Exercise in Childhood Asthma: Provoking Agent, Diagnostic Tool and Therapeutic Measure

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Asthma is one of the most common chronic diseases in pediatrics, with an estimated prevalence of 10–15%. Despite advances in the understanding of the disease and its treatment, in recent years an increase has been noted in its prevalence, severity, morbidity (hospitalizations), and even mortality.

Asthma is defined today as a pulmonary disorder characterized by reversible bronchoconstriction, inflammation, and airways hypersensitivity to various stimuli [1]. The main causes of exacerbations in children include viral upper respiratory tract infections, allergens, and physical activity. It is assumed that 50–80% of asthmatic children will suffer from exercise-induced asthma [2]. This is probably an underestimation since, with the "appropriate" (strenuous) activity, the vast majority of patients will experience EIA [3].

In discussing the relationship between asthma and physical activity one must remember that, traditionally, asthmatic patients were limited in, if not restricted from, participation in competitive sports. Today, however, even moderate-to-severe asthmatics are engaging in competitive sports [4]. It is notable that although EIA was detected among 11.2% of the American Olympic team members (67 of 597 athletes) participating in the 1984 Los Angeles Olympic Games, it did not interfere with their achievements and they walked home with 41 medals, 15 of them gold [5].

The relationship between asthma and physical activity is interesting and complex. Whereas physical exertion can exacerbate the disease, prolonged and controlled activity can assist in its management. In addition, physical activity serves as an important diagnostic and research tool. The purpose of this article is to review these interconnections.

Exercise-induced Asthma

An exercise-induced asthma attack is characterized by wheezing, cough, chest pain or discomfort, dyspnea, or any combination of the above during exertion or usually a few minutes *after* the exercise bout. These symptoms are often accompanied by lung function abnormalities, and usually pass within 30–90 minutes from cessation of the activity, although they may recur between 4 and 8 hours later.

The prevalence of EIA among asthmatics in various reports ranges from 40 to 100%. This large range arises from differing physical activity protocols and depends on the type of activity, its intensity, duration, environmental conditions (heat, humidity, etc.), severity of the disease, and the variations in preventative therapy regimens.

Type of activity

Certain sports such as long distance running, jumping, or cycling are more "asthmatogenic". In contrast, swimming is considered the least offensive sport, even after controlling for differences in temperature and humidity [6].

Duration and intensity of activity

The most problematic activity for asthmatics is relatively short and intense: lasting 6–10 minutes and causing a rise of up to 80% of the maximal in heart rate and/or 70% of the maximal oxygen uptake [7]. Moderate-intensity physical activity is less likely to induce an asthma exacerbation, while prolonged sessions may be even less provoking (the "run-through effect"). Supra-maximal-intensity exercise is most related to the induction of asthma attacks [8].

An interesting and important phenomenon is the refractory period. After the induction of bronchospasm by a certain activity, repetition of the same activity within 2 hours may evoke only mild dyspnea or even no respiratory response at all. Asthmatic children and their parents should be aware that following an exercise-induced attack it is possible to immediately return to full activity without fear of further exacerbation. Although not recommended by the medical community, elite athletes with asthma sometimes use the refractory period to their advantage by inducing an attack shortly before competing to insure an attack-free period. The physiological basis for this phenomenon is not well understood, but may be explained by the depletion of the mast cell mediators responsible for the first attack [9].

Environmental conditions and asthma

The environmental conditions before, during and after physical activity influence the extent of the response. It

EIA = exercise-induced asthma

has been shown that the flow of cold air through the respiratory system causes airway constriction, and that warming of inspired air reduces the frequency of EIA. As would be expected, physical activity in areas with an arid climate, or industrial areas with greater air pollution are known to increase the risk for EIA [10].

Pathophysiology

Despite the many years that have passed since the first description of exercise-induced asthma, much of its pathophysiology has remained an enigma. Since the results of post-exercise bronchial lavage could not always demonstrate the release of chemical mediators or cellular infiltrates that could explain the bronchoconstriction, some investigators prefer the term exercise-induced "bronchospasm" over exercise-induced "asthma" (EIA) [11]. Several theories on the pathophysiology of EIA/EIB have been proposed. They are summarized briefly below:

- **Heat and humidity exchange.** Numerous studies have shown the link between inhalation of cold air and EIB, indicating that this mechanism is a major contributor to the onset of EIA [12]. Inhalation of cold and dry air (cooler than body temperature) causes a series of processes directed at warming and humidifying the air, the result of the passage of water and heat through the mucosal layer of the respiratory system. This process occurs in the upper airways, and the temperature of the gas that reaches the lungs is identical to that of the body. When the volume of inspired air is greatly increased, during physical strain for example, the heat transfer in the upper airways is not sufficient and the process continues in the lower respiratory tract [3]. The result is heat loss from the lower airways and reduced temperature in the lungs [12]. Such changes create a hyperosmolar and arid environment, engorgement of blood vessels, and possibly the release of mediators that stimulate bronchoconstriction.
- **Inflammatory mediators.** Another explanation for the relationship between airway cooling and asthma exacerbation is based on the release of inflammatory mediators such as histamine, neutrophil chemotactic factor and leukotrienes [13]. Leukotrienes cause a decrease in respiratory cilia activity, increased airway secretions, increased permeability of the blood vessels, and migration of eosinophils to the mucosal layer of the respiratory tract. The bronchoconstriction evoked by leukotrienes is 1,000 times greater than from histamine. Early support for the above theory, especially with regard to mast cell-released mediators, is based on the preventive effect of cromolyn sodium on EIA [14]. Further evidence was based on the observation that leukotriene inhibitors prevent EIA [15]. In spite of this, an increased level of mast cell-released mediators in the plasma or respiratory secretions has not been clearly proven [16].
- **Vagal effect.** In their attempt to explain the appearance of EIA mainly after the cessation of physical activity and not during the process, some researchers emphasized the role of the autonomic nervous system. They suggested that increased sympathetic tone and related catecholamine secretion during strenuous activity induce bronchodilation (and thereby attenuate EIB), whereas cessation of the activity causes a drop in the catecholamines and a relative predominance of vagal tone, leading to bronchoconstriction [17].

Diagnosis

In order to prove the existence of asthma the following elements must be present: airway obstruction, hypersensitivity, and reversibility of the process either spontaneously or pharmacologically. The use of a peak flow meter is accepted practice for measurement of the peak expiratory flow rate before and after the use of bronchodilators. A basal measurement of 85% or less of the expected flow (corrected for age, height, and gender) together with an improvement of at least 15% after the use of bronchodilators is diagnostic for asthma. Reversible changes in pulmonary function tests may also help in the diagnosis.

The demonstration of hypersensitivity is more problematic [18]. Diurnal variation of more than 20% in the maximal PEFR between morning and evening indicates hypersensitivity, as do positive pharmacological challenge tests (histamine or methacholine) and exercise testing.

Physical activity as a diagnostic tool

In most asthmatic children the diagnosis of EIA is not difficult. A report of cough, chest pain, and dyspnea after exercise is usually enough to assume a diagnosis of EIA [19], although isolated dyspnea may represent poor physical condition in an asthmatic child and not necessarily an exacerbation. Before the subject undergoes an exercise test for the diagnosis of asthma, several points must be considered. EIA will appear after 6–10 minutes of activity at 80% of maximal heart rate or 70% of maximal aerobic capacity [7]. Appropriate environmental conditions during the test must be maintained (preferably warmed air) in order to isolate the exercise effect, although certain laboratories perform challenge tests using cool and dry air [3]. The choice of activity is not critical, although swimming is not appropriate [6], and the use of a treadmill exercise, which mimics the type of activity that usually induces attacks in everyday life, is preferred. Dyspnea at rest or PEFR less than 60% of the expected value (but not expiratory wheezing) should preclude the test. Since EIA can appear 3–20 minutes from the start of activity it is recommended that basal lung function tests be performed at time 0 and then every 3 min for 20 min. It must be remembered that some asthmatic children will develop EIA

EIB = exercise-induced bronchospasm

PEFR = peak expiratory flow rate

during spontaneous activity but not under laboratory conditions, and vice versa.

The use of exercise testing may provide answers to many questions of the patient, his/her family, and the physician [20], particularly relating to the diagnosis of EIB in children presenting with atypical clinical symptoms such as isolated cough or chest pain [21]. Finally, exercise testing is essential for assessing the child's physical condition; it can differentiate between dyspnea due to poor physical condition and true asthma, and can confidently reassure the child and the family to continue physical activity.

Physical Fitness among Asthmatic Children

Most studies have demonstrated decreased aerobic capacity among asthmatic children. The poor physical status is due mainly to the low level of daily physical activity and not to the extent of airway obstruction [22]. The fact that it is possible to reach normal aerobic capability with physical training (while other aspects of fitness such as muscle strength and anaerobic capacity are usually within the normal range) indicates that it is not the disease itself, but the sedentary lifestyle that is responsible for poor physical fitness. In essence, improved cardiorespiratory capacity can decrease the frequency and/or severity of asthma exacerbations by increasing the exercise tolerance through reduction of the stressogenic effect of a particular activity [23]. The real proof is that asthmatic athletes have achieved Olympic medals in swimming and even in so-called asthmatogenic sports such as running or cycling [24].

Treatment of Exercise-induced Asthma

The emphasis in the treatment of EIA is on prevention and can be divided into two groups: medical and non-medical.

Medical therapy

A wide variety of treatments enable asthmatics to lead an active lifestyle. The main drug options available today are summarized below.

- **Beta agonist bronchodilators (salbutamol, terbutaline)**, which act as respiratory smooth muscle relaxants. In addition to their use in the treatment of acute attacks, they can also be used for prevention 15 minutes prior to physical exercise. Beta agonists prevent EIA in 90% of patients [14], and are considered the safest and most effective treatment for the prevention of EIA [25].
- **Chromoglycate**, which stabilizes mast cell membranes, prevents mediator release, and has few if any side effects. Chromoglycate is very effective in EIA if given 20 minutes prior to the activity. The effect lasts up to 2 hours, preventing EIA in 40% of cases and reducing the severity in 70%. The synergistic combination with beta agonists imparts protection for longer periods [26].
- **Corticosteroids**, which are efficient in preventing and treating the inflammatory component of asthma. Inhaled steroids that minimize the systemic absorption of the drug have stepped to the forefront of asthma therapy. These preparations improve the basic status of the airways and reduce their overall responsiveness to challenges such as physical activity or various allergens. In addition, the use of inhaled steroids increases the effectiveness of bronchodilators used prior to physical activity (27).
- **Methylxanthines**, which until recent years played an important role in the treatment of asthma. Although their effectiveness in treating EIA is approximately 80% [28], their narrow therapeutic range, numerous side effects, and relatively slow onset of action make them a less attractive option.
- **Anticholinergics**, which cause airway dilation due to the increased airway muscle tone as a result of vagal stimulation. The efficacy of anticholinergics (ipratropium bromide) in the treatment of EIA is only moderate and, in contrast to chromoglycate, has no proven synergistic effect when given together with bronchodilators.
- **Leukotriene receptor inhibitors** (montelukast), reported to be effective in adults with asthma [13], have recently proven useful to treat EIA in children aged 6–14 [29].

Although most of the medications in the form of inhalers (chromoglycate, ipratropium bromide, budesonide, terbutaline, and salbutamol) are allowed in competitive sports, the oral forms of these drugs are forbidden to competitive athletes. Since asthmatic professional athletes often need anti-allergic medications such as antihistamines or decongestants that are not permitted in competitions, the athlete should inquire about the specific regulations concerning each medication and *must* receive medical permission to use them.

Non-medical methods

With the growing understanding of the pathogenesis of EIA, several non-medical methods have proven effective.

- **Warmed air inhalation.** The placement of a simple mask (or a regular scarf) over the nose and mouth increases the temperature and humidity of the inhaled air and thereby significantly decreases the risk of an attack [30]. An excellent solution, although not always available, is to plan activities within a climate-controlled indoor facility.
- **Warm-up exercises**. As mentioned above, 50% of asthmatic athletes experience a refractory period after physical activity that induces an asthma attack. During this period there is a minimal chance for an additional attack. Unfortunately it is not possible to predict by clinical or laboratory means which athlete will develop a refractory period, how long it will last, or what type of activity will induce it. Although inducing asthmatic

attacks is not generally recommended by the medical staff, elite athletes are aware of the fact that EIA is more common after short intense exertion, and often use a warm-up consisting of repetitive short sprints. In general, most professional athletes develop a routine warm-up appropriate to their personal needs.

- **Hypnosis**. Although reported to be effective in the prevention of EIA [31], the use of hypnosis for everyday activity or competitions is obviously limited.
- **Appropriate choice of sport**, The asthmatic athlete should be directed towards non-"asthmatogenic" sports. However, it is questionable whether a gifted athlete will heed the advice of parents or trainers to give up a particular sport for health reasons alone.

The Effect of Physical Activity on the Asthmatic Child

Physical activity has two principal effects on asthma: improved physical fitness and a reduction in the severity of the disease. Many reports have shown that training asthmatic children improves their aerobic ability, muscle strength and other aspects of fitness [32]. Early claims that physical exercise can eliminate the tendency towards EIB [33] were proven inaccurate, and moreover, numerous articles failed to prove any decrease in airway hypersensitivity after training [34]. In contrast, some studies did show that training could diminish the exertion-induced drop in forced expiratory volume in 1 second and PEFR [35]. Furthermore, children who participated in physical fitness programs reported increased ability to take part in activities, reduced frequency of attacks and medication consumption, as well as elevated self-assurance, improved peer acceptance, and fewer school absences — all of which reinforce the notion that the disease itself need not entirely dictate their lifestyle [36]. It is believed that improved physical fitness and the ensuing decreased minute ventilation significantly reduce the strain on the airways and the stimulus for EIA after activities that previously would have induced an attack [37]. It is important to note that, to the best of our knowledge, no studies have shown worsening of the disease due to physical activity.

Physical Activity Schedules

It is of paramount importance that all children enrolling in physical activity programs be under medical follow-up and treatment to ensure minimal active inflammation. After counseling on the proper use of medications, the majority of asthmatic children can participate in physical activity at a level high enough to maintain physical fitness without the need for specially organized training programs. Those who are restricted from physical activity are usually not able to participate in regular activities, such as school physical education, sport clubs, etc., and require exercise testing to assess their fitness prior to the beginning of treatment. The training schedules must include rhythmic aerobic exercising for at least 30 minutes in appropriate sports (swimming, cycling, tennis, etc.). Sessions should be at least three times a week and should reach 70–80% of the aerobic capacity, and the necessity of warm-up and cool-down routines should be emphasized [38]. Clearly, it is important that the child choose a sport of interest; a sport that does not provide enjoyment will most likely be abandoned.

Conclusion

Asthma is one of the most common chronic childhood diseases. Its treatment is multidisciplinary, requiring the participation of medical staff combined with health education in order to successfully deal with the disease and facilitate as normal a lifestyle as possible for these children.

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A man often meets his destiny on the road he took to avoid it.

Joan d'Arc

Capsule

Adenovirus attachments

Adenoviruses cause an array of diseases in animals and humans and are also used as vectors for gene therapy. They bind to their host cell receptors (the coxsackie and adenovirus receptor, or CAR) by means of a globular domain that extends from a fiber attached to the viral capsid. Two reports focus on the receptor-virus interaction. Bewley and colleagues crystallized the complex of an adenovirus knob with CAR and determined that the receptor interacts at the interface between knob monomers, specifically in a region that is highly conserved among adenoviruses. Even areas where there were shape mismatches between the receptor and the viral knob contributed to high affinity interactions. The identification of the receptor-binding region was confirmed in the mutational analysis of Roelvink et al. who were also able to redirect an adenovirus to a new receptor.

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