

# ASTHMA AND SPORT

**Samuel Malamulele Risenga, BSc, MB ChB, DCH (SA), MMed (Paed), Dip Allergology (SA)**

*Division of Paediatric Pulmonology, Department of Paediatrics and Child Health, University of Pretoria, South Africa*

## ABSTRACT

Parents of children with asthma are often worried when their children participate in sport. Many sportspeople who are asthmatic do well at a competitive level.

Most people with exercise-induced asthma (EIA) have persistent asthma which is not well controlled. There are however a few people who have exercise-induced bronchoconstriction as the only presenting sign. It is important to identify children with exercise-induced asthma by using spirometry and exercise challenge tests. This will help to differentiate between children with EIA and those who lack interest in sport or who are physically unfit.

Once the diagnosis is made, one should strive to treat these patients so that they attain normal levels of activity. These patients and their parents should be made to appreciate that asthma, if well controlled, does not preclude them from taking part in sport. Control is attained by non-pharmacological and pharmacological treatment. It is also necessary for patients and their doctors to have a thorough knowledge of drugs that can be used in sport without transgression of antidoping rules. Sportsmen and -women requiring prohibited prescribed medications can apply for therapeutic use exemption of these drugs.

## INTRODUCTION

In our daily practice of medicine in general and paediatrics in particular, we encounter children whose parents are worried about them participating in sporting activities. It is not uncommon for parents to request a medical certificate for the child to be exempted from taking part in sports at school because he/she is asthmatic. One also often encounters parents who are unhappy when their asthmatic child wants to play and swim. It is however in the nature of children to play around all day long if they feel healthy.

Regular exercise is essential to achieve and maintain a state of wellbeing and promote psychomotor development of children and adolescents.

One of the important goals of childhood asthma management is full participation in sporting activities. Because this goal is important, it is imperative to recognise exercise-induced asthma (EIA).<sup>1</sup>

## TERMINOLOGY: EXERCISE-INDUCED ASTHMA/BRONCHOCONSTRICTION

In the literature the following terms are used to describe this condition: exercise-induced asthma, exer-

cise-induced bronchoconstriction, exercise-induced bronchospasm and activity-induced asthma.<sup>2,3</sup> All these terms describe a condition in which transient narrowing of the airways follows vigorous physical activities.

The term 'exercise-induced asthma' (EIA) is used in this article despite the fact that it is a misnomer. It is a misnomer because exercise, unlike allergen inhalation or occupational sensitizers, is not known to cause asthma but causes bronchoconstriction in patients with asthma.<sup>1</sup>

EIA is common in children and young adults because of the fact that they have increased levels of spontaneous physical activity.

The diagnosis of EIA is made when there is a fall in forced expiratory volume in 1 second (FEV1) of 10-15% or a peak expiratory flow rate (PEFR) fall of 15% following any form of exercise.<sup>2</sup>

## DEFINITION AND PREVALENCE

EIA is defined as a transient narrowing or bronchoconstriction that occurs after vigorous exercise. Reasonably strenuous bouts of exercise lasting more than 2-3 minutes are required to produce symptoms. It should be noted that in most instances bronchoconstriction follows after exercise has been stopped. It begins within 3 minutes, peaks at 10-15 minutes and resolves within 60 minutes. Bronchodilatation usually occurs during exercise lasting for 1-3 minutes, although there can occasionally be bronchoconstriction from the onset.<sup>1,3</sup> According to the Global Initiative for Asthma (GINA) guidelines released in 2002 and revised in 2006, EIA is 'one expression of airway hyperresponsiveness, not a special form of asthma'.<sup>4</sup>

EIA is thought to occur in as many as 70-80% of patients with current symptoms of asthma, while in children, up to 90% are thought to have this problem.<sup>2</sup> The severity of EIA depends on the severity of the underlying condition of airway hyper-responsiveness and decreases when the asthma becomes controlled.

The prevalence of EIA has been reported to be 19.3-23.4% in Australian children. Forty per cent of the children with EIA had not been previously diagnosed by a doctor as having asthma.<sup>5</sup>

Table I lists the variables that affect the reporting of EIA.

*Table I. Variables that affect the reporting of exercise-induced asthma*

Type of exercise
Duration of exercise
Ambient temperature
Ambient humidity
Associated triggers
Controller asthma medications
Bronchoprotective treatment

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The bronchoconstriction is worse with exercise at extremely high activity levels, in cold environments, with decreased humidity and associated trigger factors

Correspondence: Dr SM Risenga, Division of Paediatric Pulmonology, Department of Paediatrics, PO Box 67, Pretoria 0001. E-mail: samuel.risenga@up.ac.za

such as pollen spores in the environment in which exercise is taking place. It might not occur if the child is taking appropriate and effective controller medications and has performed warm-up exercises.

Different types of exercise at the same load cause varying degrees of bronchoconstriction. Free range running is the most asthmagenic form of exercise, followed by uphill treadmill running. Cycling ranks third in its asthmagenicity, whereas swimming and walking are less effective in causing a postexercise fall in PEFR even when ventilation, oxygen consumption and heart rate were similar to the other forms of exercise assessed.<sup>7</sup>

Severity and duration of exercise also cause a difference in bronchoconstriction. Postexercise bronchoconstriction increases with increasing work load and plateaus at two-thirds of the subject's physical working capacity. EIA severity also increases with duration of up to 6-8 minutes and then reaches a plateau.<sup>7</sup>

## PATHOPHYSIOLOGY

The exact mechanism of bronchoconstriction in EIA is not completely understood, but it is widely accepted that the dehydrating and osmotic effects of respiratory water loss lead to the release of inflammatory mediators.<sup>8</sup> There are two main theories to explain this: the 'thermal hypothesis' and the 'osmotic theory'.

According to the thermal hypothesis there is transfer of heat from the mucosa to the airways and back to the mucosa during hyperventilation while exercising. The osmotic theory suggests that water evaporates from the airway surface of an exercising person which leads to an osmotic gradient resulting in cell volume loss.

The processes mentioned above trigger activation of mast cells and lead to the release of histamine, cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>), neutrophil chemotactic factor and prostaglandins. The histamine is preformed and leukotrienes are formed *de novo* from arachidonic acid through the lipoxygenase pathway.<sup>8</sup> The prostaglandins are formed via the cyclooxygenase pathway.

Inflammation of the airways is characteristic of persistent asthma even if the disease is asymptomatic. People with increased bronchial hyper-reactivity to exercise challenge also have evidence of airway inflammation.

Patients with EIA have also been found to have significantly higher levels of eosinophils and eosinophil cationic protein in their sputum than asthmatics without EIA.<sup>2,5</sup> There is also increased urinary LTE<sub>4</sub> in these patients.

## DIAGNOSIS

Both subjective and objective findings in EIA must be considered (Table II).

The diagnosis of EIA is made by careful history, baseline spirometry and exercise challenge.

### History

This is very important because it is easy to miss EIA, especially in patients with mild intermittent asthma and sometimes even in those with mild persistent asthma. The reason for missing EIA may be that this asthma commonly manifests itself 5 minutes after exercise and as a result exercise may not limit activity. Children may also not notice their symptoms until they take part in organised sports. Another reason for missing it is that half the children become refractory to the effect of exercise when warm ups are done or if the exercise is repeated within an hour.<sup>5</sup>

Table II. Subjective and objective findings in exercise-induced asthma

#### Subjective findings with exertion

Wheeze  
Cough  
Shortness of breath  
Perception of poor physical conditioning  
Lack of interest in physical activities

#### Objective findings with exertion

Fall in lung function of 10-15%  
Protection against a 15% fall in FEV<sub>1</sub>  
Protection with bronchodilators

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One must also ask if the child feels breathless or wheezes 5-10 minutes after stopping exercise. One must however take note that in some children bronchoconstriction occasionally occurs during exercise itself.<sup>1</sup> This phenomenon occurs in stop-and-go sports, e.g. soccer, basketball and baseball. Clinically these children may wheeze, cough or have shortness of breath.

Some children have a poor level of physical fitness and some lack interest in any physical activity. In children with underlying unstable asthma, minimal physical effort is required to induce symptoms, whereas in some patients more strenuous exercise is needed to do the same.

### Baseline spirometry

Spirometry is important because one might detect those patients with moderate to severe persistent asthma. Baseline FEV<sub>1</sub> may be normal in patients with persistent asthma even if the disease is active. PEFR and forced expiratory flow (FEF<sub>25-75</sub>) can also be measured. This will give the medical practitioner a feel for the severity of his/her patient's asthma.

### Exercise challenge test

This test can be done in the laboratory or outdoors. For outdoor challenge the patient is asked to run for about 6-8 minutes while inhaling air through the mouth. The workload should increase the patient's heart rate to 80% of predicted maximum for age.

The exercise challenge can also be done using an ergometric stationary bicycle, if this is available. In the laboratory nose clips are used with the patient mouth breathing dry cold air through a face mask.

In athletes who play sports requiring high-intensity effort of variable duration such as boxing, hockey and sprinting, it might be difficult to evoke symptoms in the laboratory. In this case it may be necessary to test these people in their sporting environment while they perform activities that induce their asthma.<sup>3</sup>

Pre-exercise FEV<sub>1</sub> or PEFR should be done before exercising in order to establish a baseline. These tests should be repeated 5 minutes post exercise. The percentage fall in FEV<sub>1</sub> or PEFR is calculated as follows:

$$\frac{E0 - E5}{E0} \times 100$$

Where

E0 = pre-exercise reading and

E5 = reading 5 minutes post exercise

The challenge test should preferably not be done on children with pre-exercise FEV<sub>1</sub> or PEF<sub>R</sub> of less than 30%.

A fall of 15% or greater is regarded as diagnostic of EIA. A fall of 15-25% is regarded as mild EIA, 26-34% as moderate EIA, and 35-55% and greater is regarded as severe EIA.

### Differential diagnosis

It is important to rule out other conditions, which might mimic EIA, by careful clinical examination (Table III). Most of them will not respond to conventional therapy for EIA and persistent asthma.

Table III. Differential diagnosis for exercise-induced asthma

Vocal cord dysfunction
Exercise-induced hyperventilation
Central airway obstruction
Cardiac disease
Other restrictive or obstructive pulmonary disease
Muscle disorders

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Allergic rhinitis and adenoidal hypertrophy which are causes of upper airway obstruction can also be confused with EIA.

*Vocal cord dysfunction (VCD)* can be excluded by the fact that it is associated with respiratory wheezing or stridor. These symptoms are refractory to standard asthma therapy. They appear and resolve abruptly.<sup>9</sup> One must also look for psychological causes of VCD. In most patients this is subconscious and may be associated with stress.

*Exercise-induced hyperventilation* has also been described as a pseudoasthma syndrome by Hammo.<sup>10</sup> It is a condition in which patients present with hyperventilation, a feeling of chest pain and discomfort after exercise. It differs from EIA in that the patients involved experience a fall in end-tidal CO<sub>2</sub>, which is equivalent to PCO<sub>2</sub> in association with chest tightness without a wheeze, cough or fall in FEV<sub>1</sub> of greater than 15%.<sup>10</sup> These individuals are generally highly competitive athletically and scholastically. The complaint of exercise-induced chest discomfort which they interpret as dyspnoea occurs most typically at times of attempted peak performance during competitive athletics.<sup>10</sup> They do not respond to normal asthma treatment or pre-exercise bronchodilators.

*Cardiac problems* might be diagnosed by the presence of murmurs.

Other differential diagnoses will be distinguished by the symptoms and signs at presentation.

## TREATMENT

The treatment of EIA can be non-pharmacological and pharmacological.

Before the different treatment options are discussed it should be re-emphasised that 70-80% of patients with EIA have underlying persistent asthma. Exercise is only one of the triggers of the disease.<sup>4</sup> In the other 20-30% signs of asthma only occur after exercise.

### Non-pharmacological treatment

This treatment includes both aerobic conditioning and warm-up exercises. Aerobic conditioning improves fitness, decreases dyspnoea associated with exercise and improves the ventilatory capacity in patients with EIA.

Warm-up exercises take advantage of exercise refractoriness and repeated bouts of exercise can lead to less bronchoconstriction and even its abolition in some cases. This refractory period lasts for less than 4 hours. Mechanisms that are thought to cause this phenomenon are depletion of preformed mediators from mast cells and increased release of catecholamines during exercise.<sup>1</sup> This does not apply to unscheduled events like running to catch a bus or playing.

### Pharmacological treatment

Prophylaxis is the primary aim of treatment. Since inflammation is important in the pathophysiology of asthma, this should be the first target in the management of EIA. The initial component of treatment is controller therapy as recommended by GINA guidelines.<sup>4</sup>

Inhaled corticosteroids are the mainstay of controller therapy and should be considered in the primary treatment of EIA in the presence of persistent asthma. Corticosteroids decrease inflammation and hyper-responsiveness of the airways more than other controller therapies.

Other controller medications that can be used are cromolyn, nedocromil, theophyllines, long-acting beta-2 agonists and leukotriene receptor antagonists. Table IV summarises the treatment options for EIA.

Table IV. Treatment options for exercise-induced asthma

Underlying persistent asthma	Isolated EIA with no underlying persistent asthma
<i>Controller therapy</i>	<i>Pre-exercise treatment</i>
1. Inhaled corticosteroids (ICS)	1. Short-acting beta-2 agonist
2. Leukotriene receptor antagonist	2. Leukotriene receptor antagonist
3. Long-acting beta-2 agonist (LABA) – not to be used as monotherapy	3. LABA
4. ICS + LABA	4. Cromolyn/nedocromil
5. ICS + leukotriene receptor antagonist	
6. Cromolyn/nedocromil	

### Short review of medications

#### Inhaled corticosteroids (ICS)

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory medications in the treatment of asthma and EIA.<sup>9</sup> They reduce asthma symptoms, improve quality of life, improve lung functions, decrease airway hyper-responsiveness, control airway inflammation, and reduce frequency of exacerbation and asthma mortality.

#### Cromolyn/nedocromil

These are not as effective as low-dose inhaled steroids and are seldom used today. A single dose of either drug

attenuates bronchospasm induced by exercise or cold air.<sup>9</sup>

### Leukotriene receptor antagonists (LTRAs)

These include montelukast, zafirlukast and pranlukast, with montelukast being used in the management of asthma in children. According to the South African package insert, Singulair (montelukast) should not be used as monotherapy for the treatment of EIA. Patients with exacerbations after exercise should be re-assessed for their level of control and put on appropriate controller therapy. They should have a short-acting inhaled beta-2 agonist available for rescue use.

LTRAs target cysteinyl leukotrienes, which play an important part in asthma pathophysiology. They have been shown to improve asthma control in children and adults. They improve lung function, symptom control and reduce use of rescue medications. They also ameliorate the hyper-reactive response to exercise in children and adults.<sup>9</sup>

Montelukast has also been shown to be bronchoprotective in asthmatics who have EIA in the long term.<sup>9</sup> It offers similar protection against EIA to patients with aspirin-induced asthma and aspirin-tolerant asthma.<sup>11</sup> This drug taken once daily orally has a protective effect on the immediate and late-phase responses induced by exercise in asthmatic children.<sup>12</sup>

Montelukast, unlike the short-acting inhaled beta-2 agonist salbutamol does not lead to development of tolerance when long-term therapy at the 10 mg dose is given. The absence of a decrease in the degree of protection against exercise-induced bronchoconstriction differentiates it from other therapies.<sup>13</sup>

### Long-acting beta-2 agonists (LABAs)

The LABAs currently available are salmeterol and formoterol. They are not recommended for use as monotherapy for the management of asthma as they do not influence airway inflammation. They may however be used to prevent EIA and may provide longer protection than short-acting inhaled beta-2 agonists.<sup>4</sup>

Formoterol has a more rapid onset of action than salmeterol. Tachyphylaxis to the protective effect of formoterol occurs after 4 weeks of regular dosing. This suggests it should be used only on an as-needed basis in EIA.<sup>9</sup> Salmeterol has also been shown to have its duration of action reduced from 12 hours to 9 hours with chronic use.<sup>9</sup>

### Long-acting beta-2 agonists plus inhaled corticosteroids

The combination of LABAs and ICS improves symptoms scores and nocturnal and exercise-induced bronchoconstriction.<sup>4,9</sup> These combinations are available as Seretide (fluticasone + salmeterol) and Symbicord (budesonide + formoterol).

### Short-acting beta-2 agonists

These are the medications of choice for pretreatment of exercise-induced bronchoconstriction. They are most useful in children with pure EIA who do not have persistent asthma. Regular use of these drugs however leads to a decrease in their protective effect after 1 week. This phenomenon is due to decreased expression of the beta-receptor and development of tolerance.<sup>4,9</sup> Examples of these drugs are salbutamol, terbutaline and fenoterol.

### Leukotriene receptor agonists plus inhaled corticosteroids

In a meta-analysis in which Currie and Lipworth<sup>14</sup> looked at various studies of LTRAs, they found that LTRAs, including montelukast, conferred a consistent degree of protection. They also showed that ICS exhibit a relatively shallow dose-response curve for anti-inflammatory efficacy and a steeper curve for systemic adverse effects.

Treatment with ICS therapy does not abolish all inflammation and has a limited impact on the cysteinyl leukotriene levels.<sup>14</sup>

When broncho-alveolar lavage is done, the level of cysteinyl leukotrienes is higher in severe asthmatics. In patients who are suboptimally controlled on ICS, addition of leukotriene receptor agonists improves the condition and decreases the need for high-dose corticosteroids.

LTRAs when used as second-line preventer therapy afford overall protection of one doubling dose.<sup>14</sup>

### GUIDE TO ASTHMA MEDICATIONS AND DRUG-FREE SPORT

The South African Institute for Drug-Free Sport has rules and regulations that classify certain drugs as performance-enhancing; these may not be used by athletes participating in competitive sports.<sup>15</sup>

It is the duty of medical professionals to be aware of these drugs so that the athletes they treat are not guilty of inadvertent doping.

All beta-2 agonists are now prohibited in sports both in and out of competition.<sup>16</sup>

#### *Therapeutic use exemption (TUE)*

Athletes taking prohibited prescribed medications must apply for TUE at least 21 days before a competition. A medical practitioner must however certify that there is no other medication available to treat the condition. South African national athletes submit their TUE applications to the South African Institute for Drug-Free Sport.

Sports people suffering from asthma or EIA may apply for an abbreviated TUE for the use of the following medications: salbutamol, terbutaline, salmeterol, formoterol and inhaled glucocorticosteroids.

Exemption is normally granted if the athlete experiences a significant improvement in health on such treatment, and if it will not produce additional enhancement of performance other than that which is anticipated by the return to a normal state of health.

### CONCLUSION

All athletes can now, and should, participate in sport at the highest professional level because of advances in the medical care of their asthma. The medical profession's understanding of the pathophysiology of EIA can help these athletes to reach goals which were previously unattainable – as a result of advances in medical therapeutics.

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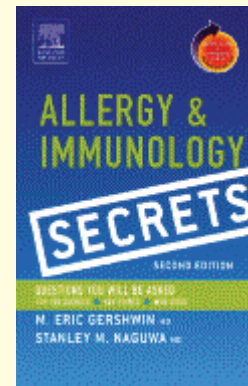
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