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Review

Exercise Induced Asthma: A Clinical Perspective

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Abstract. Exercise is a very common precipitant of asthma. Inflammation and edema are felt to be important components of the asthmatic response. Heat and water loss from the airway mucosa are most likely important in its pathogenesis, although the exact etiology remains unknown. A good history combined with proper diagnostic testing can usually determine the diagnosis, and prevention is the key to effective management. Although modified training techniques are often helpful, medications are usually needed for both prevention and treatment. While antiinflammatory agents are gaining therapeutic importance, inhaled beta-agonists remain the treatment of choice. With appropriate diagnosis and management, exercise-induced asthma should not limit participation nor performance in athletics for the great majority of the population.

Key words: Exercise—Asthma—Bronchoconstriction.

Introduction

Greater than 10% of the general population suffers from asthma, and the prevalence appears to be rising [6]. Among these asthmatics, approximately 75% cite exercise as a major precipitant [2, 4]. Thus, over 20 million Americans suffer from exercise-induced dyspnea, wheezing, or cough, with many limited by their symptoms. While noted to be a particular problem for children and young adults because of their increased activity [29, 40], recent trends towards a heightened awareness of the benefits of exercise and fitness in older adults makes exercise-induced asthma relevant to all age groups.

Although the designation "exercise-induced bronchospasm" seems more descriptive and is often encountered in the literature, we believe it is inaccurate,

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as other processes apart from bronchospasm are thought to contribute to exercise-induced airway obstruction [23]. For example, airway inflammation is now felt to be an integral component of asthma leading to contraction of the airway smooth muscle, microvascular leakage and edema, and airway hyperresponsiveness [6]. Thus, we prefer the term "exercise-induced asthma" and will use it henceforth.

After a short historical note, we will briefly review the postulated pathophysiologic mechanisms of exercise-induced asthma despite the fact that the exact mechanism remains unknown. We then focus on the clinical aspects of exercise-induced asthma, including definitions and characteristics, conditions to consider in the differential diagnosis, specific diagnostic tests, and finally, effective management of patients with this disorder.

History

The recognition of the relationship between asthma and exercise is certainly not new. As early as the second century A.D. when Aretaeus the Cappadocian noted, "If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called Asthma . . ." [38]. In 1698, Sir John Floyer, an English physician and himself an asthmatic, noted that exercise type influenced the induction of asthma. In the mid 1800s, the English physician Salter added that exercise-induced asthma was aggravated by exposure to cold [38].

The astute clinical observations reported by Floyer and Salter well before the twentieth century still hold true today. Floyer's concept that dancing was more asthmogenic than walking, and walking more asthmogenic than riding has since been expanded, with swimming least asthmogenic (probably because of environment), running most asthmogenic, and bicycling and walking in between [19, 23]. Salter's finding is incorporated in the widely held belief that exercise-induced asthma results from respiratory heat and water loss, although the exact mechanism involved is an area of much disagreement [2, 29].

In the 1972 Olympic Games, exercise-induced asthma gained considerable attention when an American lost a gold medal due to the use of a banned drug to treat this condition. Subsequent studies from the 1984 and 1988 summer Olympic Games revealed that between 8 and 11% of U.S. athletes suffered from exercise-induced asthma. Furthermore, medals won by this population were comparable to athletes without exercise-induced asthma, strongly suggesting that appropriate therapy can markedly reduce or eliminate exercise limitation among these asthmatics [41].

Etiology

After years of study, most agree that the development of airway obstruction in exercise-induced asthma is related to the thermodynamic events that occur within the airway during or after hyperpnea [20, 28, 42]. The exact mechanism,

however, remains unknown, with the extensive literature only briefly summarized below.

The initially attractive hypothesis that exercise-induced changes in arterial blood gases and acid–base balance led to airway obstruction was soon disproved [23, 32]. When airway obstruction induced by isocapnic hyperventilation was reported by Deal et al. [14], mechanistic similarities to exercise-induced asthma were immediately inferred [4]. However, numerous differences between these two challenges exist, and thus, in regards to pathophysiology, they should probably be considered as different entities [5], although some diagreement on this issue does exist [28].

The hypothesis that thermally sensitive neural receptors in the respiratory tract reflexly mediate the obstructive response to airway cooling [33] has recently been challenged. The studies supporting this hypothesis had experimental flaws that, when corrected, yielded results that were no longer in strong support of this theory [28].

The notion that a change in osmolarity of the respiratory mucosa due to water loss is a more potent stimulus for inducing obstruction than heat loss has been popularized by Anderson [3, 5]. According to this hypothesis, the osmotic stimulus most likely provokes airway mast cells to release mediators capable of bronchoconstriction. However, since temperature change and water loss are so closely associated, it may not be possible to weigh the contribution of each separately [23, 28].

McFadden [28, 30] has proposed that the bronchial circulation might play a critical role in exercise-induced asthma. As occurs in skin vessels, cold exposure and subsequent rewarming prompts a hyperemic response in the bronchial vasculature, with vascular engorgement and edema responsible for the airway narrowing. This hypothesis also has been questioned [39].

Recent attention has focused on the role of chemical mediators in exercise-induced asthma. The fact that cromolyn and other known mast cell stabilizers inhibit the development of exercise-induced asthma suggests mediator involvement [38]. In addition, the characteristic refractory period, a time when additional bouts of exercise fail to provoke the same degree of airway obstruction noted after the initial exercise period, has been postulated to be a result of mediator depletion, although little experimental evidence in support of this idea has been advanced [5]. Of the mediators studied, initial attention focused on histamine with numerous conflicting reports subsequently emerging [28]. It was concluded that some asthmatics will have increased histamine levels after exercise, but others will [17, 25]. This may in part explain why antihistamine prophylaxis results in so much inter-subject varibility in protection from exercise-induced asthma, and why in no one person was the protection complete [25].

When neutrophil chemotactic factor of anaphylaxis (NCFA) was found to increase with exercise [24], a role for mediators of anaphylaxis in exercise-induced asthma was postulated [5]. As with histamine, conflicting reports with NCFA also emerged [28]. Furthermore, the finding of such mediators, following exercise, in the blood of persons without exercise-induced asthma suggests

that these changes in circulating mediators may be a nonspecific epiphenomenon [28]. More recently, the leukotrienes have received considerable attention [25]. The leukotrienes, specifically the sulfidopeptide leukotrienes C_4, D_4, and E_4 which comprise the slow-reacting substance of anaphylaxis, are potent bronchconstrictors in both asthmatics and normals. The leukotriene D_4-receptor antagonist has recently been shown to inhibit, but not eliminate, the airway obstruction induced by exercise. Thus, support exists for the leukotrienes having a role in exercise-induced asthma, yet firm conclusions concerning their importance await further experimental clarification.

All of the etiologic postulates presented above have been critically evaluated, with much literature existing to either support or refute each hypothesis noted. As the data accumulates, the controversy seems to intensify, suggesting that a unifying mechanism probably does not exist but rather that the cause of exercise-induced asthma is most likely multifactorial.

In addition to a cold, dry environment, various factors that can increase a persons susceptibility to exercise-induced asthma have been idenitifed. Exposure to antigens and atmospheric pollutants (sulfur dioxide, nitrogen dioxide, and ozone) [29, 35] sinusitis [23], and upper respiratory tract infections [29] all are reported to be exacerbants. The augmented obstructive response seems to be related to an alteration in preexercise airway reactivity [29]. It is of interest that the converse is not true. Exercise prior to antigen exposure does not augment the obstructive response, and can actually blunt the response to antigenic stimuli [29, 43].

Characteristics

Exercise-induced asthma can be defined as a temporary increase in airway resistance after approximately 5 to 8 minutes of strenous physical exercise [4]. Once exercise is complete, a brief asymptomatic period is followed by the gradual progression of airway obstruction, with symptoms most extreme within 5 to 10 minutes [38]. The usual attack lasts 5 to 15 minutes followed by spontaneous resolution, a hallmark of exercise-induced asthma, within 45 to 60 minutes [29, 41]. In the laboratory, exercise-induced asthma exists if the forced expiratory volume in one second (FEV_1) or the peak expiratory flow rate (PEFR) decreases by at least 10% [4] (Fig. 1).

The signs and symptoms are those of classic airway obstruction, including dyspnea, wheezing, cough, and chest tightness [1, 41]. Accompanying gastrointestinal distress has been reported, especially in children [2]. The severity of obstruction is influenced by exercise intensity, environmental conditions, and the underlying state of airway reactivity. Obstruction is worse with increased respiratory rates and inhaling cold, dry air: humidification of the inspired air lessens the severity [29]. Unlike asthma that is unassociated with exercise, exercise-induced asthma has not been reported to cause a fatality [31].

Some persons with exercise-induced asthma appear to experience a late

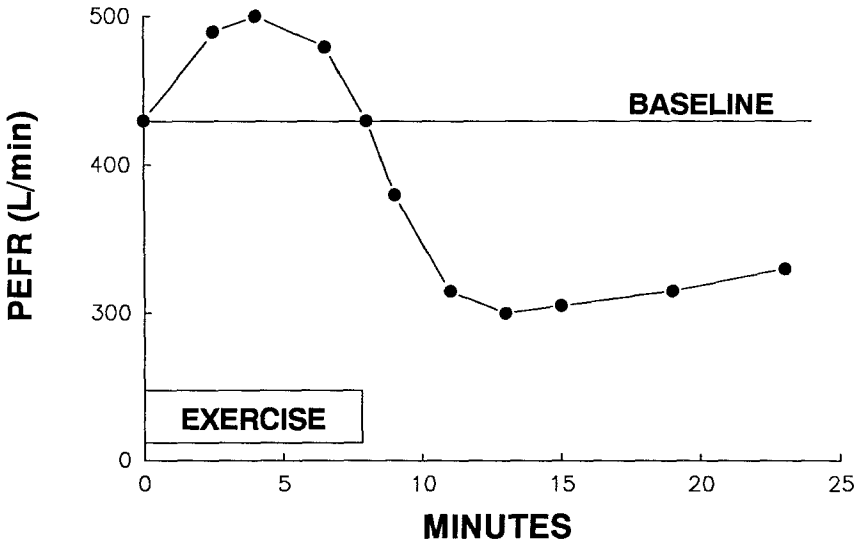

Fig. 1. Changes in peak expiratory flow rate (PEFR) during and after exercise (8 min of running on a treadmill) in a typical asthmatic patient.

asthmatic response, although this phenomenon is still debated. This results in a second bout of airway obstruction that occurs approximately 3 to 6 hours after complete resolution of the initial episode [44]. It occurs in a minority of patients and is significantly less severe than the initial response [8]. Some studies emphasize the small magnitude of change with the late response [8, 44] and Dahl and Henriksen [13] found a late response only in asthmatics with antigen challenge and not exercise challenge. Boner et al. [9] concluded that while the late response to allergen has clinical significance, the late response to exercise probably does not. Others have called the late response to exercise a "nonspecific epiphenomenon" that is not unique to exercise [36, 44]. Thus, the clinical significance to this phenomenon is unclear, but it is not likely to be important.

Another interesting feature of exercise-induced asthma is the refractory period of 30 to 90 minutes when further exercise causes markedly less bronchoconstriction [16]. Specifically, it is the time when a repeated challenge causes a reduction in the FEV_1 or PEFR less than 50% of that noted after the first test [5] (Fig. 2). Similar to the late response, a mechanism to explain this phenomenon is controversial. Several mechanisms have been proposed, including desensitization of airway smooth muscle to mast cell mediators, actual depletion of these mediators, or inhibition of mediator effect by increased catecholamine levels. Experimental data now exist disputing each of these postulates [17]. While the mechanism remains unclear, many sufferers of exercise-induced asthma take advantage of the refractory period in effective management of their asthma.

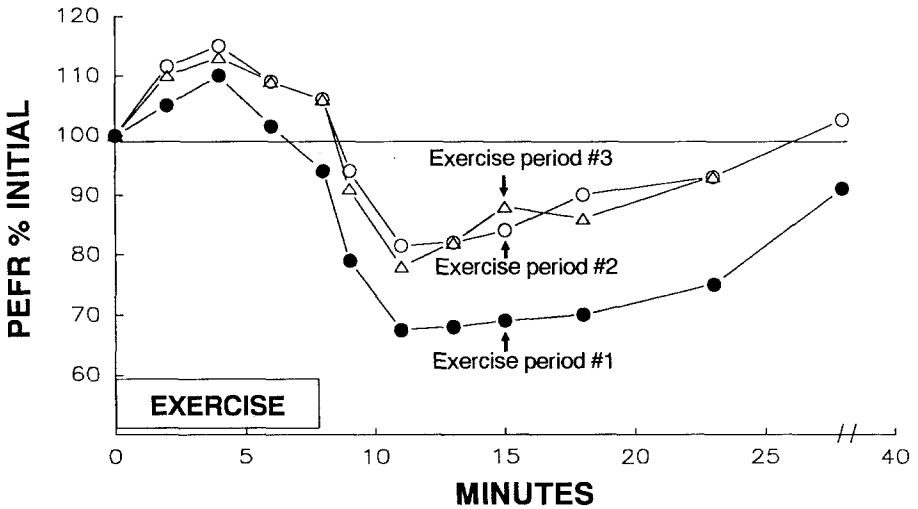

Fig. 2. Changes in peak expiratory flow rate (PEFR) during and after three successive 8 min exercise periods separated by 40 min of rest. The large drop following the first exercise period does not occur following the second and third exercise periods, demonstrating the "refractory period" which follows the initial increment in airway function associted with this disorder. (Modified from *Allergy, Principles and Practice*, Middleton EM, Reed CE, Ellis, EF, Editors. CV Mosby, St Louis MO., 1988, p 1166, with permission.)

Related Syndromes

Exercise-induced asthma is only one of several idenitifed syndromes that arise following exercise. *Exercise-induced anaphylaxis* is a distinct clinical entity characterized by the sensation of cutaneous warmth and pruritus followed by erythema, urticaria, and often hypotension and upper airway obstruction following exercise [10, 37]. Accompanying nausea, fatigue, and gastrointestinal distress have also been reported [29]. Ingestion of certain foods (commonly shrimp, grain, celery, and peanuts) or salicylates prior to exercise have been reported as predisposing events [10, 18, 23, 34]. A familial pattern is also reported with as many as two-thirds of persons having a positive family history, and one-half with personal atopy [37, 40]. Unlike exercise-induced asthma, the more significant airway problems involve the upper airway and are often more severe, with the outcome potentially fatal. Also, the airway obstruction in exercise-induced asthma is not usually accompanied by the additional symptoms listed above [18]. Conversely, exercise-induced anaphylaxis may not include symptoms of airway obstruction as part of the presentation [34]. Some overlap, however, does exist as some patients have developed exercise-induced asthma only after ingesting certain foods or salicylates before exercise [23].

Cholinergic urticaria is another condition precipitated by exercise and characterized by the sensation of generalized warmth and pruritus with distinctive

skin lesions (punctate 2–4 mm wheals surrounded by macular erythema) and systematic manifestations including confluent urticaria, angioedema, hypotension, gastrointestinal distress, wheezing, and dyspnea [10, 37]. An increase in core body temperature is thought to be the stimulus, with symptoms reproducible by warming the body [10]. Thus, exercise in warm weather or warm baths after exercise can cause this reaction, with adolescents and young adults the usual population affected [18].

Exercise-induced stridor is an uncommon disorder that has many synonyms including pseudoasthma, vocal cord dysfunction, or nonorganic acute upper airway obstruction [11]. Patients with this syndrome are not aware of their upper airway obstruction and believe they are experiencing a bronchial asthma attack. The involuntary vocal cord dysfunction may be a type of conversion reaction, as speech therapy and psychotherapy are reported to have a dramatic response. This entity is different from *fictitious stridor* which often involves young females employed in the medical field, is voluntary, and is usually not exercise related [15].

Diagnosis

A high index of suspicion is essential in making the diagnosis of exercise-induced asthma. The history is vital as the usual signs and symptoms of exercise-induced asthma are often misinterpreted as simply fatigue or a lack of conditioning, especially when wheezing is not a major component. Coaches, trainers, teammates, close relatives, and friends are often helpful in augmenting the history, and many times actually prompt the person's visit to a physician [26].

With the baseline exam and resting pulmonary function tests often normal, several methods are used in helping make the diagnosis of exercise-induced asthma. An empirical approach is to assess the clinical response to a therapeutic trial of beta-adrenergic agonists or cromolyn sodium [1]. This method, however, fails to provide objective evidence and is probably best used as confirmatory evidence after other tests have been obtained.

Inhalation challenge with pharmacologic agents and exercise testing are two useful tests in making the diagnosis and quantitatively assessing the severity of exercise-induced asthma. An inhalation challenge requires that the patient inhale gradually increasing concentrations of a bronchoconstrictor, usually methacholine, while noting spirometric changes in airflow obstruction [12, 26]. Assuming that asthmatics have latent hyperreactive airways, the less inhaled bronchoconstrictor needed to alter pulmonary function, the more severe the airway hyperreactivity [26, 35].

An exercise challenge involves spirometric measurements obtained before and at varying intervals (usually 5–10 minutes) after 6–10 minutes of exercise. A decrease in forced expiratory volumes of at least 10–20% is considered diagnostic [4, 26, 35]. The exercise challenge can be as simple as having the patient exercise in the office for 6–10 minutes using steps, a long hallway, or running in place, or can involve a more formal and controlled setting utilizing

a treadmill or cycloergometry. Formal testing allows for cardiovascular monitoring following a defined exercise protocol with the ability to obtain measurements of lung function throughout. Formal testing is especially important in patients with other medical problems, mainly cardiac disease, and can be helpful in distinguishing cardiac dyspnea from exercise-induced asthma [12, 26].

The major limitations to exercise challenge include the inability to adequately reproduce both the intensity of exercise and the exercise environment [35]. Laboratory or office ambient air is typically warm and humid, and thus, not similar to cool, dry air most likely to produce airflow obstruction in these patients [26]. One solution to this problem is to employ compressed air which has the advantage of being very dry. Furthermore, expensive equipment is needed to perform a formal exercise test [12, 26]. A portable peak flow meter is an alternative way to assess for bronchospasm and may simplify diagnostic testing in some circumstances [35]. A final important point to note is that all asthmatics do not have a positive response to an exercise challenge. Thus, negative results do not exclude the diagnosis of exercise-induced asthma [1].

Treatment

Prevention is the cornerstone of therapy for exercise-induced asthma and can be achieved through both pharmaceutical and nonpharmaceutical means [22]. The nonpharmaceutical interventions focus on modification of training techniques, some of which can limit the athlete's activities, and thus, must be individualized to suit each patient [26].

The following techniques can help prevent an attack of exercise-induced asthma [2, 23, 26, 40]. Advise one to exercise, whenever possible, in a warm, humid environment. If exposure to cold air is inevitable, the use of a scarf or mask can help increase the humidity of inhaled air. Nasal breathing, which allows the air to be warmed and humidified in the nasal passages, should be encouraged. Warm-up exercises performed 45–60 minutes prior to a workout or competition can take advantage of the refractory period that most asthmatics experience. Alternatively, exercise in spurts of less than 5 minutes each, less than 40 minutes apart, and avoidance of continuous activity may be helpful. Swimming, preferably in a heated pool, and playing tennis, with short bursts of exertion, are likely to be the most desirable exercise modalities for the exercise-induced asthmatic.

Medications

Although some patients can prevent asthma attacks solely with modified training techniques, the vast majority require the addition of medications. The conventional approach to treatment has been through the use of bronchodilators, with more recent attention focused on the use of antiinflammatory agents,

predominantly in long-term management [6, 22] (Table 1). In general, medications used in the management of exercise-induced asthma are more effective when inhaled, and preparations of most are available for administration by this route. Aside from the advantage of delivering the drug to its desired site of action, inhalation requires lower drug doses (reducing the incidence of potenital systemic side effects), allows for a quicker onset of action, and is acceptable to organizations with an interest in policing competitive athletes for illicit drug use, such as the International Olympic Committee.

The beta-adrenergic agonists are the drugs of choice in preventing exercise-induced asthma [1, 23, 26] and are successful in approximately 80–95% of patients [1, 2] (Fig. 3). They are the most effective bronchodilators in current use and act predominantly by reversing the contraction of airway smooth muscle. The selective $beta_2$-adrenergic agonists (albuterol, terbutaline, fenoterol, and bitolterol) should be used exclusively, as the nonselective beta-agonists (isoproterenol) carry the risk of additional cardiovascular side effects [6]. Inhaled $beta_2$-agonists are taken several minutes before exercise, with the effect lasting up to 6 hours [1, 6, 22]. Oral preparations are less useful mainly because of increased side effects, often tachycardia, tremors, and palpations [6, 26]. In addition to prevention, the $beta_2$-agonists are the treatment of choice for acute exacerbations of asthma. Thus, when and if prevention is not completely successful, the patient has the preferred medication immediately available to treat his or her symptoms acutely. Another advantage is that clinically important tolerance does not develop with beta-agonists, even after regular long-term use [2, 6]. Overall, these drugs are the mainstay of treatment for most patients with exercise-induced asthma.

Theophylline is a less effective bronchodilator than the beta-agonists and must be taken orally [6]. Although it has been shown to modify the response in exercise-induced asthma, a large dose is required [22, 23]. Theophylline can be given in combination with a beta-agonist and a synergistic effect has been reported [6, 40]. As a supplement to a usual daily dose taken chronically by many asthmatics, a patient may take an additional dose approximately 1 hour prior to exercise. This use of high-dose theophylline therapy, however, is often not well tolerated by patients [22, 40]. The major side effects include tachycardia, irritability, and various gastrointestinal and CNS complaints, with the relatively high incidence of these effects being a major limitation to theophylline use [22, 23, 26]. Seizures and cardiac arrhythmias are potentially lethal side effects that occur when plasma drug concentrations become toxic, with numerous drugs and conditions known to alter the plasma concentration [6]. Thus, careful monitoring is essential with patients taking theophylline, especially when an additional preexercise dose is considered. For these reasons, the role of this drug is controlling exercise-induced asthma is small and may be limited to patients incapable of properly using metered-dose inhalers despite repeated coaching and the use of reservoir devices.

Anticholinergic inhalers (ipratropium bromide, atropine sulfate) are nonspecific bronchodilators and help prevent the symptoms of exercise-induced asthma, but not the bronchospasm itself [2, 22]. Unlike the beta-agonists, which

Table 1. Effective pharmacologic agents in the treatment of exercise-induced asthma

Agents	Primary route	Use	Side effects	Comment
Bronchodilators				
$Beta_2$-adrenergic agonists	Inhalation	Acute treatment Prophylaxis	Palpitations, tachycardia, bronchodilator tremor	Most effective
Theophylline	Oral	Prophylaxis	Tachycardia, irritability, GI discomfort, seizures, arrhythmias	Large doses required, limited by side effect profile
Anticholinergics	Inhalation	Prophylaxis	Rare	Least effective bronchodilators
Antiinflammatory agents				
Cromolyn sodium	Inhalation	Prophylaxis	Rare	Often dose-related effect
Corticosteroids	Inhalation	Prophylaxis	Oropharyngeal candidiasis, dysphonia	Long-term treatment necessary

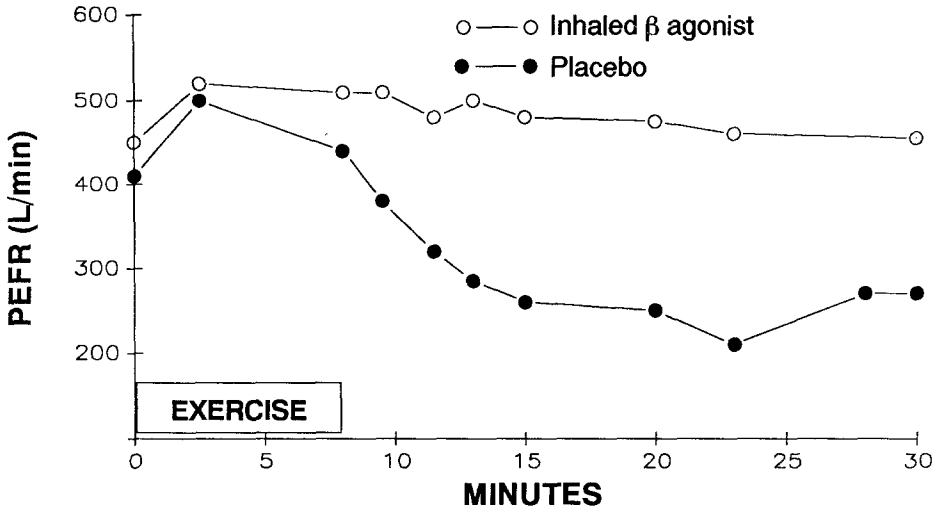

Fig. 3. Changes in peak expiratory flow rate (PEFR) during and after exercise following administration of inhaled placebo (closed circles) and an inhaled β-agonist drug, in this case terbutaline (open circles). This treatment abolishes the decrease in lung function observed with exercise in this patient. (Modified from Anderson, SD EIA: New thinking and current management. J Resp Dis 1986;7:48–61, with permission.)

inhibit the bronchoconstriction irrespective of the stimulant, the anti-cholinergic agents only inhibit the component of bronchoconstriction due to cholinergic nerve stimulation. Compared to the beta-agonists, their onset of action is slower and they are significantly less effective in the overall management of exercise-induced asthma [6].

Anti-histamines (hydroxyzine, terfenadine) have been shown to inhibit or decrease the severity of bronchospasm in some individuals [2, 22]. The positive effect, however, was noted in only certain individuals, and currently available antihistamine preparations are not felt to be effective in preventing exercise-induced asthma [1, 22].

Of the antiinflammatory agents, cromolyn sodium seems to be most effective in preventing exercise-induced asthma, with a success rate reported to be approximately 70–85%, and side effects exceedingly rare [1, 2, 6, 23]. When cromolyn is used in combination with the beta-agonists, a synergistic effect has been noted [1]. Although its exact mechanism is still not known, it seems to work at least partly through stabilization of mast cell membranes [2, 6]. Cromolyn also appears to inhibit the late phase response, a phenomenon that is probably not clinically relevant in exercise-induced asthma [2, 22]. Cromolyn is most effective when taken 10–45 minutes prior to exercise, and the effect is often dose-related [22] (Fig. 4).

A second group of antiinflammatory agents, the corticosteroids, also help prevent exercise-induced asthma [6, 21, 35, 40], although prior reports have

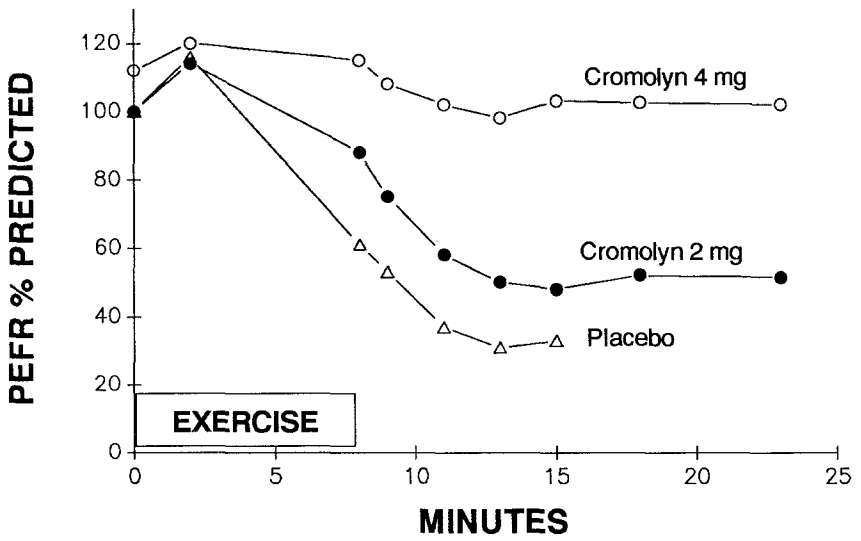

Fig. 4. Changes in peak expiratory flow rate (PEFR) during and after exercise following administration of inhaled placebo (triangles), cromolyn Na^+ 2 mg (closed circles), and cromolyn Na^+ 4 mg (open circles). This drug abolishes exercise induced airflow obstruction in a dose dependent fashion. (Modified from *Allergy, Principles, and Practice,* Middleton EM, Reed CE, Ellis, EF, Editors. CV Mosby, St Louis MO., 1988, p 1167, with permission.)

noted this not to be the case [1, 2]. The corticosteroids have no immediate bronchodilator effect and, therefore, must be given on a long-term basis to be effective. When used in this fashion, they gradually decrease airway hyperreactivity by suppressing various parts of the inflammatory response in asthma, the details of which are still uncertain [6, 35]. Inhaled steroids (beclomethasone dipropionate, triamcinolone acetonide, flunisolide) are more effective than oral or injected preparations, and inhalation greatly limits side effects, a dreaded and justified fear of long-term oral steroid use. Adverse effects are uncommon with low doses (<400 μg daily). The major side effects of inhaled steroids include oropharyngeal candidiasis and dysphonia, with the incidence lessened with good oral hygiene (adequate mouth rinsing immediately after all treatments) and the use of a "spacer" device. The well known complications of oral steroids, including weight gain, diabetes, cataracts, osteoporosis, myopathy, and psychiatric symptoms makes use of these agents by mouth much less desirable [6].

Other medications, most notably the alpha$_1$-adrenergic receptor blockers and calcium-channel blockers have been proposed for possible use in exercise-induced asthma [22, 27]. The therapeutic benefit of these agents, however, has not been adequately proven, and thus, they are not presently recommended for prevention or treatment of exercise-induced asthma [2, 22].

The exact drug regimen the patient will require depends mostly on the

severity of his or her asthma. A poorly controlled asthmatic who notes exercise as one of many precipitants is obviously treated differently than a patient who notes exercise as the sole precipitant. Also, individuals often respond differently to different pharmaceutical agents, and thus, some degree of trial and error is needed in finding an effective therapeutic regimen for each patient [6].

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