Exercise-Induced Asthma Among Thai Asthmatic Children

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Abstract

Background: Approximately seventy per cent of asthmatic children from temperate climates, with normal lung function, have exercise-induced asthma (EIA). There is certain evidence to suggest that EIA may be less frequently encountered among children who live in tropical climates. Prevalence of EIA in Asian asthmatic children has never been thoroughly studied.

Objective: To study the prevalence of EIA among Thai asthmatic children.

Method: A prospective study was performed to determine the prevalence of EIA in 44 Thai asthmatic children who were able to perform the spirometric maneuver. Subjects were randomly selected asthmatic children from the Pediatric Allergy Clinic, Department of Pediatrics, Siriraj Hospital. They were subjected to exercise testing on a steady state, motor-driven treadmill for 6 minutes (mean speed ± SD = 3.7 ± 0.4 km/h, mean level of inclination ± SD = 15.0 ± 5.2 degrees). The testing was conducted in a temperature-controlled (mean temperature ± SD = 24.4 ± 0.8°C) and humidity-controlled environment (mean relative humidity ± SD = 41.7 ± 2.1 %). Lung function tests were performed before exercise, immediately after and at 3, 5, 10, 15, 20 and 30 minutes after exercise. Results of the lung function test were calculated as per cent falls of forced expiratory volume in 1 sec (FEV_1), peak expiratory flow rate (PEFR), and forced expiratory flow at 25 per cent-75 per cent (FEF_{50}) from baselines. EIAs were diagnosed when drops of FEV_1, PEFR and FEF_{50} were greater than 20 per cent, 25 per cent and 25 per cent from baseline values, respectively.

Results: Of the 44 patients studied (31 boys and 13 girls; mean age 11.9 years), 34 per cent had mild asthma. Fifty-nine per cent had moderate asthma and 7 per cent had severe asthma. Eleven patients (25%) had EIA diagnosed by significant falls of FEV_1's (26 ± 12.6%), whereas, 13 patients (30%) and 20 patients (45%) had EIA defined by significant drops of PEFR's and FEF_{50}'s, respectively. A total of 23 patients (52%) had EIA by one or more diagnostic criteria. Peak times for EIA as diagnosed by FEV_1, PEFR and FEF_{50} occurred at 3, 10, and 10 minutes respectively, after exercise. Most EIA episodes observed were of mild degree.

Conclusions : The prevalence of EIA in Thai children is much lower than figures reported in studies from Western countries. By using a significant fall of FEV_1's as the diagnostic criteria, only 25 per cent were diagnosed as having EIA. By PEFR and FEF_{50} criteria, percentages of EIA increased to 30 per cent and 45 per cent respectively. Screening for EIA, therefore, may not be an appropriate diagnostic tool for the diagnosis of childhood asthma in tropical climates.

Key word : Exercise-Induced Asthma, EIA, Asthma, Children, Tropical, Thailand

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Exercise-induced asthma (EIA) is a temporary increase in airway resistance occurring several minutes after completion of strenuous exercise(1). EIA has been observed in a majority of children with asthma living in Western countries (60%-70%)(2-4). It is believed that EIA is initiated by an abnormally high rate of water and heat loss from alveoli and from conducting airways to external environment in a relatively short period of time(5). The mechanism by which water-loss can induce bronchospasm is through a transient increase in osmolarity of the periciliary fluid in airways and through a reduction in the temperature of the bronchial mucosa(6,7). However, the precise mechanism of how the increase of osmolarity and/or a reduction in temperature causes bronchial smooth muscle contraction is not known. Nevertheless, mast cell mediators are released in the airways in response to these physical stimuli during EIA(8). Vagal afferent pathways can be activated directly by a change in osmolarity and temperature or by inflammatory mediators resulting in reflex bronchoconstriction(9).

It has been a consensus among pediatricians in Thailand, though not fully substantiated, that EIA is infrequently observed among Thai asthmatic children. In support of this contention, a study from Ghana demonstrated a low prevalence of EIA among normal 9-16 years old school children (3.8%)(10), whereas, a similar study in normal British children reported a much higher prevalence of 14.9 per cent (11). Possible explanation for low prevalence of EIA in tropical countries could be due to a relative high humidity and temperature in these climates. Thus far, no thorough study on EIA has yet been reported from South East Asian countries.

The main objective of this study was to determine the prevalence of EIA among Thai asthmatic children.

METHOD

The study was a prospective study involving 44 asthmatic children randomly recruited from the Pediatric Allergy Clinic, Siriraj Hospital, Bangkok, Thailand. Asthma was defined as episodic airway obstructions which showed a reversibility of at least 15 per cent, as measured by FEV_1 or PEFR, after inhalation of 200 mcg of salbutamol delivered from a metered-dose inhaler(12). All Thai asthmatic children, over 6 years of age, who were not having acute attack and able to perform the spirometric maneuver, were invited to participate in the study. Exclusion criteria were chronic heart disease, significant hypertension, thyrotoxicosis, musculoskeletal disease, active bronchospasm, and cases with an upper respiratory tract infection within 10 days prior to the study(13). All eligible recruits were subjected to a blinded randomization code (0-exclusion, 1-inclusion) and only those with positive responses (i.e. code-1) were included in the study. Anthropometric details and asthma medication regimens were recorded. Asthma severity were classified according to the 1991 Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma, the prevailing guideline during the time of the study(12). According to this guideline, 16, 25, and 3 patients fell into the severity classification of mild, moderate

and severe asthmatics, respectively. Most moderate asthmatics received daily inhaled steroids (less than 200 mcg/day) to optimally control their asthma symptoms.

Asthma medications were withheld for a certain length of time prior to the study as follows: β_2-agonists (inhaled/oral) for 6-8 hours, anticholinergics, cromolyn sodium and ketotifen for 72 hours, sustained-release theophyllines, long-acting antihistamines, slow release oral β_2-agonists and inhaled steroids for 24-36 hours[14]. None of the patients had taken any oral steroids prior to the study. Patients were instructed to abstain from large meals, smoking, coffee and coca-cola drinks for at least 4 hours before the exercise testing[15].

Lung function testings were performed using a hot-wire computerized spirometer (Minato-Pal, Minato Medical Science, Osaka, Japan) before and after an exercise challenge following guidelines from the American Thoracic Society[16]. The study was performed in an exercise laboratory which maintained a constant ambient environment (mean temperature ± SD = 24.4 ± 0.8°C and a mean relative humidity ± SD = 41.7 ± 2.1 %). Exercise challenges performed on a steady-state, motor-driven treadmill with slopes and velocities adjusted until the predicted workload of 80 per cent maximum for age was achieved[17]. Exercise was then maintained at this level for a duration of 6 minutes[15]. Electrocardiogram (EKG) and oxygen saturation (SaO_2) were monitored continuously during the exercise challenge.

At the end of the exercise period, spirometric maneuvers were repeated immediately after and at 3, 5, 10, 15, 20 and 30 minutes after exercise. The highest of the two spirometric values, at each time point were used to calculate per cent fall of FEV_1, PEFR and FEF_{50}. Auscultation was performed to detect any overt wheezing. Bronchoconstriction was detected clinically in one patient and by spirometry in the other. Both were rapidly reversed by 0.5 ml. of 5 per cent nebulized salbutalmol solution in 2 ml. of normal saline. Although safety precautions included preparation of CPR instruments and drugs [15], no patient developed serious adverse effects from the exercise.

The per cent fall of FEV_1, PEFR and FEF_{50} was calculated by using the formula[18]:

$$\text{Maximum \% fall} = \frac{100 \times (\text{baseline lung function} - \text{lowest lung function})}{\text{baseline lung function}}$$

Table 1. Criteria for scoring of EIA severity.

	Mild %	Moderate %	Severe %
FEV_1	20-34	35-50	>50
PEFR	25-39	40-60	>60
FEF_{50}	25-39	40-60	>60

EIA was defined as a drop below baseline value of 20 per cent for FEV_1, 25 per cent for PEFR or 25 per cent for FEF_{50}. Severity of EIA is graded as in Table 1[15].

Ethics

Parents and children gave written and verbal informed consent prior to the study. The study was approved by the Human Ethic Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University.

Statistics

Analyses of variance (ANOVA) with repeated measures were used to detect any significant differences between percentages of predicted lung functions, at different time points, between EIA positive and EIA negative patients. Statistical significance was ascertained at a p-value of < 0.05.

RESULTS

Forty-four patients (31 boys and 13 girls, mean age ± SD = 11.9 ± 7.9 years and mean height ± SD = 137.6 ± 13.9 cm) were included. The mean speed (± SD) of the treadmill was 3.7 ± 0.4 km/h and mean level (± SD) of inclination of the slopes was 15.0 ± 5.2 degrees. Mean values of per cent-predicted baseline lung functions (± SD) in these patients were 89.8 ± 16.9 per cent for forced vital capacity (FVC), 89.1 ± 13.3 per cent for FEV_1, 93.5± 30.4 per cent for PEFR and 84.8 ± 20.1 per cent for FEF_{50}.

By using various EIA criteria as described above, eleven patients (25%) had EIA by falls of ≥ 20 per cent of FEV_1, 13 patients (30%) had falls of PEFR of ≥ 25 per cent and 20 patients (45%) had falls of FEF_{50} of ≥ 25 per cent. Eight patients

(18%) met criteria for EIA by both FEV_1 and PEFR criteria; 11 patients (25%) by both FEV_1 and FEF_{50} criteria; 10 patients (23%) by both PEFR and FEF_{50} criteria, and 8 patients (18%) met all three criteria. Overall, 23 patients (52%) had EIA by one or more diagnostic criteria.

Fig. 1 illustrates the time course of FEV_1 in patients with and without EIA. Peak times for EIA to occur for FEV_1, PEFR and FEF_{50} were 3, 10 and 10 minutes after exercise, respectively. At these time points, maximal falls (± SD) of FEV_1, PEFR and FEF_{50} were 26.4 ± 12.6 per cent, 33.0 ± 14.2 per cent and 30.5 ± 20.2 per cent, respectively.

Most of the EIA occurring in these patients were of mild degree. Table 2 shows the number of patients who developed EIA classified by EIA severity.

DISCUSSION

To our knowledge, this is the first study from Asia to establish the frequency of EIA among Asian asthmatic children. The prevalence of EIA from this study was 25 per cent (FEV_1), 30 per cent (PEFR) and 45 per cent (FEF_{50}) which is relatively low compared to values in previous reports (60-70%) [2-4]. Low prevalence of EIA among these children rendered the exercise challenge a poor clinical test for the diagnosis of childhood asthma in Thailand.

The prevalence of EIA by FEV_1 of 25 per cent in Thais is much lower than 70 per cent from Italy[4], 71 per cent from Canada[3] and 60 per cent from USA[2]. A previous study among randomly selected children in Ghana also observed a low prevalence of EIA (3.8%)[10]. Since one mechanism for the development of EIA is a loss of fluid from the airway during exercise as well as a decrease in airway temperature, the lower prevalence of EIA in children from tropical regions could be due to high humidity and temperature in this climate.

However, when a less stringent criteria for EIA were applied (per cent fall of $FEV_1 \geq 10\%$ from baselines)[3], the prevalence of EIA in the present

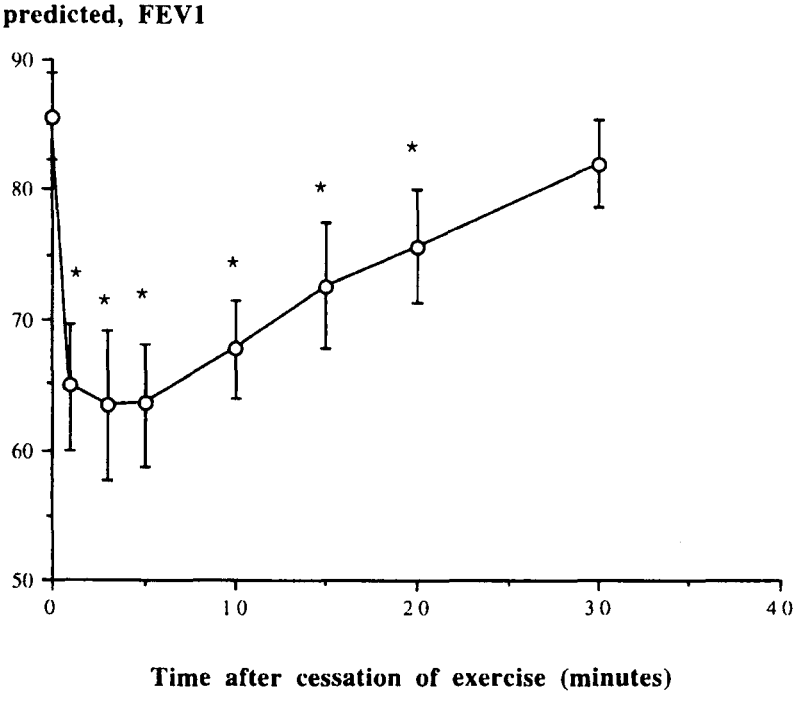

Fig. 1. Time course of changes in per cent predicted of FEV_1's among EIA positive patients (11 patients) *vs* EIA negative patients (33 patients).

Table 2. Number of patients who developed EIA classified by EIA severity.

	FEV_1	%	PEFR	%	FEF_{50}	%
Mild	7	15.9	7	15.9	12	27.2
Moderate	3	6.8	5	11.4	5	11.4
Severe	1	2.3	1	2.3	3	6.8
Total	11	25	13	29.5	20	45.4

study was still low (22 children or 50% had EIA). Since workload during exercise is a major factor involved in the occurrence of EIA, the authors were meticulous that children achieved their maximal efforts during exercise by the fact that all cases achieved greater than 80 per cent of their maximum heart rate for age (mostly over 180 beats per minute). In addition, all exercise challenges were performed in an environment much milder than the normal all year round outside ambient environment for Thailand (mean temperature = 27.5°C, mean relative humidity = 75%, Department of Meteorology, Ministry of Transport and Communications, Thailand). For all these reasons, the authors feel that the low prevalence of EIA is real and the figure of EIA in normal outside conditions for Thailand could have been even lower than the figures observed in the present study. Some may argue that the treadmill exercise is less asthmogenic than free running but an investigation in controlled environmental conditions, exercise intensity, and airway status, indicated that treadmill and free running provoked similar rates of EIA and could be used interchangeably for EIA testing[19].

Since results of exercise challenge correlates well with PC_{20} from histamine and methacholine challenges[20], low prevalence of EIA in the present study could suggest a lower degree of airway inflammation among the children studied. Although most of the moderate asthmatics in the present study were on low dose inhaled corticosteroids (less than 200 mcg/day) prior to the time of challenge which could have lowered their degree of airway reactivity, Kerrebijn et al have shown that even with a treatment of high dose inhaled budesonide (600 mcg/day) for 6 months, five of the twelve children with mild atopic asthma failed to show an increase of their PD_{20} of methacholine 2 fold over their baselines [21]. Similarly, at least 5 of the 14 severe adult asthmatics failed to show a substantial improvement in their PD_{20} after 10 weeks treatment with high dose inhaled beclomethasone (800 mcg/d)[22]. Thus, it is unlikely that low dose inhaled steroids as in the present study would have changed much of the airway reactivity in our study group. It is unfortunate that methacholine challenges were not performed concomitantly with exercise challenges which would clarify this issue in the present study.

The timing of maximal fall of FEV_1 from this study occurring at 3 minutes after exercise, differed from 10 minutes observed among subjects of all age ranges in most studies[18]. Reasons for this difference is unknown but it was pointed out by Godfrey et al that the most severe airway obstruction, after exercise, tended to occur earlier among children than in adults[19].

Among all lung function parameters, FEF_{50}'s had the highest sensitivity for diagnosing EIA in the present study followed by PEFR's and FEV_1's which is in agreement with findings from other studies[23,24]. This could be due to the fact that changes of FEF_{50} represent changes occurring in small airways whereby the major pathology of asthma is located[25]. In clinical practice, PEFR is often used to establish EIA. However, a recent study indicated that PEFR with free running might not be appropriate for such a diagnosis[26].

In summary, the result of the present study indicates that in this group of patients, a low prevalence of EIA was observed. Even with the most sensitive parameters (FEF_{50}), the prevalence of EIA (45%) in this group of asthmatic children is still too low for one to accept exercise testing as the clinical diagnostic test for childhood asthma in Thailand.

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อาการหอบหืดที่เกิดจากการออกกำลังกายในเด็กที่เป็นโรคหอบหืด

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อาการหอบหืดจากการออกกำลังกายพบได้บ่อยในผู้ป่วยเด็กชาวตะวันตกที่เป็นโรคหอบหืด (พบบ่อยได้ถึงร้อยละ 70%) แต่การศึกษาถึงอาการดังกล่าวในผู้ป่วยเด็กในทวีปเอเชียยังมีน้อย และไม่เคยได้รับการศึกษาในประเทศไทยมาก่อน ในการศึกษาครั้งนี้ผู้วิจัยศึกษาอุบัติการณ์ของอาการหอบหืดจากการออกกำลังกายในผู้ป่วยเด็กไทยที่เป็นโรคหอบหืดจำนวน 44 คน ซึ่งอาสาสมัครมาจากคลินิคโรคภูมิแพ้เด็กของโรงพยาบาลศิริราช (ชาย 31 คน, หญิง 13 คน, อายุเฉลี่ย 11.9 ปี) โดยผู้ป่วยร้อยละ 34 จัดอยู่ในกลุ่ม Mild asthma, ร้อยละ 59 อยู่ในกลุ่ม Moderate asthma และร้อยละ 7 อยู่ในกลุ่ม Severe asthma ผู้ป่วยทั้งหมดได้รับการตรวจโดยวิ่งบนสายพาน (Treadmill) เป็นเวลา 6 นาที (ความเร็วเฉลี่ย 3.7 $\pm$ 0.4 กม/ชม และความชัน 15 $\pm$ 5.2 องศา) ในห้องที่มีอุณหภูมิและความชื้นที่คงที่ ผู้ป่วยได้รับการตรวจการทำงานของปอดที่เวลา 0, 3, 5, 10, 15, 20 และ 30 นาที หลังการออกกำลังกาย การวินิจฉัยว่าเกิดอาการเกิดการหอบหืดหลังการออกกำลังกายทำโดยใช้ค่า FEV_1 ที่ลดลงร้อยละ 20 (จากค่า Baseline) หรือค่า PEFR ที่ร้อยละ 25 หรือค่า FEF_{50} ที่ร้อยละ 25 ตามลำดับ จากการศึกษานี้พบว่าผู้ป่วยเด็ก 11 คนได้รับการวินิจฉัยว่าเกิดอาการหืดหลังการออกกำลังกายจากการลดลงของ FEV_1 (ร้อยละ 25) และ 13 คน (ร้อยละ 30) จากการลดลงของค่า PEFR และ 20 คน (ร้อยละ 45) จากการลดลงของค่า FEF_{50} โดยอาการที่เกิดขึ้นอยู่ในขั้นที่ไม่รุนแรง อาการหอบหืดที่เกิดจากการออกกำลังกายในเด็กเกิดขึ้นมีอุบัติการณ์น้อยกว่าในผู้ป่วยเด็กจากประเทศตะวันตก ดังนั้นการตรวจว่าผู้ป่วยเด็กเป็นโรคหอบหืดโดยการตรวจการทำงานของปอดหลังการออกกำลังกาย อาจจะไม่เป็นการตรวจที่ไวเพียงพอในการวินิจฉัยโรคนี้ในผู้ป่วยเด็กไทย

คำสำคัญ : หอบหืด, การออกกำลังกาย, เด็กไทย

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