Allergology International (1999) 48: 145–148

Short Communication

Exercise challenge in patients with asthma whose peak expiratory flow values are controlled within the green zone

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Abstract

Recent guidelines for the management of asthma recommend that peak expiratory flow (PEF) should be measured to monitor the level of airflow limitation and to maintain PEF values within the green zone (80–100% of the patient's highest PEF value). Because no studies have evaluated the efficacy of PEF zone management on the basis of patients' physical activity, we studied the appearance of exercise-induced asthma (EIA) using treadmill exercise challenging in asthma patients whose PEF values had been maintained in the green zone for at least 3 months. Exercise-induced asthma was induced in nine of 44 (20.5%) asthma patients. The acetylcholine concentration required to cause a 20% fall in forced expiratory volume in 1 s (log PC_{20}) was significantly lower in patients with EIA (2.39 ± 0.21 μg/mL) compared with patients without EIA (3.22 ± 0.12 μg/mL; $P < 0.03$). These results suggest that PEF green zone management alone does not ensure the ability to perform vigorous physical activity, especially in patients whose airway reactivity remains enhanced. Therefore, airway reactivity should be considered for asthma management.

Key words: airway hyperreactivity, exercise-induced asthma, green zone, peak expiratory flow.

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Received 21 August 1998. Accepted for publication 21 January 1999.

Introduction

Exercise-induced asthma (EIA) occurs in 40 to 90% of patients with asthma not treated with steroids.[1] Because EIA is an early manifestation of asthma and is associated with enhanced airway reactivity, exercise challenge is a useful method for diagnosing asthma. Furthermore, the presence of EIA suggests a lack of control of asthma and appropriate treatment can prevent EIA.[2] Recent guidelines for asthma treatment recommend a system in which peak expiratory flow (PEF) values are divided into three zones: a green zone of 80 to 100% of the patient's highest PEF value, a yellow zone of 60 to 80% and a red zone of less than 60%. The goal of treatment is to maintain PEF values within the green zone. An additional goal of treatment is to control the symptoms of asthma without limiting vigorous physical activity, including exercise.[3] Therefore, in the present study, we performed a treadmill exercise challenge test in asthma patients whose PEF was within the green zone to evaluate the efficacy of the asthma zone management system for allowing physical activity.

Methods

Fifty asthma patients whose PEF values had been in the green zone for at least 3 months and ten normal volunteers were enrolled. At the time of enrolment, none of the subjects had had upper respiratory tract infections in the previous 6 weeks. Thirteen asthma patients were being treated with bronchodilators (slow-release theophylline, inhaled β_2-adrenoreceptor agonists as required, or both) and 37 patients were being treated with bronchodilators and inhaled glucocorticosteroids (beclomethasone dipropionate, BDP; 400–1200 μg/day). The patients' morning, daytime and evening PEF were confirmed to be in the green zone on the basis of their highest values as measured with a Mini-light peak flowmeter (Clement Clark International Ltd, Harlow, UK). No patients had received oral steroids in the previous 12 weeks.

All patients underwent blood tests and evaluation of airway reactivity to acetylcholine (ACh). Within 2 weeks, the treadmill exercise challenge test was performed and respiratory function was measured by spirometry before and after exercise challenge. All examinations were performed at approximately the same time each day by the same investigators. All bronchodilators were withheld for at least 12 h and inhaled glucocorticosteroids were withheld for at least 24 h before examinations. Plasma concentrations of theophylline in subjects receiving this drug were measured before ACh and exercise challenges and were confirmed to be less than 5 μg/mL. Informed consent was obtained before the start of the study.

Airway reactivity to ACh was measured. Briefly, after inhalation of normal saline, dilutions of ACh, doubling in concentration, were inhaled with the Devilbiss 646 nebulizer (Somerset, PA, USA) operated with 5 L/min compressed air for 2 min by tidal breathing until forced expiratory volume in 1 s (FEV_1) had decreased by more than 20% of the baseline value. Results are expressed as the provocative concentration causing a 20% decrease in FEV_1 (PC_{20}).

The exercise test consisted of steady-state running for 6 min on a treadmill inclined to produce a heart rate of at least 85% of the maximum predicted for age (calculated as 220 – age).[4] In a preliminary study, we found that running at 100 m/min on a treadmill inclined 10° would produce the desired heart rate in normal adult subjects. The exercise test was performed when room temperature ranged from 25 to 26°C and humidity ranged from 59 to 62%. After FEV_1 had been confirmed to be at least 70% of the predicted value in patients with asthma and normal volunteers, exercise challenge was performed and FEV_1 was measured 1, 5, 10, 15 and 30 min after the end of exercise. Plasma concentrations of potassium and lactic acid in whole blood were measured before and after exercise challenge. The diagnosis of EIA was confirmed by a recorded fall in FEV_1 of 15% or more from the baseline value.[5,6]

The Mann–Whitney *U*-test was used for statistical analysis. Data for PC_{20} were expressed as geometric means with the geometric standard error of the mean (GSEM), and

Table 1

	Patients		Normal subjects
	EIA (+)	EIA (–)	
n	9	35	10
Age (years)	30.7 ± 4.1	30.9 ± 1.4	38.6 ± 3.5
Sex (M/F)	5/4	18/17	4/6
Duration of asthma (years)	15.0 ± 2.8	9.0 ± 1.6	
IgE (U/mL)	546 ± 216	406 ± 93	38.8 ± 18.8
Eosinophils (cells /μL)	379 ± 95	397 ± 155	118 ± 42
Log PC_{20} (μg/mL)	2.39 ± 0.21	3.22 ± 0.12	
Pre-exercise			
FVC (% of predicted)	106.5 ± 7.6	106.8 ± 2.7	107.3 ± 4.0
FEV_1 (% of predicted)	77.5 ± 2.3	79.7 ± 1.3	86.7 ± 1.9
FEV_1%	74.1 ± 1.4	76.4 ± 1.3	85.6 ± 2.3
$\dot{V}_{50}$	2.99 ± 0.31	3.34 ± 0.18	4.20 ± 0.33
$\dot{V}_{25}$	1.28 ± 0.18	1.48 ± 0.09	1.83 ± 0.14
PEF (% by best values)	90.8 ± 2.9	91.5 ± 2.0	97.0 ± 2.1
Exercise challenge			
Maximum HR (%)	93.5 ± 3.9	92.9 ± 2.1	97.7 ± 6.2
Maximum decrease in FEV_1 (%)	28.5 ± 3.6	2.23 ± 0.50	1.71 ± 1.01
Increase in potassium (mEq/L)	0.81 ± 0.21	0.91 ± 0.06	0.93 ± 0.14
Increase in lactate (mmol/L)	5.64 ± 0.59	5.41 ± 3.18	6.54 ± 0.62

Results are expressed as the means ± SEM for patients with (+) and without (–) exercise-induced asthma (EIA) and for normal subjects. Maximum heart rate (HR) and maximum percent decrease in forced expiratory volume in 1 s (FEV_1) are shown as percentages after exercise. PEF, peak expiratory flow; FVC, forced vital capacity; $\dot{V}_{50}$, $\dot{V}_{25}$, maximum expiratory flow at 50 and 25%, respectively, of FVC; PC_{20}, concentration of acetylcholine required to decrease FEV_1 by 20%.

other data are expressed as mean ± standard error of the mean (SEM). Differences with $P < 0.05$ were considered significant.

RESULTS

Forty-four asthma patients completed the trial but six patients, three treated with bronchodilators and three treated with both bronchodilators and inhaled glucocorticosteroids, dropped out because of an increase in blood pressure or general fatigue during exercise. Characteristics of subjects who completed the study are shown in Table 1. After treadmill exercise, peak heart rates in all subjects exceeded 85% of the maximal rates for their ages. Blood analysis revealed no significant differences in increases in potassium and lactic acid between asthma patients with and without EIA, and normal subjects (Table 1). Therefore, a similar intensity of exercise was induced in all subjects.

Maximal decreases in FEV_1 after exercise are shown in Table 1. Exercise-induced asthma was induced in nine of 44 (20.5%) asthma patients; four patients were being treated with bronchodilators alone and five were being treated with inhaled glucocorticosteroids and bronchodilators. No significant decreases in FEV_1 were observed in normal subjects. The log PC_{20} was significantly lower in patients with EIA (2.39 ± 0.21 µg/mL) than in patients without EIA (3.22 ± 0.12 µg/mL; $P < 0.01$; Fig. 1). The log PC_{20} values of the patients with EIA who were treated with bronchodilators or bronchodilators and inhaled glucocorticosteroids were 2.29 ± 0.17 µg/mL ($n = 4$) and 2.46 ± 0.36 µg/mL ($n = 5$), respectively. The log PC_{20} values of the patients without EIA who were treated with bronchodilators or bronchodilators and inhaled glucocorticosteroids were 2.64 ± 0.28 µg/mL ($n = 6$) and 3.34 ± 0.11 µg/mL ($n = 29$), respectively. There was no significant relationship between airway reactivity to ACh (PC_{20}) and FEV_1, maximum expiratory flow at 50% and 25% of forced vital capacity ($\dot{V}_{50}$ and $\dot{V}_{25}$, respectively) or PEF variability in patients with EIA (data not shown).

DISCUSSION

Recent guidelines for the management of asthma recommend that PEF should be measured to monitor the level of airflow limitation; PEF can even be measured by patients themselves.[3] However, to our knowledge, no studies have evaluated the efficacy of PEF zone management on the basis of patients' physical activity. Therefore,

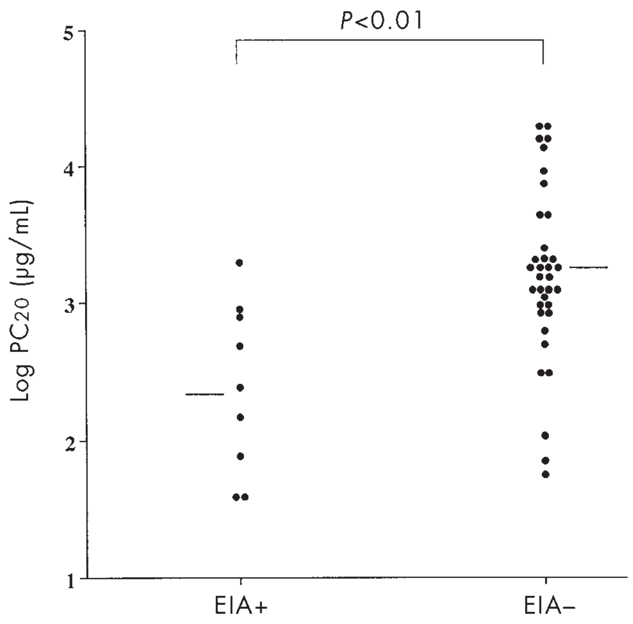

Fig. 1 Airway reactivity to acetylcholine in asthma patients with (+) and without (–) exercise-induced asthma (EIA) whose peak expiratory flow values were in the green zone. The horizontal bar shows the geometric mean value of PC_{20} (log PC_{20}). Log PC_{20} in patients with EIA and without EIA was 2.39 ± 0.21 and 3.22 ± 0.12 µg/mL, respectively.

we studied the appearance of EIA by treadmill exercise challenge in asthma patients whose PEF values had been maintained in the green zone for at least 3 months.

We found that 20.5% of asthma patients with PEF values in the green zone experienced EIA on treadmill exercise challenge. There are several possible explanations for the high incidence of EIA in these asthma patients. First, PEF was confirmed to be in the green zone on the basis of measurements at rest, but not after exercise. Second, patients performed exercise at maximal levels. Third, bronchodilators used by patients were withheld before exercise. However, because all guidelines for asthma recommend that normal activity levels, including exercise, should be maintained, but do not specify exercise levels, we presented patients with an exercise challenge to produce a heart rate of at least 85% of the maximum predicted for age.

Our finding that EIA was induced, despite treatment with inhaled glucocorticosteroids, in five of 37 patients in whom asthma was controlled in the green zone supports the findings of a previous study in which EIA occurred in asthma patients with normal lung function who were receiving inhaled glucocorticosteroids.[7]

Because decrease in FEV_1 after exercise is reported to correlate with airway hyperreactivity,[8] we compared airway reactivity between patients with and without EIA. We found that airway reactivity to ACh was higher in patients with EIA than in patients without EIA. However, the fact that EIA was not induced in some patients with asthma whose airway reactivity to ACh was enhanced suggests that EIA was not only associated with the degree of airway reactivity. Furthermore, we also found that EIA was not associated with baseline respiratory function including FEV_1, $\dot{V}_{50}$, $\dot{V}_{25}$ and PEF variability. These results suggest that the induction of EIA is not merely regulated by the dilation of central and peripheral airways.

Correlation between airway reactivity to exercise and methacholine has been studied but the results were controversial.[9–11] One study showed a significant correlation between airway reactivity to methacholine and exercise[9] but another failed to demonstrate the significant relationship, especially in asthma children who were treated with inhaled glucocorticosteroids.[10] Although airway reactivity to ACh in patients with EIA was significantly enhanced compared with patients without EIA in the present study, there was no significant correlation between decreases in FEV_1 and PC_{20}. Therefore, the association between airway reactivity to exercise and ACh seems to be complex in patients with asthma.

The asthma guidelines of the National Heart, Lung and Blood Institute (NHLBI) distinguished EIA from spontaneous asthma symptoms.[3] Exercise-induced asthma is not a determining factor for the classification of persistent asthma. Exercise-induced asthma is appropriately managed with pretreatment with inhaled β-adrenoreceptor agonists and, if necessary, cromolyn.[12] Therefore EIA, by itself, is not an indication for long-term control medication. Although the presence of EIA after treadmill challenge in some patients with asthma whose PEF readings are within the green zone would not be an indication for more intensive anti-inflammatory treatment, use of inhaled β-adrenoreceptor agonist and/or cromolyn should be recommended for these patients before exercise.

We conclude that PEF green zone management alone does not ensure the ability to perform vigorous physical activity, especially in patients whose airway reactivity remains enhanced. Therefore, airway reactivity should be considered for asthma management and exercise challenge is a useful method for evaluating the efficacy of treatment aimed at allowing vigorous physical activity.

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