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Review Article

EXERCISE-INDUCED ASTHMA: FRESH INSIGHTS AND AN OVERVIEW

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ABSTRACT
Exercise-induced asthma (EIA) is a common condition affecting 12-15% of the population. Ninety percent of asthmatic individuals and 35-45% of patients with allergic rhinitis are afflicted by EIA, while 3-10% of the general population is also believed to suffer from this condition. EIA is a condition which is more prevalent in strenuous outdoor, cold weather and winter sports. The pathophysiology of EIA continues to intrigue medical physiologists. However, the water-loss hypothesis and the post-exertional airway-rewarming hypothesis are as yet the best accepted theories. EIA is best diagnosed by a good medical history and a free-run challenge test. A post-exertion decrease by 15% in FEV1 and PEFR is diagnostic of EIA. Sensitivity of exercise testing ranges from 55% to 80% while specificity is as high as 93%. EIA is a disorder that can be successfully treated by combining both non-pharmacological and pharmacological treatment options. Prompt diagnosis and treatment of this condition is vital if we hope to provide our patients with better overall health, better social life and a better self-image.
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INTRODUCTION

Bronchial asthma is defined as a chronic inflammatory disorder of the air passages in which many cellular elements play a role, namely, mast cells, eosinophils, neutrophils, epithelial cells, T lymphocytes and macrophages. In susceptible individuals this inflammation results in increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli.

This is manifested physiologically by a widespread narrowing of the air passages which may be relieved spontaneously or as a result of therapy and is clinically characterised by paroxysms of dyspnoea, cough and wheeze. It is an episodic disease, acute exacerbations being interspersed with symptom–free periods.

Exercise-induced asthma (EIA) is an asthma variant which may be defined as a condition in which exercise or vigorous physical stress triggers acute bronchospasm in people with increased airway reactivity. It is primarily seen in people who are asthmatic but can also be found in patients who have atopy or allergic rhinitis and even in healthy individuals.

Exercise-induced asthma is even more important to the chest specialist because it is a neglected diagnosis and the underlying asthma could be silent in as many as 50% of patients,[1] becoming apparent only during exercise.

EPIDEMIOLOGY

EIA affects 12-15% of the population. Ninety percent of asthmatic individuals and 35-45% of patients with allergic rhinitis experience EIA, but even when this group of patients is excluded, a 3-10% incidence of EIA is seen in the general population.[2]

EIA seems to be more prevalent in some winter and cold-weather sports.[3] Some studies have demonstrated rates as high as 35% or even 50% in competitive-caliber figure skaters, ice hockey players, and cross–country skiers.[4,5]

FUNCTIONAL ANATOMY AND PATHOPHYSIOLOGY

The problem in EIA occurs distal to the glottis, in the lower respiratory tract. Bronchoconstriction is involuntary and is distinguishable from laryngospasm which can occur in other exercise-related conditions.

EIA usually affects individuals who participate in sports that include an aerobic component. This condition can be seen in any sport, but EIA is much less common in predominantly anaerobic activities. This is possibly due to the role of consistent and repetitive air movement through the air passages which is mainly seen in aerobic sports thereby affecting airway humidity and temperature. As a result an unknown biochemical and neurochemical pathway is triggered resulting in bronchospasm.

The classical presentation of EIA lends some insight into the possible causative mechanisms. In people prone to EIA the first 3-5 minutes of physical activity usually have no adverse effects. When the physical activity is stopped, the lung functions decrease.

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The PEFR and the FEV1 levels fall within 5-10 minutes after the activity stops. On resuming the physical activity symptoms begin to manifest within the first 5-10 minutes of resumption of the activity. The decrease in lung functions accompanied by symptoms usually persists for 15-40 minutes followed by normalisation of lung functions and resolution of symptoms. During this time the PEFR and FEV1 fall by 20-50%. This early-phase response is the classic manifestation of EIA.

A refractory period ranging from 40 minutes to 2 hours follows the episode of EIA and during this refractory period it is difficult to replicate the symptoms.

In some individuals a late-phase response also occurs which is related more to inflammatory changes. This normally occurs within 3-10 hours after the physical exertion stops and the degree of fall in lung function is *greater* and more prolonged than in the early-phase response.

Multiple factors appear to affect the frequency and severity of the change in pulmonary function and symptoms:

A. The greater the person's baseline level of bronchial hyperreactivity as measured by histamine or methacholine challenge, the greater the likelihood of EIA developing or worsening.
B. The greater the minute ventilation (with other factors controlled), the greater the intensity and duration of EIA up to a maximum of two thirds of the individual's maximum working capacity.[6]
C. The less humid the inspired air, the greater the trigger for EIA.[7-9]
D. The cooler the air, the greater the trigger for EIA.[7-9]
E. Exposure to airborne allergens worsens EIA.
F. Certain air pollutants (e.g. ozone) may worsen EIA.

The currently preferred hypothesis also known as the *water–loss hypothesis* is that exercise causes decreased airway humidity through more rapid ventilation and thus increases mucosal osmolarity. As a result, osmoreceptors trigger increased bronchial blood flow, which causes oedema. Simultaneously, the increased osmolarity induces release of mediators that induce contraction of smooth muscle and further obstruction of the airway. Slower production of inhibitory prostaglandins results in bronchodilatation that ultimately reverses the smooth muscle contraction and manifests as the refractory period. Evidence against this hypothesis is that it does not explain why the most major constriction of the airways occurs after cessation of hyperpnoea.

Another hypothesis known as the *post-exertional airway–rewarming hypothesis* states that the initial airway heat loss associated with hyperpnoea causes a vascular dilatation and oedema that physically narrows the airways. This hypothesis is supported by the fact that some vasodilatation in systemic vasculature occurs after cold exposure and also that alpha-adrenergic agonists limit hyperventilation-induced asthma. The cellular mechanism of this process has yet to be explained. Sensory neurons have been implicated in animal models as possible pathways but have not been identified in humans.

Though the above two hypotheses attempt to explain the pathophysiology behind exercise-induced asthma there is still no plausible explanation for the mechanism behind the refractory period when on persistent exertion the person fails to get a further attack. Could it be a complete degranulation of the mast cells and their inability to degranulate further which is responsible for this refractoriness or the slow production of inhibitory prostaglandins causing bronchodilatation? Also, what is the mechanism behind the late-phase response in some patients where hours after the physical exertion stops, the fall in lung function is more pronounced than in the early-phase. Is it mast cell reactivation and mediator release attracting inflammatory cells to the airways which causes this response? I believe, in the years to come the pathophysiology of this oft neglected diagnosis will be revisited time and again.

CLINICAL MANAIFESTATIONS

The pathophysiologic mechanisms of asthma result in a multiplicity of physiologic changes occurring within the pulmonary tree during or following exercise.[2,10] These include: cough, shortness of breath, wheezing, tightness of chest or chest discomfort, fatigue, below par performance on the field of play, gastrointestinal discomfort, prolonged recovery time,

Contributing factors include: cool temperatures, low-humidity environment, poor air quality, high content of pollen, concomitant respiratory infection

Exercise factors include the following: Aerobic exercise predisposes more to EIA than anaerobic exercise. Duration of aerobic exercise exceeding 10 minutes rapidly provokes an attack in a susceptible individual. High–intensity aerobic exercise predisposes to EIA.

Refractory phase in EIA

This phase starts less than 1 hour after the initial aerobic exercise and lasts up to roughly 3 hours. The refractory phase results in as little as one half the degree of bronchospasm as in the first episode. In sports this fact can be used to advantage by utilizing the warm–up period in such a way that the actual competition occurs during the refractory phase. Though the exact mechanism of this phase is unknown, it is believed to involve the possible depletion of mast cell mediators, release of endogenous catecholamines and the release of endogenous protective prostaglandins.

Sports requiring continuous activity, played in cold weather and most likely to trigger an attack of EIA in a susceptible

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individual, e.g. cross–country skiing, ice hockey, basketball, soccer, long-distance running

Sports less likely to trigger an attack of EIA are those that require short bursts of activity and are interspersed with breaks. These include: swimming, walking, hiking, golfing, baseball or softball, football, volleyball, gymnastics, wrestling, downhill skiing

DIAGNOSIS

EIA is invariably diagnosed by the medical history. Atopic individuals with or without asthma should be questioned regarding possible EIA symptoms. Persons who give a history of cough, wheezing, dyspnoea, chest pain or chest tightness following aerobic activity should be questioned in detail regarding other symptoms related to EIA. Children who cannot keep pace with their peers during sporting activities should be asked whether breathing becomes difficult during those activities.

EIA is best detected by a free-run challenge test. Here, the patient is asked to run at full speed for 3-5 minutes and achieving a heart rate at least two-thirds of their target heart rate (or 180 beats per minute in children). The patient should stop after 5 minutes or earlier if symptoms arise. Pulmonary function should be measured by PEFR and FEV1 at baseline, immediately after stopping the run and at 5, 10, 15, 20 and 30 minutes after the activity is completed. A decrease of 15% in FEV1 and PEFR is diagnostic of EIA. Sensitivity of exercise testing ranges from 55% to 80%, and specificity is approximately 93%.[2]

It must be remembered however, that testing is contraindicated during acute exacerbations of asthmatic attacks.

TREATMENT MODALITIES

EIA has several treatment modalities. The aim of treatment should always be to help maximise the patients ability to participate in aerobic activity be it at his work place, recreation, serious athletics or school-related activities. The purpose of treatment in EIA is to enhance the patients' sense of self worth, physical conditioning, socialization and sometimes even to help retain employment.

Can EIA be successfully treated? YES!!

The 1988 US Olympic team included 67 members (of 597) affected with EIA. These athletes won 15 gold, 21 silver and 5 bronze medals in multiple sporting events including long–distance running.

Non-pharmacological treatment

Medication is not the only way to treat EIA but type of physical activity undertaken is also very important. Clinicians should encourage patients to choose less asthmogenic activities whenever possible. Ambient conditions should also be considered – the more humid and warmer the air, the less the chance of provoking EIA. Thus indoor activities are less likely to provoke an attack of EIA. Wearing a face mask may also help to warm and humidify the outdoor air. Physical activity on days of high air pollution should be avoided. For asthmatic patients who are highly sensitive to pollen, activity should be timed to occur when diurnal pollen counts are lowest.

The refractory period may also be used beneficially by encouraging athletes to exercise in several 2-3 minute increments as "warm ups", 10-20 minutes before the main event. As a result this may induce a period of up to one hour during which EIA would not develop. This would certainly help those whose duration of planned physical activity is short such as sprinters.

Pharmacological treatment

Many factors play a role while initiating treatment:

- Does the patient have predictable periods of aerobic activity (e.g. jogs every morning, is a day labourer, or is a playful 5-year-old child).
- Are the ambient conditions in which activity takes place controllable?
- Can the patient effectively use a metered-dose inhaler?
- How long will the physical activity continue and how intense aerobically is the physical activity?

In general, drug therapy is effective for patients whose physical activity is brief and predictable and who can use the metered-dose inhaler effectively. However, if physical activity continues for more than 2-3 hours or if the patient cannot use a metered-dose inhaler effectively, consideration of oral medication may be warranted.

Treatment is chosen from three types of medication: beta-adrenergic drugs, mast cell inhibitors and leukotriene antagonists. Beta-adrenergic drugs are the first-choice medication for treating patients whose activity is limited in duration i.e. less than 3 hours. These drugs can be used 15 minutes before activity is begun and are relatively safe. Since bronchospasm is the main component of EIA, these drugs are highly effective. Salbutamol and terbutaline are most commonly used. Recent data indicate that salmeterol remains effective for 10-12 hours.[11] Clinicians should emphasize to patients that salmeterol dosing should never be repeated more frequently than every 12 hours because overuse can induce cardiac toxicity. Oral beta-adrenergic agents may also be used but must be taken at least 30-45 minutes before the activity is

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begun. Beta-adrenergic agents may cause more side-effects when taken orally than when they are administered by metered-dose inhalers.

Another group of medications used in the treatment of EIA are called the mast cell inhibitors, but whether inhibition of mast cells is their primary role is unclear. They are a very good choice for preventing EIA and they have an excellent safety profile. Among them cromolyn and nedocromil also have the twin advantage of blocking early-phase and late-phase responses. These drugs are delivered by metered–dose inhalers, 2-3 sprays being administered 10-15 minutes before the onset of activity. They are also usually needed after 2-4 hours of continuous activity.

Leukotriene antagonists constitute the third group of medications used in the treatment of EIA. Of this group, montelukast (Singulair) is effective in preventing EIA. It has been observed that long-term use (longer than 12 weeks) is not associated with shortened duration of action or with diminution in protection offered as measured by FEV1.[12] The medication is given orally in tablet form in a single dose each day. However, montelukast is not approved for children less than 6 years of age.

Other medications such as inhaled steroids have been used to decrease airway hyperreactivity. For this, a month or more of moderate-to-high dose daily use may be required. These drugs are best reserved for use in controlling asthma that is not specifically related to exercise. Theophylline can also be used and may be beneficial, but timing its use to activity is more difficult. Overall, medications benefit 60-80% of patients who are susceptible to EIA and reduce the decrease in FEV1 in these patients from 40-80%.[12]

Athletic activities and EIA

Diagnosis and treatment of athletes who participate in competitive sporting activities is essentially the same as for other people except that competitive athletes tend to recognise even small changes in airway function, and this small amount of change may not respond noticeably to medication therapy. In addition, the degree of response achieved by using these medications may not warrant use of the large amounts of medication needed to relieve all symptoms. This fact needs to be discussed carefully with each affected athlete.

In addition, athletes in competition are also likely to behave stoically when experiencing physical discomfort and thus may underreport symptoms. This may be due to peer pressure, embarrassment, fear of losing position on the team, or plain misinterpretation as post-exercise fatigue.

CONCLUSION

EIA is a common problem that affects millions of people annually all over the world. It is often unrecognised by patients and physicians. However, a high index of suspicion and some simple screening methods can lead to a presumptive diagnosis in most cases. EIA is treated both, by pharmacological and non-pharmacological means. Most important, control of any underlying asthma is essential for control of EIA.

The importance of recognising and treating EIA therefore cannot be over-emphasised if we hope to provide all affected persons with the opportunity for better overall health, better social life and better self-image.

REFERENCES

1. Rupp NT, Guill MF, Brudno DS. Unrecognised exercise-induced bronchospasm in adolescent athletes. *Am J Dis Child.* 1992;146(8): 941-4
2. Hough DO, Dec KL. Exercise-induced asthma and anaphylaxis. *Sports Med.* 1994;18(3):162-72
3. Stensrud T, Berntsen S, Carlsen KH. Exercise capacity and exercise-induced bronchostriction (EIB) in a cold environment. *Respir Med.* 2007;101(7):1529-36
4. Butcher JD. Exercise-induced asthma in the competitive cold weather athlete. *Curr Sport Rep.* 2006;5(6):284-8
5. Dickinson JW, Whyte GP, McConnell AK, Harries MG. Screening elite winter atheletes for exercise induced asthma: a comparison of three challenge methods. *Br J Sports Med.* 2006;40(2):179-82
6. Cypcar D, Lemanske RF Jr. Asthma and exercise. *Clin Chest Med.* 1994;15(2): 351-68
7. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Jaeger JJ. Hyperpnea and heat flux: initial reaction sequence in exercise-induced asthma. *J Appl Physiol.* 1979:46(3):476-83
8. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, *et al.* Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol.* 1979;46(3):467-75
9. Strauss RH, McFadden ER Jr, Ingram RH Jr, *et al.* Influence of heat and humidity on the airway obstruction induced by exercise in asthma. *J Clin Invest.*1979;61(2):433-40
10. National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma Report 2007. Bethesda, Md: NHLBI; August 2007.
11. Nelson JA, Strauss L, Skowronski M, *et al*. Effect of long term salmeterol treatment on exercise-induced asthma. *N Engl J Med.* 1998;339(3):141-6
12. Leff JA, Busse WW, Pearlman D, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of mild asthma and exercise induced bronchoconstriction. *N Engl J Med.* 1998;339(3):147-52