in PEFR after onset of EAR (h)	
Range	1–6
Mean ± SD	2.0 ± 1.2
95% CI	0.2–3.8

PEFR, peak expiratory flow rate; CI, confidence interval; EAR, early asthmatic reaction.

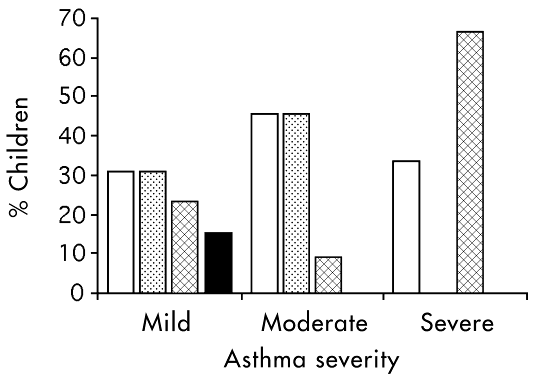

Fig. 4 Prevalence of different degrees of severity of the late asthmatic reaction (LAR) according to the severity of asthma among asthmatic children with a dual-waved response. (□), mild LAR; (⚄), moderate LAR; (⊠), severe LAR; (■), very severe LAR. There were 12 children with mild asthma, 12 with moderate asthma and three with severe asthma. PEFR, peak expiratory flow rate.

The prevalence of different degrees of severity of LAR according to the severity of clinical asthma is presented in Fig. 4.

The severity of the LAR was not dependent on the severity of clinical asthma ($\chi^2 = 7.179$; d.f. $= 6$; $P > 0.05$).

No correlation was observed between baseline PEFR values and maximum fall in PEFR during LAR (Fig. 5). However, a correlation between maximum falls in PEFR for EAR and LAR was noted (Fig. 6).

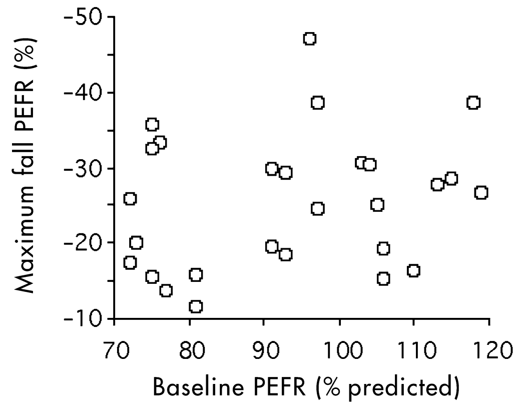

Fig. 5 Relationship between baseline peak expiratory flow rate (PEFR) values and maximum fall in PEFR during the late asthmatic reaction (LAR) in asthmatic children with a dual-waved response ($r = -0.221$; $P > 0.05$).

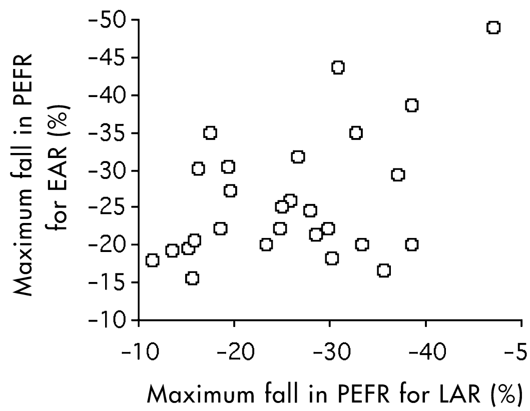

Fig. 6 Relationship between maximum fall in peak expiratory flow rate (PEFR) during the early airway response (EAR) and the late asthmatic reaction (LAR) in asthmatic children with a dual-waved response ($r = 0.4429$; $P < 0.01$).

Discussion

Two basic types of response have been determined in many studies of the effects of exercise on changes of airflow in asthmatic subjects. The first type of response is non-obstructive, or the EIB-negative type, which is characterized by an absence of airflow limitation after exercise, with a prevalence of 10–60%. The second type of response is Isolated EAR, or an EIB-positive response, which has been recognized in 40–90% of asthmatic patients and is characterized by the presence of differing degrees of severity of disturbance of airway permeability.[2–4,12] At the same time, some investigators indicated the presence of a third type of responses, namely the biphase or dual-wave, which has been observed in 30–89% of EIB-positive asthmatic patients and is characterized by a second disturbance in bronchial permeability (LAR) after recovery of EAR.[13–17] Speelberg *et al.* have reported that 8% of a group of 86 adult patients with asthma and chronic obstructive pulmonary disease had an isolated LAR response.[18] In the present study, we found four types of response to exercise among the studied groups of asthmatic children, who were divided into EIB-negative and EIB-positive groups. The first group of children was defined as having a non-obstructive type of response and this was observed in 33.0% of asthmatic children. The EIB-positive group included children with three types of response to exercise challenge and was found in 67.0% of children in the present study. The isolated EAR response was observed in 59.4%, whereas the dual-wave response was seen in 39.1% of EIB-positive asthmatic children. The last type of response seen was a prolonged EAR, with immediate airflow limitation peaking at 15 min after exercise and prolonged recovery over a period of 4 h (Fig. 1d). This type of response was rare and was observed in only one patient. No cases of biphasic-waved, progressive and early–late responses, which have been identified for allergen-induced bronchial challenge in asthmatic subjects,[19] were observed in the present study. In fact, all EIB-positive types of response had an EAR phase.

We did not observe any significant effect of the clinical features of asthma, such as severity and duration of disease, baseline bronchial permeability, atopic status, age and gender of children on the prevalence of the four types of response to exercise. However, our research has shown that the severity of the asthma does have an effect on the prevalence of EIB-positive types of responses among asthmatic children and this confirms previous observations.[12,20]

Some investigations have reached very different conclusions about the correlation of the severity of EAR and the severity of asthma.[21–23] In the present study, no relationship between the clinical severity of asthma and the severity of EAR was observed. Moreover, our observations confirm the conclusions of Linna regarding the absence of any correlation between the severity of the EAR and baseline status of bronchial permeability.[24] Thus, we did not observe any dependence of the severity of EAR on the duration of asthma, atopy status, age and gender of the patients.

Comparative analysis of the basic characteristics of EAR has shown an absence of any significant difference between asthmatic patients with isolated EAR and dual-waved responses.

A LAR to exercise has been demonstrated in different studies of EIB-positive patients. That is, Sano *et al.* have reported that 28.1% of a group of 32 EIB-positive asthmatic children also had LAR after exercise.[25] Bierman *et al*. recorded a LAR in eight of nine adult asthmatic patients (89%).[14] Meanwhile, Iikura *et al.* and Chhabra and Ojha have observed a 50% prevalence rate of EAR in EIB-positive asthmatic children and adults, respectively.[15,26] In the present study, the prevalence of LAR among EIB-positive asthmatic children was 39.1%. Because the mean of the maximum fall in PEFR on the control day was significantly smaller that at the same periods of time on the study days, we consider the LAR to be a true phenomenon and not an artefact.

As known, LAR is a process related to the inflammation reaction in the bronchi and it is characterized by a long duration.[27] A previous study has shown that the duration of LAR after exercise ranges from 3 to 12 h.[18] We have not observed a duration of LAR for more than 8 h and, most often, the LAR lasted for approximately 4–5 h. Our research data demonstrate no difference between subjects with an isolated EAR and dual-waved response with respect to age, gender, baseline expiratory flow, duration of disease or atopic status and this confirms results from previous studies.[15] Like Chhabra and Ojha, we did not find any correlation between baseline PEFR values and maximum fall in PEFR.[26]

Boulet *et al*. established the dependence of the severity of the LAR on the severity of EAR in children, but not in adults.[17] The same results (a correlation between maximum falls in PEFR for EAR and for LAR) was obtained in children in the present study.

It is well known the mechanisms of broncho-obstruction after exercise are indirect and depend on the release of mediators from mast cells.[27] Inhaled β_2-adrenoceptor agonists, which are traditionally used in the treatment of EIB in asthmatic children, have only a direct bronchodilator effect and they do not block the development of LAR. Because their efficacy is limited among patients with a dual-waved response, combined therapy with mast cells stabilizers, such as nedocromil sodium, sodium cromoglycate or the loop diuretic furosemide, is necessary. Because inhaled furosemide has an equal bronchoprotective effect to that of nedocromil sodium[28] or sodium cromoglycate[29] and a similar bronchodilator effect to that of salbutamol,[30,31] without any of the side effects, its use as monotherapy for EIB in children may be effective.

Thus, the results of the present study show that responses to exercise in asthmatic children may be one of four types. The clinical features of the disease, such as severity and duration of disease, baseline values for bronchial permeability, atopic status, gender and age of patients, do not predict the development of one or another type of response. However, children with moderate and severe asthma more often have an EIB-positive type of response than do children with mild asthma.

In conclusion, we consider that the response to exercise in asthmatic children is heterogeneous and, quite possibly, is an individual feature of each asthmatic child.

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