RESPIRATORY MEDICINE (1999) 93, 734–738

Exercise-induced respiratory symptoms are not always asthma

O. LÖWHAGEN, M. ARVIDSSON, P. BJÄRNEMAN AND N. JÖRGENSEN

Asthma and Allergy Centre, Sahlgrenska University Hospital, Göteborg, Sweden

Eighty-eight patients with a history of exercise-induced respiratory symptoms performed a maximal exercise test in order to study the reasons for stopping the test. There was a wide range of percentage maximal fall in peak expiratory flow (PEF), from minus 3% to 63%, mean 11%, recorded 0–30 min, mean 12 min after the break. In the controls the maximal decrease was 0–16%, mean 6%. Diagnostic criteria for asthma were fulfilled by 48 patients (55%). Of these patients 42% had a fall in PEF $\geq$ 15% (exercise-induced asthma). Of the non-asthma patients 10% had a fall $\geq$ 15%. The most common reason for stopping the exercise in the asthma group was breathing troubles (46%), the most common reason in the non-asthma group was chest pain/discomfort (35%). In about 20% of the patients dizziness and/or pricking sensations in arms or legs indicated hyperventilation as an additional reason for stopping the exercise. It is concluded that other kinds of reaction, than bronchial obstruction such as breathing troubles not directly related to bronchial obstruction and chest pain, may be important factors that can restrict physical capacity in patients with exercise-induced respiratory symptoms.

RESPIR. MED. (1999) 93, 734–738

Introduction

Physical exercise provokes bronchoconstriction in the majority of patients with clinically recognized asthma. Most exercise tests have been carried out as submaximal tests over 6–8 min on a bicycle ergometer or a motor-driven treadmill (1–3). After this period of time there may be a progressive bronchoconstriction which reaches its maximum within 10 min. A fall in forced expiratory volume in 1s (FEV_1) or peak expiratory flow (PEF) of more than 15 % is usually considered as abnormal and is used as the definition of exercise-induced asthma. As greater ventilation and cold and dry air increases the tendency for bronchoconstriction, these factors have to be considered and standardized (2).

Most studies of exercise-induced asthma have focused on bronchial obstruction as the main clinical variable (3,4). Prevention and treatment of bronchospasm with inhaled β_2-agonists and other drugs have also been successful in reducing patients complaints. However, many patients with airway or breathing problems do not report any significant effect of inhaled of the β_2-agonist, and some exhibit symptoms not typical of asthma. Little attention has been paid to signs and symptoms other than bronchial obstruction and few researchers have discussed bronchoconstriction in relation to airway symptoms and physical capacity. In an earlier study using a standardized bicycle test, it was shown that a group of patients with asthma-like symptoms could be distinguished from patients with carefully defined asthma, especially regarding bronchoconstriction, oxygen saturation and rating of dyspnoea (5). The aim of this study was to observe different symptoms in relation to airway function tests, after a maximal exercise test in patients with a history of exercise-induced respiratory problems. The study was approved by the local scientific ethical committee.

Patients and method

Eighty-eight consecutively selected patients, (62 women and 26 men, mean age 37, range 16–70 years) with a history (identified by a questionnaire) of exercise-induced asthma-like symptoms, were included. All patients were referred to our outpatient asthma and allergy clinic for investigation of suspected asthma. The exercise test was part of this investigation. For the pupose of this study the criteria for the diagnosis of asthma were; 1. a history of wheezing, 2. β_2-reversibility $\geq$15% in FEV_1 or $\geq$20% in diurnal variation of PEF or a positive methacholine test (provocational concentration coursing a 20% fall in FEV_1 PC20) $\leq$ 4 mg ml^{-1}). The exercise test was performed by running up a staircase in a building with six indoor floors (temperature 18–20°C, humidity 40–50 %). Ten healthy controls, eight women and two men, mean age 39, range 18–49, served as controls. The participants were instructed to run up and down the staircase without warming up and at a moderate tempo (not rushing and not walking), one floor higher each time for as long as possible, and to report the reason for stopping the exercise. If the patient was able to run up to

Paper Received 22 October 1998 and accepted in revised form 25 June 1999.
Correspondence should be addressed to: Olle Löwhagen, Assoc. Prof., Asthma and Allergy Centre, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden. E-mail ollelowhagen@hjlgu.se

0954-6111/99/100734+05 $12·00/0

the sixth floor he/she was instructed to repeat this for as long as possible.

In 66 patients (75%) one or more drugs had earlier been prescribed for treatment of asthma and prevention of exercise-induced asthma; inhaled steroids (budesonide or beclomethasone 400–1600 μg day^{-1}) in 39 patients, an additional long-acting β_2-agonist (salmeterol) in eight patients and short-acting β_2-agonist (terbutaline or salbutamol) in 66 patients. Before the exercise test the patients were instructed not to take any bronchodilators for 12 h. Medication with inhaled steroids was not changed before the exercise. As an indication of atopy, 43 patients had a positive skin prick test to one or several common allergens (mite, pollen and animal dander). None of the patients had recently been exposed to allergens and none had a history of cardiac disease or other diseases relevant to the test.

Before and 0, 5, 10, 15, 20 and 30 min after finishing the exercise test, PEF (peak expiratory flow in 1 min^{-1}), peripheral oxygen saturation, pulse and heart rate and end-tidal CO_2 (Oscaroxy multigasmonitor and pulsoximeter, Datex instrument. corp.) were measured. The main reason for stopping the exercise was noted. The first recording after the test was performed immediately after returning to the ground floor which took less than 1 min.

STATISTICS

Standard statistical methods were used for analysis of correlation (r). Fishers exact test was used for analysis of symptoms (reasons for stopping) in the asthma and non-asthma group. $P < 0{\cdot}05$ was considered significant.

Results

All 88 patients and the 10 controls completed the test. All patients were able to run at least up to the second floor, 25 patients were able to run up and down six floors 2–6 times. All controls were able to run six floors up and down 1–5 times. The main reasons for stopping the exercise fell into four main categories: symptoms related to breathing (34%), symptoms related to chest pain/discomfort (26%), tiredness of the legs (27%) and other symptoms such as problems with the knees (13%). No injury or other unexpected event occurred. Mean pulse rate at the ground floor 0–1 min after exercise was 135, range 72–203, in the patients and 125, range 95–147, in the controls. Three patients ending with a pulse rate below 100 per min complained of dizziness, chest pain and breathing problems, respectively. One of the controls ending with a pulse rate below 100 complained of dizziness.

PEF and other data before and after the test are summarized in Table 1. As illustrated in Fig. 1 there was a wide range in the percentage maximal fall in PEF in the patients, from −3% to +63% (mean 11%) recorded 0−30 min (mean 12 min) after stopping exercise. Only eight patients (9%) had a maximal fall ≥15% within 5 min. In the controls the maximal decrease was 0–16% (mean 6%) recorded 5–45 min (mean 18 min) after stopping exercise Analyses of the relationships between maximum percentage

TABLE 1. Peak expiratory flow rate (PEF), respiratory rate (RR), pulse rate (PR), peripheral oxygen saturation (O_2) and end-tidal CO_2 (CO_2) before and after maximal physical exercise

	Patients		Controls	
	Mean	Range	Mean	Range
PEF before (l min^{-1})	487	220–750	509	340–660
PEF % max fall after	11	−3–63	6	0–16
RR before (min^{-1})	14	6–25	14	6–21
RR after 0–1 min	23	11–42	19	12–26
PR before (min^{-1})	74	56–108	70	53–90
PR after 0–1 min	135	72–203	125	95–147
O_2 before (%)	98	96–99	98	97–99
O_2 lowest after (%)	97	90–99	97	96–97
CO_2 before (%)	4.8	3·3–5·8	4·9	4–5
CO_2 lowest after (%)	3·7	1.6–5·1	4	3·1–4·8

fall in PEF and other variables showed a significant relationship with fall in O_2 saturation ($r = 0{\cdot}62$, $P = 0{\cdot}0001$), respiratory rate at 0 min ($r = 0{\cdot}25$, $P = 0{\cdot}02$) and sensitivity to methacholine ($r = 0{\cdot}47$, $P = 0{\cdot}0001$).

A fall in PEF ≥15% (exercise-induced asthma) was observed in 20/48 asthmatics (42%) and in 4/40 non-asthmatics (10%). In the controls, 1/10 individuals (10%) had a maximum fall ≥15% (Table 2). The most common reasons for stopping the exercise in the asthma group were breathing trouble (42%), tired legs (25%) and chest pain/discomfort (19%). The most common reasons for stopping the exercise in the non-asthma group were chest pain/discomfort (35%), tired legs (30%) and breathing trouble (20%). Significantly more patients in the asthma group compared with the non-asthma group reported breathing trouble ($P<0{\cdot}05$). When the patients were further separated into those treated with and without inhaled steroids (Table 2), a PEF fall ≥15% was seen in 13/27 (48%) asthmatics treated with steroids and in 7/21 asthmatics treated without steroids (33%). The most common reason for stopping the exercise in the steroid treated patients of the asthma group ($n=27$) was breathing trouble (52%) (Table 2).

Mean end-tidal CO_2 in the patients before the test was 3·2–5·8% (mean 4·8%). The lowest value after the test was 1·6–5·1% (mean 3·7%), recorded 0–55 min (mean 18 min) after stopping. Dizziness and/or pricking sensations in the arms or legs as possible signs of hyperventilation were reported in 18/88 patients (20%). In these patients the lowest post-exercise CO_2-value was 1·6–4·7% (mean 3·3%) recorded 5–35 min (mean 19 min) after stopping. The lowest CO_2-value in all patients was 1·6–5·1 (mean 3·7%).

Discussion

The study has shown that not only bronchial obstruction, but also other types of reaction, may be of considerable

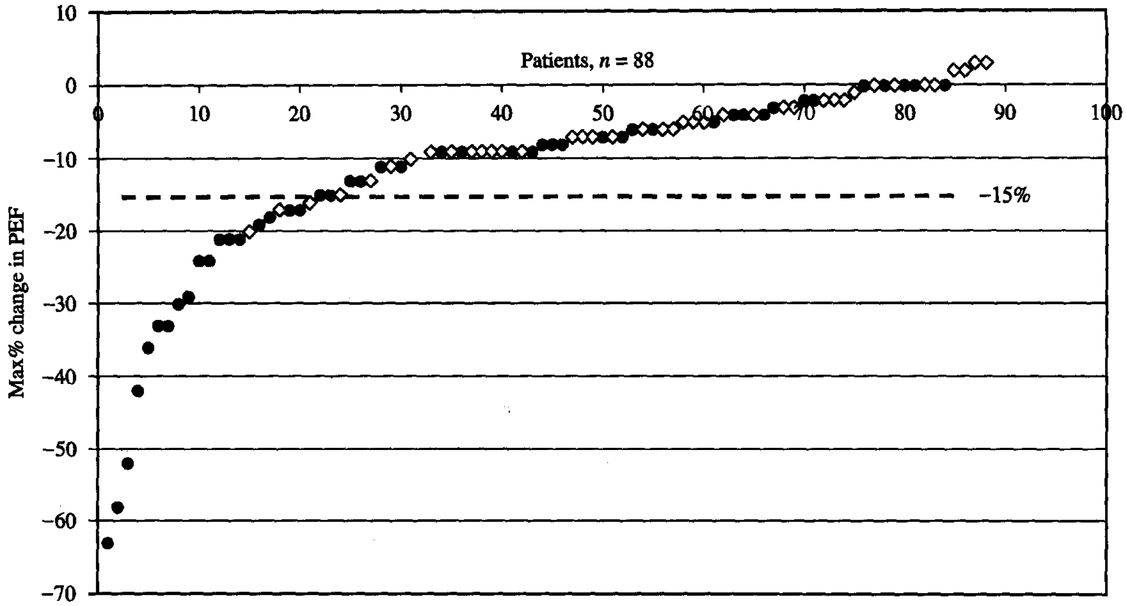

FIG. 1. Maximal percentage change in peak expiratory flow PEF after physical exercise in 88 patients sorted in ranking order. The dotted line shows the level of a 15 % decrease in PEF. ●, asthma group; ◇, asthma like group.

TABLE 2. Number (percentage) of patients with a maximum fall in peak expiratory flow (PEF) ≥15% and the main reasons for stopping the exercise.The patients are separated into those treated with and without inhaled steroids

	Asthma +steroid	Asthma no steroid	Asthma-like +steroid	Asthma-like no steroid	All patients	Controls
Number of pat. Units	27 (31%)	21 (24%)	12 (14%)	28 (32%)	88	10
PEF fall ≥ 15 %	13 (52%)	7 (28%)	3 (12%)	1 (4%)	25 (28%)	1 (10%)
Breathing trouble	17 (57%)	5 (17%)	3 (10%)	5 (17%)	30 (34%)	0 (0%)
Chest pain	3 (13%)	6 (26%)	7 (30%)	7 (30%)	23 (26%)	0 (0%)
Tired legs	5 (21%)	7 (29%)	2 (8%)	10 (42%)	24 (27%)	7 (70%)
Other	2 (18%)	3 (27%)	0 (0%)	6 (25%)	11 (13%)	3 (30%)

importance in patients with a history of exercise-induced airway/chest symptoms. By including patients with a history of exercise-induced asthma-like symptoms it was shown that the degrees of bronchoconstriction, ranging from none to very strong. The fact that bronchial obstruction is not an 'all or nothing' reaction is well illustrated in Fig. 1 where the maximal decreases in PEF are shown in ranking order. The patients were instructed to make a maximal effort and to give the reason why they could not run any longer. If the reason for stopping the exercise had been bronchoconstriction one would have expected a greater fall in PEF immediately after stopping. However, the mean time for the maximal decrease in PEF was 12 min and in only eight patients (9%) the maximal fall was ≥ 15% within 5 min of stopping, strongly indicating that bronchoconstriction may not explain the reason for stopping the exercise in the majority of patients. The PEF values were continuously checked during the exercise (every time on the ground floor) and none of the patients had a fall in PEF that was later restored during the running. This control may rule out the possibility of 'running out of bronchoconstriction' in any of the patients.

Tiredness of the legs, seen in the controls may be considered as a natural reason for stopping strenuous work but breathing troubles and chest pain, found in 60% of the patients, are abnormal reactions. These factors hampered further exercise and may, therefore, be seen as factors that restrict physical capacity. From a clinical point of view it is of fundamental importance to consider all factors that may restrict physical activity, not only bronchoconstriction.

With the diagnostic criteria used, exercise-induced asthma was seen in 42% of asthmatic patients, which is a figure lower than generally reported. This may partly be due to the selection of patients, mild asthma in some cases and the way of assessing bronchial obstruction. PEF is a relatively insensitive measure, especially as regards changes in small airways. However, changes in PEF were significantly related to changes in peripheral oxygen saturation, and it is unlikely that changes in small airways, in the absence of changes in PEF, may explain the reason for stopping the exercise. Another reason for using a measure other than PEF is the inability of many patients with an asthma-like disorder to perform a complete and reproducable forced expiration.

When patients were separated into those treated with and without inhaled steroids, exercise-induced asthma was found in about 50% of asthmatic patients treated with steroids and in about 30% of asthmatic patients treated without steroids. The study was not designed to analyse differences in effects of drugs, but the difference may indicate that inhaled steroids are not very effective in preventing exercise-induced asthma; is more likely however, that patients treated with steroids had a more severe asthma. Another explanation may be lack of compliance. It is possible that many patients do not like to take medicine for preventive purposes.

The test model was chosen to observe different airway and chest symptoms in relation to airway function tests after a maximal exercise test. Although some interesting findings were obtained it should be pointed out that the test was not fully standardized. There was no perfect control of degree of ventilation and exercise load, these factors being better controlled in a test on a treadmill or a bicycle (2,5). Another factor that was not possible to control was the speed of running. To start at a higher tempo may lead to a different response than starting at a lower tempo, and it is often reported by patients that warming up before starting exercise has an inhibiting effect on the exercise-induced respiratory symptoms.

A lot of data were obtained in this study but only some are presented in this report. This is mainly a qualitative or observational study, where we focus on a few important observations that have not earlier been reported in the literature. The number of controls could have been higher in this study. However, the normal reaction to physical exercise in healthy people is well known (tired legs but no unpleasant breathing, no chest pain and no bronchoconstriction) and a higher number of controls may not have changed the outcome. We think that the most interesting comparison is that between patients with asthma and patients with asthma-like symptoms. The symptoms reported were classified into four categories, breathing trouble, chest pain/discomfort, tiredness of legs and other symptoms. Several patients reported more than one symptom but only the major symptom was included in the analysis. The results indicate that patients with asthma have more trouble breathing and that patients with non-asthma have more chest pain/discomfort as a reason for stopping exercise. This difference may have important differential diagnostic significance.

Of special interest was the observation that every fourth patient complained of chest pain or other kind of discomfort in the chest. This symptom may be an important factor in restricting physical activity and is reported to be a frequent symptom in children and young people (6,7,8). As the patients in this study were otherwise healthy, chest pain could not be explained by a cardiac disease. Further studies are needed to clarify the origin of these symptoms. Some patients reported dizziness and other symptoms associated with hyperventilation but there was no relation between symptoms and levels of end-tidal CO_2 after exercise suggesting an individually different reaction or sensitivity to low CO_2. It is possible that some patients stopped the exercise partly due to an abnormal hyperventilation. However, in the majority of the patients the lowest value was recorded 10–20 min after stopping, which is coincidental with the time of maximal fall in PEF. This issue has to be further investigated.

Most studies of exercise-induced airway complaints are based on tests in which a certain decrease in airway function test is required, e.g. a fall in FEV_1 or PEF $\geq 15\%$. However, such a method excludes individuals with other kinds of reactions, which seriously restricts the research area. In recent years it has been observed, in an increasing number of reports, that asthma-like symptoms may not be the same as asthma (5, 9–16). In our experience, separating asthma from asthma-like symptoms based on the patient's history is not easy, and a mix up between patients with asthma and asthma-like disorders is often seen in the clinic, especially in patients not investigated by relevant pulmonary function tests and tests of bronchial hyper-reactivity (17,18). An earlier study using a standardized exercise test showed that a group of patients with asthma-like symptoms could clearly be separated from patients with a carefully defined asthma (5).

The most common trigger factors seen in an asthma-allergy clinic are exercise, cold air, strong scents and allergens. In the literature all of these are reported as possible asthma triggers. However, recent studies have shown that there may also be other kinds of reactions, and a sensory hyper-reactivity has been proposed in individuals highly sensitive to strong scents (13) and inhaled capsaicin (in press). As some of the symptoms seen after exercise, are similar to those found after provocation to strong scents (perfume) and capsaicin the sensory nerve system may also be involved in patients with exercise-induced respiratory symptoms. Earlier proposed mechanisms, behind the development of exercise-induced bronchoconstriction include transient hyperosmolarity of the airway surface liquid as a result of evaporative water loss (19) and a rapid airway rewarming after exercise, causing vascular congestion, increased permeability and oedema (20,21). However, our observations of an individually different degree of bronchial obstruction, not directly associated with time and type of airway symptoms, strongly indicate that additional primary mechanisms in exercise-induced respiratory reactions have to be considered.

References

1. Anderson SD. Asthma provoked by exercise, hyperventilation, and the inhalation of non-isotonic aerosol. In: P Barnes, Rodger IW and Thomson NC Eds. *Asthma. Basic mechanism and clinical management,*

London, San Diego, New York, Boston, Sydney, Tokyo, Toronto: Academic Press, 1992, pp 473–486.
2. Sterk PJ, Fabbri LM, Quanjer PhH *et al.* Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993; **6:** 64–66.
3. Mahler DA. Exercise-induced asthma. *Med Sci Sports Exer* 1993; **25:** 554–561.
4. Tan RA; Spector SL. Exercise-induced asthma. *Sports Med* 1998; **25:** 1–6.
5. Ringsberg KC, Wetterqvist H, Löwhagen O, Sivik. Physical capacity and dyspnea in patients with asthma-like symptoms but negative asthma tests. *Allergy* 1997; **52:** 532–540.
6. Wiens L, Sabath R, Ewing L, Gowdamarajan R, Portnoy J, Scagliotti D. Chest pain in otherwise healthy children and adolescents is frequently caused by exercise-induced asthma. *Pediatrics* 1992; **90:** 350–353.
7. Jonides L, Rudy C, Walsh S. Chest pain in a young athlete. *J Pediatr Health Care* 1995; **9:** 87.
8. Selbst SM. Consultation with the specialist. Chest pain in children. *Pediatr Rev* 1997; **18:** 169–173.
9. Löwhagen O. Functional respiratory disorders as significant differential diagnosis in asthma. *Läkartidningen* 1989; **86:** 57–59.
10. Löwhagen O, Balder B. Histamine and methacholine tests in cases of hyperreactive bronchi—a 10-year experience. *Lakartidningen* 1990; **87:** 3413–3418.
11. Ringsberg KC, Löwhagen O, Sivik T. Psychological differences between asthmatics and patients suffering from an asthma-like condition, functional breathing disorder: a comparison between the two groups concerning personality, psychosocial and somatic parameters. *Integr Physiol Behav Sci* 1993; **28:** 358–367.
12. Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M. Are asthma-like symptoms due to bronchial extra-thorasic airway dysfunction ? *Lancet* 1995; **346:** 791–795.
13. Millqvist E, Löwhagen O. Placebo-controlled challenges with perfume in patients with asthma-like symptoms. *Allergy* 1996, **51:** 434–439.
14. Siersted HC, Mostgaard G, Hyldebrandt N, Hansen HS, Boldsen J, Oxhoj H. Interrelationships between diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour in adolescence: the Odense Schoolchild Study. *Thorax* 1996; **51:** 503–509.
15. Sue-Chu M, Karjalainen EM, Altraja A *et al.* Lymphoid aggregates in endothelial biopsies from young elite cross-country skiers. *Am J Respir Crit Care Med* 1998; **158:** 597–601.
16. Remes ST, Korppi M, Remes K. Outcome of children with respiratory symptoms without objective evidence of asthma: a two year, prospective, follow-up study. *Acta Pediaetr* 1998; **87:** 165–168.
17. Löwhagen O, Ellbjär S, Jörgensen N, Toss L. Severe asthma was found to be an asthma-like condition. Consider reduced doses of cortisone. *Läkartidningen* 1996; **93:** 3711–3713.
18. Löwhagen O, Ellbjar S, Jörgensen N. Asthma or asthma-like condition? *Nord Med* 1997; **112:** 119–121.
19. Andersson SD. Is there a unifying hypothesis for exercise-induced asthma. *J Allergy Clin Immunol* 1984; **73:** 660–665.
20. McFadden ER. Hypothesis: Exercise-induced asthma as a vascular phenomenon. *Lancet* 1990; **1:** 880–882.
21. Gilbert IA, McFadden ER. Airway cooling and rewarming. The second reaction sequence in exercise-induced asthma. *J Clin Invest* 1992; **90:** 699–704.