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Role of leukotrienes in exercise-induced bronchoconstriction before and after a pilot rehabilitation training program

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Background: Whatever the initial stimulus for the exercise-induced bronchoconstriction (EIB) observed in asthmatic patients after exercise, the final effect is release of bronchoactive mediators, especially cysteinyl leukotrienes. Exercise rehabilitation training programs have been reported to protect against EIB. The exact mechanism(s) involved are not well understood. However, this protective effect may be related to adaptation and better coordination during exercise, depletion of cysteinyl leukotrienes, and/or a sluggish cysteinyl leukotriene response to exercise. The aim of the present work was to test the hypothesis that improvement in the incidence and severity of post-exercise bronchoconstriction after a rehabilitation training program is related to a change in leukotriene levels in response to exercise.

Methods: Twenty asthmatic children aged 6–12 years and known to develop EIB were enrolled in an exercise training program for 12 weeks. The severity and incidence of EIB before and after training was assessed. Baseline and post-exercise sputum cysteinyl leukotriene levels were assessed before and after the training program.

Results: The training program offered significant protection against EIB with a concomitant decrease in sputum cysteinyl leukotriene levels in response to exercise.

Conclusion: A training program can result in depletion and/or a sluggish cysteinyl leukotriene response to exercise and may be responsible for the protective effect of training programs on EIB. It is recommended to use an exercise rehabilitation training program as a complementary tool in the management of bronchial asthma, especially EIB.

Keywords: asthma, leukotrienes, exercise-induced bronchoconstriction, sputum, cysteinyl leukotriene, rehabilitation training program

Introduction

Exercise in asthmatic patients is considered to be a double-edged sword. Subjects with asthma may show less tolerance to exercise due to worsening of asthma symptoms after exercise. However, physical training programs aiming to improve physical fitness, neuromuscular coordination, and self-confidence have been reported to have beneficial effects in asthmatics. However, the results of training protocols have been inconsistent and difficult to compare because of the different study designs used. The safety of exercise programs needs to be considered.[1]

Exercise-induced bronchoconstriction (EIB) occurs in 70%–80% of patients with symptomatic asthma. Cysteinyl leukotriene $(LT)_1$ has been recovered from urine during EIB, and cysteinyl LT_5 plays a central role in causing EIB and bronchoconstriction in response to cold air, as shown by the effects of a variety of cysteinyl LT_5 receptor antagonists and inhibitors of leukotriene synthesis.[2,3] Administration of these agents markedly attenuates the bronchoconstriction response after exercise.[4]

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Exercise rehabilitation training programs have been reported to protect against development of EIB in asthmatics. The exact mechanisms underlying this improvement are not fully determined. The protective effect may be because of better conditioning to exercise and/or blunting of the leukotriene response to exercise.[3] The aim of the present study was to test the hypothesis that improvement in incidence and severity of post-exercise bronchoconstriction after a rehabilitation training program is related to a change in leukotriene levels in response to exercise.

Materials and methods

Subjects

Twenty asthmatic children aged 6–12 years were included in this study, and were selected from the Children Health Insurance Hospital in the period between May 2008 and March 2011. Patients were diagnosed as having asthma according to the American Thoracic Society definition.[3] A thorough history-taking and clinical examination was performed for all the children, including their symptoms, attack pattern (whether perennial or seasonal), and duration and frequency of attacks. Family and personal history of atopic disease was also taken. Patients were asked about known provocational stimuli, including viral infection, irritants, and environmental allergens, and these data were recorded as an airway reactivity score.[5]

All the study subjects had a known history of EIB but were asymptomatic with clinically stable asthma at the time of the study. They were free from respiratory tract infection for at least 4 weeks prior to the study and also free from parasitic infection. Corticosteroids were withheld for at least 2 weeks before the first day of the study. Other antiasthmatic drugs were withheld for least 8 hours before the study day. The quantity and frequency of antiasthmatic medications before and after participation in a training program are part of the criteria used to assess improvement in the clinical severity of asthma.[6]

Clinicophysiologic assessment

Clinical severity score

Severity of asthma was assessed using the subjective clinical severity score devised by Brooks, which is based on common clinical parameters in the previous month.[7] On the basis of this subjective clinical score, four patients were assigned as mild (score ≤21), 14 as moderate (score 22–33), and two as severe (score >33) asthmatics. In addition, the overall status of asthma disease was assessed by airway reactivity score (ARS) which depends on the number of triggering exogenous physical factors that precipitate asthmatic attack.[7]

Pulmonary function testing

This measurement is based on examination of dynamic lung function via a so-called open system using dry computerized spirometry (Jaeger, Germany). Values recorded include forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC%, minute ventilation, and forced expiratory flow between 25% and 75% ($FEF_{25\%–75\%}$). All spirometric data are presented as percent predicted.

Exercise challenge test

The children underwent a protocol of muscle exercise using a bicycle ergometer (ER-900, kg 6/95, Ergoline GmbH and Co, Bitz, Germany). All children subjected to the exercise challenge test performed pre-exercise pulmonary function tests to obtain pre-exercise FEV_1, which needed to be >70% predicted in order to perform the exercise challenge test. Prior to the test, children were asked to rinse their oral cavity with saline solution and were encouraged to cough in order to expectorate sputum into sterile cups.

Exercise challenge protocol

The exercise challenge protocol consisted of warming up by pedaling at 0 W for 2 minutes, followed by a standard graded protocol of incrementally increasing workloads (20 W every 2 minutes). Heart rate and minute ventilation were measured at rest and with each load change. Once the target heart rate was reached (85%–90% of predicted maximum heart rate), a constant load protocol was applied, which required the subject to exercise at steady state for a further 5 minutes at the target heart rate. The exercise test protocol lasted approximately 10 minutes. FEV_1 was recorded at 5, 10, and 15 minutes post exercise. The maximum reduction in FEV_1 reported after exercise was taken as an indicator of response to exercise challenge. Another sputum sample was collected after the exercise challenge test. Pulmonary flow rates, exercise challenge protocol, and sputum analysis for cysteinyl leukotriene levels were done before and after 12 weeks of the rehabilitation training program.

Rehabilitation training program

The rehabilitation training program was applied using a protocol of incrementally increasing work load of 15 W every 2 minutes until heart rate reached 75% of the predicted maximum value. Once the target heart rate was reached, the load was maintained for 5 minutes. This was repeated three times in each session, two sessions per week, for 12 weeks. Breathing exercises were done between each session (the total duration of each session was 45 minutes).

Sputum induction and processing

The sputum samples were processed using accepted protocols.[8,9] Each child inhaled salbutamol (0.15mg/kg) 10 minutes before inhalation of hypertonic saline (3%, 4%, then 5%; 7 minutes for each inhalation). After each set of inhalations the FEV1 was measured and the child was asked to rinse their mouth and throat carefully with water. Then they were asked to expectorate sputum into a container, and the sample was immediately placed on ice. Saline inhalation was stopped if there was a reduction in $FEV_1 \geq 20\%$ of the post bronchodilator value, a troublesome cough or shortness of breath, or obtaining a sputum sample of good quality. Plugs of sputum were selected and dispersed using four volumes of cooled 0.1% dithiothreitol (Sigma Pharmaceuticals, Dorset, UK) freshly diluted in Dulbecco's phosphate-buffered saline (D-PBS) (Sigma). After 15 minutes an equal volume of cooled D-PBS was added and the sample was filtered through a 48 mm nylon gauze and centrifuged at 2000 rpm for 10 minutes. The supernatants were stored immediately at –80°C. Measurement of a mixture of crude cysteinyl leukotriene (C4, D4, and E4) levels in induced sputum at rest and post-exercise were completed using an enzyme linked immunosorbent assay.

Statistical analysis

The results obtained were analyzed using the Statistical Package for the Social Sciences version 20.0 software (IBM, Armonk, NY, USA). The data were calculated as the mean ± standard deviation, and the paired *t*-test was used to compare values before and after the training program. $P \leq 0.05$ was considered to be statistically significant.

Results

Table 1 shows a significant decrease in both airway reactivity score (from 8.50 ± 1.93 to 4.06 ± 1.06, $P < 0.01$) and clinical severity score (from 26.7 ± 5.30 to 15.10 ± 4.24, $P < 0.01$) after three months of the training program. Baseline pulmonary function (FVC, FEV_1, $FEF_{25\%–75\%}$) in the asthmatic children was within the normal range before and after the training program, with a significant increase in FEV_1 after the program. According to the case selection criteria, all patients showed a ≥12% post-exercise reduction in baseline FEV_1 (ie, positive exercise-induced asthma). FEV_1 and FVC post-exercise after the training program were significantly greater than the corresponding values before the training program. The mean percent fall in FEV_1 post-exercise before the training program was 25.57 ± 1.59, which was significantly attenuated after the training program (10.29 ± 16.58). After the training program, only eight of the 20 children developed positive exercise-induced asthma. By expressing the difference between the percent fall in FEV_1 post-exercise before and after the training program as a proportion of the percent fall before the training program, the result is considered as the percent protection. The training program offered significant protection (≥50%) against development of exercise-induced asthma in 16 cases. Exercise challenge resulted in a significant increase in sputum leukotriene levels before and after the training program. Sputum leukotriene levels post-exercise after the training program were significantly lower than before the training program. Also, the percent change in sputum leukotriene levels due to exercise before the training program (86.67 ± 93.03) was less than that after

Table 1 The effect of the training program on the pulmonary functions and sputum leukotrienes

	Before training program		After training program	
	Baseline	**Post-exercise**	**Baseline**	**Post-exercise**
Demographic data				
Age: 9.75 ± 1.55 (years)				
Wt: 35.35 ± 9.23 (kg)				
Ht: 139.70 ± 9.76 (cm)				
Clinical scores				
CSS	26.70 ± 5.30		15.10 ± 4.24*	
ARS	8.50 ± 1.93		4.06 ± 1.06*	
P. flow rates	82.09 ± 14.89	61.01 ± 13.22	86.61 ± 8.78	77.32 ± 10.72#
FVC in (% P)	92.04 ± 15.21	68.43 ± 15.3	99.35 ± 10.73*	87.45 ± 12.46#
FEV_1 in (% P)	83.34 ± 29.58		88.83 ± 19.38	
$FEF_{25\%–75\%}$ (% P)				
Percent fall in FEV_1	25.57 ± 1.59$		10.29 ± 16.58$,§	
Sputum cysteinyl leukotriene (pg/mL)	338.50 ± 210.85	536.65 ± 95.42	296.7 ± 95.42	397.80 ± 143.69#
Percent change in LT	86.67 ± 93.03$		33.70 ± 42.06$,§	

Notes: *$P < 0.05$, significant difference versus the baseline value before training program; #significant difference versus post-exercise value before training program; $significant change; §significant difference versus corresponding value before training.

Abbreviations: CSS, clinical severity score; ARS, airway reactivity score; FVC, forced vital capacity as percent predicted (% P); FEV_1, forced expiratory volume in one second; $FEF_{25\%–75\%}$, maximum mid-expiratory flow rate; LT, leukotrienes; Wt, weight; Ht, height.

the program (33.70 ± 42.06), but the difference did not reach statistical significance.

Discussion

Asthma is an obstructive disease of the airways characterized by airway inflammation and hyperreactivity. Airflow obstruction is influenced by bronchial wall edema, mucus production, smooth muscle contraction, and hypertrophy. The obstruction may be initiated by inflammatory events in the airways, particularly the release of inflammatory mediators from mast cells, macrophages, and epithelial cells. Airway hyperreactivity is an exaggerated bronchoconstrictive response to a variety of stimuli, including allergens, environmental irritants, viral respiratory infection, cold air, and exercise.[10]

Subjects with asthma have a unique response to physical activity. Exercise can provoke an increase in airway resistance leading to EIB. On the other hand, regular physical activity and participation in sports are considered to be beneficial in the management of asthma, especially in children and adolescents.[11,12]

EIB is defined as transient constriction of the airways as a consequence of vigorous exertion, and 70%–90% of patients with chronic asthma have EIB. Further, 40% of patients with allergic rhinitis have EIB. However, 5%–10% of subjects with EIB have no respiratory or allergic disease.[13] EIB is an exaggerated airway response to dehydration of the airways in the presence of inflammatory cells and their mediators. The airway narrowing is caused primarily by contraction of bronchial smooth muscle. The ability to humidify inspired air may be overwhelmed, causing significant dehydration of the airway mucosa and an increase in osmolarity, even in the small airways. As a result, the airways become inflamed and smooth muscle in the airways becomes more sensitive.[14]

In the present study, there was a significant increase in sputum leukotriene levels after exercise challenge both before and after the training program. The decrease in percent fall in FEV_1 after the training program was accompanied by a significantly decreased percent change in cysteinyl leukotriene levels. Exercise induced elevation of sputum cysteinyl leukotriene levels; however, this elevation was less after the training program than that before training. This means that training reduced the degree of mediator release in response to exercise and also decreased EIB, indicating that training resulted in depletion of the mediator. In agreement with the present results, several other studies have reported a significant increase in leukotrienes after exercise challenge in asthmatic patients, strongly suggesting that leukotrienes are important mediators of EIB.[15,16]

In the present study, the rehabilitation training program resulted in significant improvement in severity of asthma (assessed by clinical severity and airway reactivity scores), improvement in baseline FEV_1, and significant protection against EIB (with regard to both the number of patients developing EIB and the severity of EIB).[17,18]

Rehabilitation for patients with chronic lung disease is well established and widely accepted as a means of enhancing standard therapy in order to alleviate symptoms and optimize function. Exercise capacity in asthmatic children has been reported to be impaired in some studies, but not in others. Few studies have been performed to assess the impact of regular physical training on the clinical management of bronchial asthma, and have yielded conflicting results.[19] Significant improvement in ventilatory capacity and aerobic fitness was reported in five mild asthmatics after a 10-week rehabilitation training program, but without any change in pulmonary function (FEV_1). A significant improvement in ventilatory capacity, cardiovascular conditioning, and baseline pulmonary function (FEV_1) along with significantly reduced occurrence of EIB was reported in 26 asthmatic adults with mild to moderate disease after a 10-week training program.[20] The effect of a training program on aerobic capacity and clinical status in subjects with moderate to severe asthma was also studied, and the conclusion was that the training program led to significant improvement in aerobic capacity and a significant reduction in medication score and daily use of both inhaled and oral steroids.[21]

Our previous studies[22,23] showed significant improvements in baseline pulmonary function and exercise capacity, as well as significant protection against EIB; the severity as well as incidence of EIB were significantly decreased in asthmatic children with mild to moderate disease after a 12-week rehabilitation training program.

In contrast with our results, another study found that physical training had no effect on lung function at rest.[24] However, the authors reported that physical training is important in improving exercise performance and quality of life. Moreover, it was reported that aerobic conditioning and aerobic capacity improved without a change in pulmonary function (FEV_1 and FEV_1/FVC%). This contradiction may be explained by differences in the study populations and duration of training between the studies, ie, their study was carried out in adult asthmatics participating in ten weeks of aerobic training whereas our study was carried out in asthmatic children who participated in three months of training.[19,24]

Regular physical activity of sufficient intensity reduces ventilatory requirements and lowers minute ventilation dur-

ing mild to moderate exercise. Further, exercise training may also reduce the perception of breathlessness in patients with respiratory disease by strengthening the respiratory muscles. Anaerobic threshold is the point at which anaerobic metabolism begins, and has been shown to be higher in athletes than in untrained individuals, Exercise training increases maximum ventilatory oxygen uptake by increasing both maximum cardiac output and the ability of muscles to extract and use oxygen from blood.[25] Rehabilitation training programs have been reported to improve post-exercise bronchoconstriction significantly. However, the exact mechanism is not understood as yet. This may be due to depletion of mediators (leukotrienes) or a change in their sensitivity. Exercise training has been reported to lead to a reduction in the response of hormone (leptin, testosterone, prolactin, cortisol, and thyroid) levels to the same level of exercise.[26–28]

Among the benefits of training is an improvement in the severity of asthma, and this may be due to improvement in bronchial hyperresponsiveness. This is in agreement with a study by Scichilone et al,[29] who reported that methacholine inhalation produces a sluggish response after training. Exercise training rapidly alters the counterregulatory hormonal response to submaximal exercise.

Most studies have reported that, with the same submaximal work load, there is lesser elevation of plasma sympathoadrenal hormones, glucagon, and growth hormones after training. It was found that the adrenocorticotropin (ACTH) response to both maximal and submaximal exercise is blunted after a training program. This blunted ACTH response to submaximal exercise after training may be explained by increased sensitivity to control of cortisol by ACTH. This is mediated by an alteration in plasma catecholamine and cortisol levels or the sluggish ACTH response.[30] Beneficial effects of aerobic exercise in reducing expression of Th2 cytokines and allergic airway inflammation was reported using guinea pig and mouse models of allergic asthma, suggesting an immunoregulatory role of exercise training on airway epithelium.[31,32]

Disclosure

The authors report no conflicts of interest in this work.

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