EXERCISE-INDUCED ASTHMA

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DEMITRI CONSTANTINOU

MB BCh, BSc (Med) (Hons) Sports Science

Director

Sports and Exercise Science

University of the Witwatersrand

Johannesburg

Dr Constantinou is a Sports Physician in Johannesburg. He is President of the SA Sports Medicine Association and Regional Medical Co-ordinator for Gauteng of the national High Performance Programme. He was Chief Medical Officer of the SA team to the Paralympics in Sydney in 2000 and the All Africa Games in 1999, and Team Physician to the All Africa Games in 1995 and the Commonwealth Games in 1998. His current interests include exercise in the management of chronic disease, bone stress injuries, and exercise-associated muscle cramps.

WAYNE DERMAN

MB ChB, BSc (Med) (Hons) Sports Science, PhD, FACSM

Associate Professor

MRC/UCT Research Unit for Sports Science and Sports Medicine

Sports Science Institute of South Africa

Cape Town

Medical Co-Director

Chronic Disease Rehabilitation Programme and Sports Medicine Practice

Sports Science Institute of South Africa

Cape Town

Wayne Derman is Past President of the South African Sports Medicine Association. He was the Chief Medical Officer of the National Olympic Committee of South Africa for the Sydney 2000 Olympic Games and has been appointed as Chief Medical Officer for Athens 2004.

Asthma is a reversible airways disease, characterised by hyper-responsiveness of the bronchial tree to a variety of stimulants. These include, among others, allergens (such as house dust mite, pollen, mould, and animal dander), viral infections, cigarette and other smoke inhalation, cold air and exercise.

Exercise-induced asthma (EIA) is reversible airway obstruction that occurs during or soon after physical activity. The stimulus of exertion leads to post-exertional bronchoconstriction. EIA can affect anyone at any level of exercise participation, from school-children to Olympic-level international elite athletes. Eighty to ninety per cent of known asthmatics will also have EIA and it is found in 40% of individuals with allergic rhinitis, atopic dermatitis or eczema. A number of individuals may have the condition associated only with exercise. The exact prevalence is difficult to ascertain, but is estimated to be around 15%. Frequently young children and adolescents with EIA avoid physical activity because of their symptoms.

In normal individuals following a bout of exercise early bronchodilation occurs due to catecholamine release. This does not occur in patients with EIA — in fact bronchoconstriction occurs 6 - 8 minutes after exercise. The lung function continues to decrease, with the peak effect about 15 minutes after exercise. The lung functions will usually return to normal within 2 hours after exercise.

The extent of EIA is exercise-intensity related. Usually exertion above 75 - 80% of predicted maximum heart rate (predicted maximum heart rate is calculated as 220 – age) will induce EIA. The nature of physical activity may have an influence (Table I), but the minute-ventilation parameter is essentially comparable with the different sports or activities at which the stimulus for EIA occurs.

There is a refractory period in which there is a blunted response to a repeat bout of intense exercise within 2 hours after an initial EIA response. In this period, there is a weaker or absent bronchospasm response. The refractory period can be used to the advantage of athletes, if the athlete then competes following a warm-up in this period. The exact mechanism of the refractory period is unknown, and perhaps could be related to bronchodilatory prostaglandin and catecholamine release.

PATHOPHYSIOLOGY OF EIA

The exact pathophysiology of EIA is unknown, but two theories currently prevail. The first is the water loss theory. Increased osmolarity of the bronchial mucosa is thought to result from the typical tachypnoeic mouth breathing with exercise, without the

Table I. **Asthma-inducing physical activities**

Highly inducing

- Outdoor running
- Treadmill running
- Soccer
- Rugby
- Cycling
- Basketball
- Winter sports (cold dry air) e.g. ice skating, ice hockey, cross-country snow skiing (relevant for vacationing South Africans, residents of Northern hemisphere countries and competitive athletes in these sports)
- Swimming in pools with high chlorine concentration

Less inducing

- Squash
- Netball
- Volleyball
- Badminton
- Martial arts
- Wrestling
- Weightlifting
- Swimming in pools with low chlorine concentrations
- Golf
- Tennis

nasal warming, and loss of water from the bronchial epithelium. The effect is a change in osmolarity, pH and temperature, with the release of mediators (including histamine, leukotrienes and prostaglandins), leading to bronchoconstriction.

The other theory is the heat exchange theory with increased ventilation leading to cooling of the airways. The effect post exertion is rebound warming that occurs with dilation of the vessels in the bronchi. This causes mechanical narrowing of the airways, and perhaps a mediator release phenomenon leading to bronchospasm.

CLINICAL MANIFESTATIONS OF EIA

Symptoms of EIA can include chest tightness, shortness of breath, coughing, wheezing during exercise, fatigue, prolonged recovery after exercise, poor exercise performance or even chest pain during exercise. Typically respiratory symptoms occur within 5 - 10 minutes after starting a vigorous exercise bout but maximal bronchospasm may occur 3 - 15 minutes after the cessation of exercise. There is usually spontaneous recovery within 60 minutes after cessation of exercise.

Factors that can affect the usual timing of onset and severity of EIA include:

- environmental conditions such as temperature (worse in cold temperatures), humidity, air pollution and pollens
- underlying infections of the respiratory tract
- the type, duration or intensity of the exercise
- lack of warm-up
- the time elapsed since the previous exercise session.

Activities such as running and cycling which require high-intensity exercise are most likely to cause EIA. Generally, the colder the climate and the more vigorous the exercise, the more rapid and severe the bronchospasm.

DIAGNOSIS OF EIA

An important clinical differentiation must be made between EIA and mild, or more severe grades of chronic, persistent asthma with an exercise-induced component. This distinction is important with regard to treatment, because many patients with EIA require only pre-exercise treatment, whereas those with persistent asthma require daily anti-inflammatory therapy plus pre-exercise treatment.

It is also apparent that bronchial hyperreactivity during exercise can occur following an upper respiratory tract infection and that the management of this is of relatively short duration (6 weeks - 3 months) while asthma usually requires long-term management.

Diagnosis therefore requires an accurate history, physical examination, and lung function testing at rest, during and after exercise.

The clinical history should include questions to determine the presence or absence of the symptoms listed above.

The physical examination focuses on the respiratory system and ear, nose and throat evaluation. Usually the physical examination is non-contributory, but clinical signs of chronic asthma (including wheezing), underlying respiratory tract infection or symptomatic allergy are important to exclude. An algorithm for the clinical work-up of the patient with suspected EIA is presented in Fig. 1.

A number of different methods can be used to assess pulmonary function. Peak flow meters are an inexpensive, effective and widely available tool to measure pulmonary function immediately before and after exercise at 1, 3, 5, 10 and 15 minutes. Peak flow meters can also be effectively used to monitor the response to therapy in the field.

Spirometry and exercise testing form the gold standard for the diagnosis of EIA. Chronic asthma is differentiated

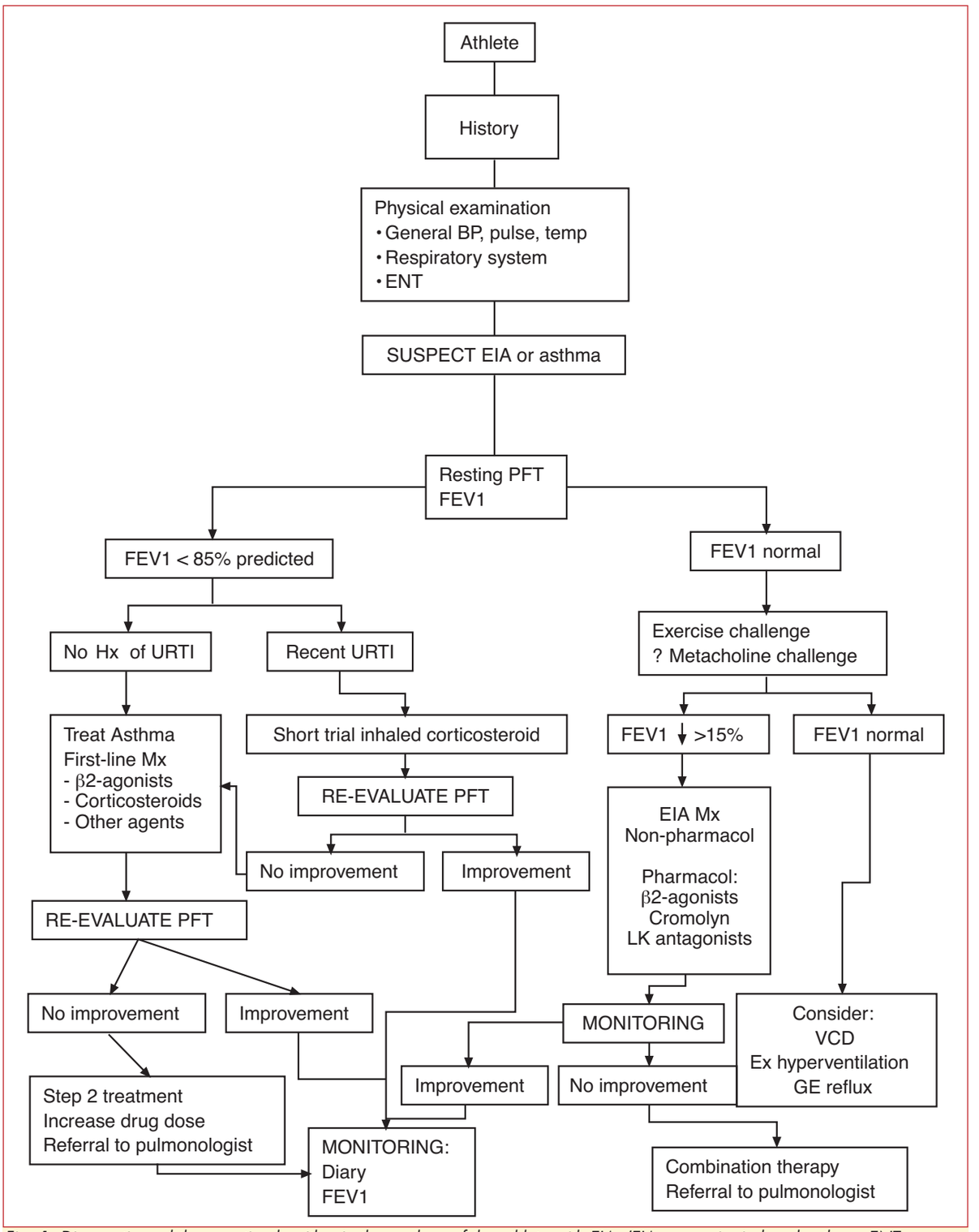

Fig. 1. Diagnostic and therapeutic algorithm in the work-up of the athlete with EIA. (EIA = exercise-induced asthma; ENT = ear nose and throat; FEV1 = forced expiratory volume in one second; PFT = pulmonary function tests; Hx = history; Mx = management; URTI = upper respiratory tract infection; VCD = vocal cord dysfunction; GE = gastrointestinal; LK = leukotrine.)

from EIA alone by the absence of symptoms and the FEV1 persistently within the normal range at rest. When the FEV1 is 85% of the predicted value or less, the diagnosis may be asthma or alternatively a chronic lung disorder, and this should be investigated and treated according to established guidelines (Guidelines for management of asthma in adults, 1990; National Heart, Lung and Blood Institute guidelines 1991). However, it

Table II. **Severity of EIA based on decrease of FEV1 and PEFR post exertion**

15 - 20% Mild EIA	20 - 30% Moderate EIA	> 30% Severe EIA

is important to note that an FEV1 within the normal range does not exclude chronic asthma and is in fact a feature of mild intermittent asthma. If the FEV1 at rest is within the predicted range, an exercise challenge should be undertaken. The exercise test should be undertaken in a cold laboratory using either a treadmill or cycle ergometer. The workload is rapidly increased to reach > 80% max HR within 2 - 3 minutes. The exercise should be sustained for at least 5 minutes. Spirometry could be performed at 1, 3, 5, 10 and 15 minutes after exercise. If no symptoms occur with laboratory testing the patient should be tested before and after exercise during participation in his or her own sport. A histamine or methacholine challenge may be undertaken in sophisticated pulmonary laboratories. This provides a more sensitive test for bronchial hyperreactivity and if present increases the probability that the athlete's symptoms represent EIA.

The spirometry criteria after exercise for the diagnosis of EIA are listed in Table II.

At a different occasion, the patient's response to inhaled bronchodilators can be determined by measuring pulmonary functions following administration of a bronchodilator. The improvement in FEV1 after administration of a bronchodilator should be at least 12% (American Thoracic Society guidelines) but preferably 15% (BTS guidelines).

Other investigations that may be appropriate, depending on the history, include chest X-rays, sinus X-rays, full blood count, and serum IgE.

MANAGEMENT

Education on the nature of the condition is a very important aspect of managing EIA. Often this is directed not only to the patient, but their parents, coaches and peers. This includes an understanding of the condition, factors that may influence it, how to try and avoid acute attacks, management of attacks, and how to use the inhalers and/or their spacer devices correctly.

Non-pharmacological management approaches are summarised in Table III. One needs also to take into account allergens and other environmental conditions when athletes are travelling to other locations to compete. Some asthmatics deteriorate when travelling, possibly based on time zone changes and travel fatigue, apart from the environmental factors, which include humidity, heat and pollution. Patients should have sufficient medication with them to last the duration of the journey.

A low salt diet may have benefits in some athletes' lung functions.

Pharmacological management is summarised in Tables IV and V. The pharmacological treatments include inhaled bronchodilators, inhaled anti-inflammatories (corticosteroids), inhaled mast cell stabilisers and leukotriene modifiers (receptor antagonists and 5-lipoxygenase inhibitors).

Inhaled corticosteroids would, specifically in those with chronic asthma, be used on a long-term basis and assist in reducing airway responsiveness. In patients with pure EIA, using corticosteroids on a long-term basis may have benefits in some, but not all patients. These may be used on a trial basis when other modalities have not had the desired response.

Intranasal corticosteroids are important adjunct treatments for those with EIA as well as chronic or seasonal rhinitis.

Inhaled beta-adrenergic drugs are either short- or long-acting. These increase the concentration of cAMP in cells, affecting the smooth-muscle

Table III. **Non-pharmacological management of EIA**

Management	Mode of action
Maintaining aerobic fitness	Can exercise at lower ventilatory rate for given workload Perhaps reduced airway responsiveness
Adequate warm-up/pre competition exercise	To induce refractory period
Avoid exercise in excessively cold and/or dry air	Reduced responsiveness of airways
Avoid exercise/intense exercise when related symptoms present	Rhinitis, sinusitis, allergies indicate hyper-responsive state in airways
Adequate warming down	Avoids rebound warming and reduces oedema
Change of exercise/sport	With severe symptoms, changing activities to sports less likely to induce EIA
Wearing of face mask	Reduces inhalation of pollutants and irritants
Avoiding known allergens or irritants	Prevents allergic reactivity

Table IV. **Pre-exercise medication for EIA**

Medications	Mode	Recommended dosage	Onset of action	Duration of effects (hours)
Beta-2 agonists				
Salbutenol	Metered dose inhaler (MDI), dry powder device	2 puffs 15 min before exercise for adults and children ≥ age 4	Within 5 min	3 - 6 hr
Terbutaline sulfate	MDI	2 puffs every 4 - 6 hr for adults and children ≥ 12	5 - 30 min	3 - 6 hr
Salmeterol	MDI, dry powder device	2 puffs ≥ 30 - 60 min before exercise or 12 hourly	Within 20 min	12 hr
Formoterol	MDI, dry powder device	2 puffs ≥ 30 - 60 min before exercise or 12-hourly	Within 15 min	12 hr
Mast-cell stabilisers				
Cromolyn sodium	MDI	2 puffs within 60 min of exercise for adults and children ≥ age 5	–	2 hr
Nedocromil sodium	MDI	2 puffs, qid for adults and children ≥ age 6	May take up to 1 week of use for full effect	2 hr

Table V. **Long-term medication for EIA**

Medications	Mode	Recommended dosage	Onset of action	Duration of effects (hours)
Inhaled corticosteroids				
Beclomethasone dipropionate	MDI	≥ age 12, 2 puffs (84 µg) tid or qid; age 6 - 12, 1 or 2 puffs (42 - 84 µg) tid or qid	1 or 2 days	–
Budesonide	MDI	Adults, 1 - 2 puffs bid; children ≥ age 6, 1 puff bid	24 hours	–
Fluticasone propionate	MDI	≥ age 12, 2 puffs (88 - 440 µg) bid	24 hours	–
Triamcinolone acetonide	MDI	Adults, 2 puffs (200 µg) tid or qid; children age 6 - 12, 1 or 2 puffs (100 - 200 µg) tid or qid	1 week	–
Leukotriene modifiers				
Montelukast	Tablet	10 mg daily for those ≥ age 15; 5 mg daily for children age 6 - 14	3 - 4 hours	Up to 24 hours
Zafirlukast	Tablet	20 mg bid for adults and children ≥ age 12	30 min	12 hours

Eighty to ninety per cent of known asthmatics will also have EIA and it is found in 40% of individuals with allergic rhinitis, atopic dermatitis or eczema.

Symptoms of EIA can include chest tightness, shortness of breath, coughing, wheezing during exercise, fatigue, prolonged recovery after exercise, poor exercise performance or even chest pain during exercise.

Activities such as running and cycling which require high-intensity exercise are most likely to cause EIA.

contractions of the bronchioles. They essentially act as bronchodilators and are very useful when used prior to exercise. There may also be anti-inflammatory effects by reducing the release of mediators by mast cells, specifically in the long-acting beta-agonists.

The short-acting beta-2-agonists should be used 20 - 30 minutes before exercise and not immediately prior to exercise. It is apparent that frequent repeated use of these agents without the protective effect of inhaled corticosteroids might lead to a decreased efficacy over time. The longer acting drugs may have a slower onset of action, but last for up to 12 hours, and so should be used as a morning or twice daily dose regimen and not too soon before the onset of exercise — a period of 4 hours before exercise is a safe margin. The long-acting beta-agonists are clearly useful for endurance athletes and children.

It is advisable that all athletes with EIA carry with them short-acting beta-adrenergic inhalers for times where symptoms may develop despite their regular management.

Mast cell stabilisers are inhalers that include nedocromil sodium and sodium cromoglycate/cromolyn sodium. They appear to be less effective than the beta-agonist, but where the latter side- effects (palpitations, insomnia, tremors) are a problem, they can be used. They may also be used in combination with the beta-agonists when those are not as effective as desired. The mast cell stabilisers can be used repeatedly and frequently in a day, unlike the beta-agonists.

Leukotrienes can cause smooth-muscle contraction. **Leukotriene modifiers** are being used in chronic asthma sufferers, usually alone in mild asthma, or in combination with other drugs. They are convenient, as oral formulations, have few side-effects and are long-acting. They are useful in EIA, when the symptoms are mild, but often need to be used as adjunct therapy to optimise control.

Theophylline, an oral asthma treatment, is useful in chronic asthmatics who may require this for their management. It has not been found to be specifically beneficial in those with pure EIA.

Anticholinergic inhaler treatment, both short- and long-acting, is not as effective in EIA as it is in chronic obstructive pulmonary disease.

Oral **antihistamines** are not specifically indicated for use in EIA, but are useful as adjunct treatment in those athletes who have atopia in addition to their EIA.

Commonly a combination of therapies is required to achieve optimum control. Caution should prevail with prescribing anti-inflammatory medications and beta-adrenergic blockers, which can cause bronchoconstriction.

MONITORING ATHLETES

After the athletes have been on a trial of active medication, they should be reassessed by means of repeat exercise testing and spirometry and symptom diary monitoring, to assess the effect of the management. Athletes showing no or only minor response to the treatment or when the diagnosis of EIA is in doubt (e.g. signs and symptoms of EIA without abnormality demonstrated on spirometry before or after exercise) should be evaluated for vocal cord dysfunction, exercise-induced hyperventilation, or chronic gastro-oesophageal reflux.

IMPORTANCE OF SCREENING

As EIA is generally underdiagnosed, it is suggested that team physicians have an increased index of suspicion of this condition and include screening questions in their history taking. When indicated, spirometry before and after exercise should be conducted during the pre-participation athlete evaluation. EIA can be successfully diagnosed and managed, allowing athletes with EIA to compete at the highest level of sport.

EIA AND DOPING OFFENCES

The World Anti-Doping Agency (WADA) has published the prohibited substance list and anti-doping code. This is a universal code, and has strict rules and regulations pertaining to doping control matters. It is imperative that prescribing treatment to any patient is done so with the Code in mind to avoid any positive drug tests that the athlete may undergo. This pertains to any athlete at any level, not only elite or highly competitive athletes. The relevant article related to asthma medication states:

- *'Category S6: Beta-2 agonists. The use of these inhalers requires Therapeutic Use Exemption. See below for details on this.*
- *Category S9: Glucocorticosteroids. These are prohibited in any form and by any route. Therapeutic use exemption needs to be applied for in inhaler or intranasal use for asthmatics.'*

Therapeutic use

International standards apply for the process of granting therapeutic use exemption (TUE), such as indicated above for beta-agonist inhaler therapy and inhaled or intranasal corticosteroids in asthmatics. TUE is applied for the use of inhaled beta-agonists and non-systemic corticosteroids with an abbreviated application form. The National Anti-Doping Agency (South African Institute for Drug Free Sport (SAIDS)) has processes in place to grant TUE, according to international standards and formats. This institute can grant TUE for national athletics and international level athletes who are not in the top 50 in the world for their particular sport. Elite internatinal athletes who are within the top 50 have to apply to their sports federation for TUE. All these results will be submitted to the WADA. Specific forms supplied by the institute must be completed by the athlete together with a medical report by a pulmonologist or team physician and be submitted to the SAIDS for granting of TUE. This will include lung function tests (pre- and post exercise) and bronchodilator therapy. Any additional results, if available, should also be submitted (e.g. blood tests, skin prick allergy tests, radiology). An athlete may be granted TUE by written notification, which will also be submitted to WADA. Athletes have leave to appeal with WADA, should they not be granted TUE by the National Anti- Doping Agency or their sports federation.

EIA can easily be missed or overlooked, and when appropriately assessed and managed affords athletes the opportunity of performing at their optimal level without compromise. Exercise-induced asthma needs to be monitored to ensure adequate control at all times. Patients are advised to monitor their symptoms and peak flow readings, which can easily be achieved by keeping a logbook, and seek assistance when appropriate.

IN A NUTSHELL

Exercise-induced asthma (EIA) is found in about 80 - 90% of asthmatics

About 15% of athletes have EIA.

Common symptoms include coughing, wheezing, and dyspnoea during or after exercise.

Lung function test in conjunction with exercise challenge test imperative.

The condition can be adequately treated, which permits exercise without constraint.

The refractory period can be used to an athlete's advantage in reducing competition symptoms.

Pre-exertional use of beta-agonists is the commonest mode of management.

Environmental factors must be taken into account and manipulated when possible.

Regular follow-up is often necessary.

Be aware of doping regulations and applications of therapeutic use exemption.

Further Reading

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