

Exercise-induced asthma: Is it the right diagnosis in elite athletes?

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Exercise-induced asthma, as recognized in asthmatic subjects, is an exaggerated airway response to airway dehydration in the presence of inflammatory cells and their mediators. The airway narrowing is primarily caused by contraction of bronchial smooth muscle. The milder airway narrowing documented in response to exercise in elite athletes and otherwise healthy subjects may simply be the result of the physiologic responses and pathologic changes in airway cells arising from dehydration injury. These changes, which include excessive mucus production and airway edema, would serve both to cause cough and to amplify the narrowing effects of normal bronchial smooth muscle contraction, resulting in symptoms. These changes are more likely to occur in healthy subjects who exercise intensely for long periods of time breathing cold air, dry air, or both. Under these conditions, the ability to humidify inspired air may be overwhelmed, causing significant dehydration of the airway mucosa and an increase in osmolarity, even in small airways. In addition to dehydration injury, airway narrowing to pharmacologic and physical agents may occur as a result of injury caused by large volumes of air containing irritant gases, particulate matter, or allergens being inspired during exercise. As a result, the airways may become inflamed, and the airway smooth muscle may become more sensitive. These events could result in the same exaggerated airway response to dehydration, as documented in asthmatic subjects. (*J Allergy Clin Immunol* 2000;106:419-28.)

Key words: Exercise-induced asthma, athletes, dehydration, airway injury, osmolarity

OVERVIEW OF CLASSICAL EXERCISE-INDUCED ASTHMA AND ITS DIAGNOSIS

Exercise-induced asthma (EIA) or *exercise-induced bronchoconstriction* are the terms used to describe the transient narrowing of the airways that follows vigorous

Abbreviations used

ASL: Airway surface liquid
BHR: Bronchial hyperresponsiveness
EIA: Exercise-induced asthma
NCA: Neutrophil chemotactic activity

exercise.¹ EIA is documented by measuring a reduction in FEV₁ or peak expiratory flow in response to exercise. The pattern of response of the airways to exercise is similar in asthmatic children and asthmatic adults, although its time course can vary. In the laboratory, using a standardized protocol, EIA is usually diagnosed if there is a fall in lung function of 10% or more from the baseline level.¹ A value of 15% or more is usual for field studies. These values are based on the responses to exercise in healthy nonasthmatic subjects.²⁻⁵ There is a normal distribution for the percentage fall in peak expiratory flow^{6,7} and FEV₁⁵ in the healthy population. Fifty percent or more of healthy subjects have falls in flow rates less than 5% of baseline, and mean values are usually between 3% and 4%.

In persons with clinically recognized asthma, the prevalence of EIA has been reported to be 70% to 80% in the laboratory and between 45% and 73% in the field.^{5,7-9} Fifty percent of asthmatic subjects being treated with inhaled steroids have been shown to have EIA.¹⁰ Atopy is significantly associated with EIA, so that in asthmatic subjects there is a strong relationship between the number of positive skin test responses and the severity of EIA.^{11,12}

The severity of EIA is determined primarily by the level of ventilation achieved and sustained during exercise, reflecting the intensity of the exercise and the water content of the air inspired.¹³ Exercising for 6 to 8 minutes while breathing dry air and sustaining a ventilation rate 17 to 20 times the FEV₁ for 4 minutes is suitable for identifying EIA in the laboratory.¹⁴ Eucapnic hyperpnea with dry air and hyperosmolar aerosols are surrogate challenge tests also used in the laboratory and field to identify EIA.¹⁵⁻¹⁹ When the inspired air is cold, the airway response may be more severe,²⁰ and the duration of exercise required to provoke EIA may be shorter, relative to exercising while inspiring warm dry air. Some 50% of asthmatic subjects are refractory to a repeated exercise challenge for about 2 hours after EIA.²¹ Prostaglandins

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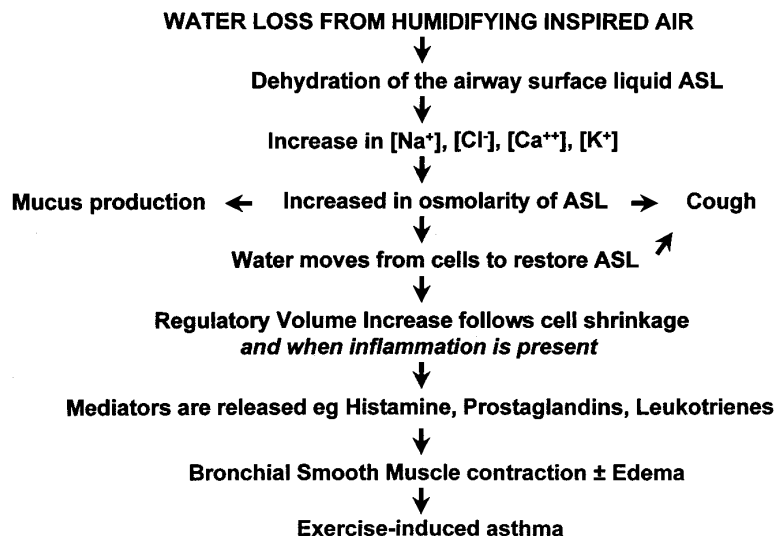


FIG 1. Flow chart describing the events leading to cough, mucus production, and EIA.

are thought to play a role in this refractory period because it has been shown to be prevented by indomethacin.^{22,23}

The stimulus for the airways to narrow is the consequences of the water lost by evaporation in conditioning large volumes of inspired air in a short time (Fig 1).^{13,24} This loss of water is thought to stimulate the release of a number of mediators, such as histamine and the eicosanoids (leukotrienes and prostaglandins), resulting in contraction of the bronchial smooth muscle.²⁵⁻²⁹ Importantly, leukotrienes are much more potent than histamine in causing the airways to narrow (Fig 2).³⁰ For this reason, EIA cannot be excluded on the basis of a negative response to inhaled histamine. Conversely, a histamine positive response may occur in the absence of EIA,^{5,8} which infers that a histamine test cannot be used to diagnose EIA. By contrast, a positive response to a hyperosmolar aerosol is associated with a positive response to exercise both in the laboratory¹⁶ and in the field.¹⁷

Although EIA may be associated with symptoms, such as shortness of breath, cough, wheeze, chest pain, and poor performance, it may occur in the absence of symptoms. These symptoms are not specific to EIA and may occur in the presence or absence of airway narrowing. In addition, individual asthmatic subjects vary in the way they perceive symptoms of EIA, making the diagnosis on the basis of symptoms alone unreliable.³¹ If, however, a subject complains of breathlessness that is most severe 5 to 10 minutes after exercise, the diagnosis of EIA on history is highly likely.

Often, a diagnosis of EIA can be made simply on the airway response to a medication used to treat asthma. For example, if the breathlessness and other symptoms are prevented by taking sodium cromoglycate or nedocromil sodium immediately before exercise or immediately reversed by taking a β_2 -adrenoceptor agonist (β -agonist), then a diagnosis of EIA is highly likely. In most asthmatic subjects EIA is reversed rapidly by inhaling a β -

agonist. This provides evidence for the airway narrowing being primarily a result of contraction of bronchial smooth muscle.

AIRWAY INFLAMMATION ASTHMA AND EIA

In an asthmatic subject the documented presence of EIA is likely to indicate that the disease is currently active. Thus a significantly higher sputum eosinophil number and concentration of eosinophilic cationic protein has been found in subjects with EIA compared with those asthmatic subjects without EIA and healthy control subjects.³²

The severity of EIA is likely to be related to both the amount of airway inflammation present and the reported severity of asthma. Thus studies in schoolchildren have shown that the severity of EIA increases with the number of "attacks of asthma" reported per year. Children with 12 or more attacks per year had a mean (SD) percentage fall in FEV₁ of 25% after exercise.⁵ In contrast, between exacerbations of asthma, EIA often cannot be demonstrated. EIA severity is reduced by treatment with inhaled steroids in a dose-dependent fashion (Fig 3).³³ EIA is one of the first symptoms of asthma and is the last to resolve after treatment with inhaled steroids.¹⁰

THE RISE AND RISE OF EIA

Over the last decade, there have been an increasing number of reports of "exercise asthma" being documented in otherwise healthy subjects. This observation has come about as a result of EIA prevalence studies in both random and specific populations. In a study of Australian schoolchildren, 19.5% (152/802) had a fall in FEV₁ greater than 15%.⁵ Only 60% of these children were known to have asthma. Similarly, others have found EIA in asymptomatic children.^{8,34} The prevalence of EIA in Wales increased over the 15 years from 1972-1989 in the

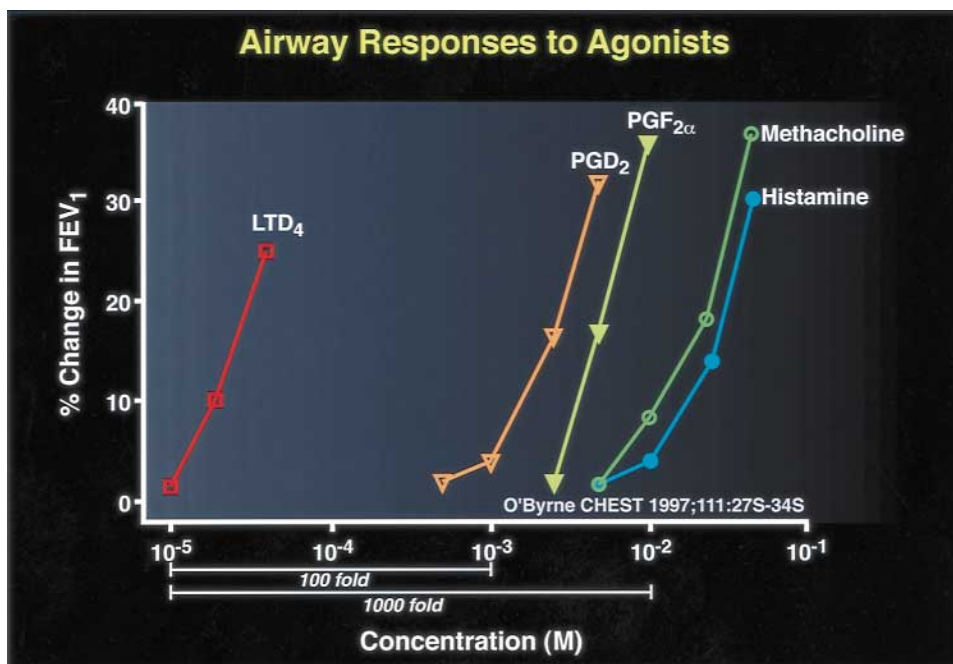


FIG 2. The change in FEV₁ in relation to the concentration of agonist required to induce this change. Note that the airways are more sensitive to inhalation of leukotriene compared with methacholine or histamine. (Reprinted with permission from *Chest*. 1997;111[Suppl 2]:27S-34S.)

The dose response reduction of EIA severity to inhaled corticosteroids

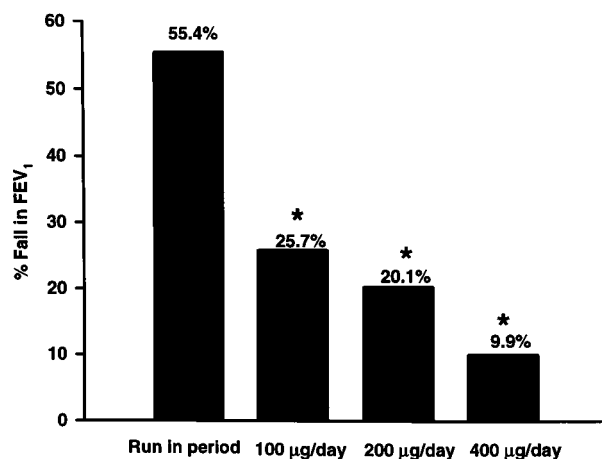


FIG 3. The percentage fall in FEV₁ before and during treatment with different doses of budesonide administered by means of inhalation. Asterisks denote a significant difference between the percentage fall compared with the control exercise test. Adapted from *J Allergy Clin Immunol*. 1995;95:29-33.

same school.^{6,35} A surprising number of adolescent athletes have been found to have EIA.³⁶

In addition to nonsymptomatic children having EIA, there are now reports of healthy adults having changes in lung function after exercise consistent with a diagnosis of EIA. Of the US athletes who competed in the 1996 Atlanta Summer Olympic Games, 16.7% had a history of

asthma, took asthma medication, or both.³⁷ In the 1984 Los Angeles Olympic Games, 11.2% of the US athletes were diagnosed with EIA.³⁸ These reports also include defense force recruits^{39,40} and elite athletes from a range of sports.⁴¹⁻⁴⁴ In the elite athletes a high prevalence of bronchial hyperresponsiveness (BHR) to the pharmacologic agents methacholine and histamine has been report-

ed.⁴⁵⁻⁴⁷ The high prevalence of BHR to these agents, EIA, and EIA-like symptoms³¹ in elite athletes raises many questions.

The first and most important question is whether the exercise-induced airway narrowing in asymptomatic healthy subjects and elite athletes is the same as the EIA in subjects with clinically recognized asthma. What factors put healthy subjects at increased risk of developing BHR either to pharmacologic agents or exercise? Is exercise itself important in the cause of BHR and EIA, especially the repetitive exercise at high intensity as performed by elite athletes? Is the BHR and airway narrowing in response to exercise in these subjects reflecting airway injury from dehydration? Is BHR to methacholine or histamine predictive of the presence of EIA in this group? Is airway inflammation associated with classical EIA present in these subjects, and are mediators of inflammation involved? How important are inhaled allergens, irritant gases, and pollutants in the development of BHR, and how do they relate to the airway response to exercise? Do viral infections play a role in the development of BHR? Are the drugs normally used to treat or prevent EIA, such as the β -agonists, inhibiting dehydration injury, or are they enhancing the exposure of the lower airways to environmental stimuli and contributing to the subsequent development of EIA in this population? What facts about classical EIA can help us understand how BHR and EIA can develop in people exercising regularly?

WATER LOSS AS THE STIMULUS FOR AIRWAY INJURY

The stimulus for the airways to narrow in response to exercise in asthmatic subjects is the water lost by evaporation from the airway surface and the osmotic and thermal effects arising from this. During intense exercise, the nose is bypassed, and the lower airways are recruited into heating and humidifying the inspired air. The drier and cooler the air and the higher the ventilation rate, the greater the number of airways recruited into the conditioning process. The estimated volume of airway surface liquid (ASL) in the first 10 generations is less than 1 mL.⁴⁸ When breathing air of temperate conditions (26°C at 35% relative humidity), the amount of water lost from the lower airways is estimated to be 7.4 mg/L. This loss is sufficient to cause some airway cooling⁴⁹ and a transient dehydration and increase in osmolality of the ASL. The osmotic gradient created by the increase in concentration of the ions in the ASL causes water to move from the epithelial cells to the airway surface, and therefore the epithelial cells lose volume.⁵⁰

With air of temperate conditions, up to 12 generations of airways are required to heat and humidify the air while breathing at 60 L/min.^{13,24,51} Generations 10 to 12 are 0.9 to 1.3 mm in diameter and are considered by physiologists to be small airways. It is the recruitment of these small airways into the humidifying process that is likely to enhance or even maximize the airway response to exercise in asthmatic subjects, and it may be important in the cause of the airway narrowing observed in healthy

subjects.¹³ The higher the ventilation rate, the lower the concentration of the inspired water; the lower the temperature and the longer the duration of exercise, the greater the likelihood of these small airways being recruited to humidify and heat the air. Although generations beyond 12 may be required to condition the inspired air, the chances of those generations becoming significantly dehydrated is less because considerably more water is available than in the earlier generations as the surface area increases exponentially.

Theoretically, conditioning of inspired air that is cold involves a greater surface area of the airways to heat and humidify the air than warmer more humid air. Thus it is likely that the smaller airways will be recruited more quickly when cold air is inspired so that even exercise of short duration can provoke an airway response. If the air inspired is hot and dry, a longer duration of exercise will be needed to recruit the same airways and to elicit the same severity of airway response. Thus the airway mucosa of the small airways of persons performing vigorous exercise under cold, dry, or both types of inspired air conditions are likely to be subjected to dehydration.

CELLULAR RESPONSES TO TRANSIENT INCREASES IN OSMOLARITY

All the cells in the airways have the potential to lose volume by the movement of water to the airway lumen in response to an increase in osmolality of the ASL. As cells lose volume, they are subjected to the biochemical events involved in regulatory volume increase. Included in these events is an increase in the intracellular concentration of calcium and inositol triphosphate,⁵² a requirement for the release of intracellular mediators. The difference between asthmatic and nonasthmatic subjects may be the presence in asthmatic subjects of inflammation and associated inflammatory cells, such as mast cells and eosinophils. Inflammation may alter cell volume regulation^{53,54} and result in the release of a range of inflammatory mediators with consequent airway narrowing. In the presence of inflammation, the airway epithelium may not produce normal amounts of bronchodilator substances, such as PGE₂, that are known to be stimulated by increased osmolality and hyperpnea with dry air.⁵⁵⁻⁶¹

There are a number of cellular responses that have been documented in vivo in animals and in vitro with human and animal cells in response to transient increases in osmolality. Human lung mast cells rapidly release histamine in response to a transient osmotic stimulus, and this is optimal at an osmolality of 770 mOsm/kg, at a temperature of 32°C, and at concentrations of calcium found in ASL.^{62,63} The histamine release is markedly enhanced when the cells are sensitized or desensitized with anti-IgE.^{62,64} Sensory nerves located between the epithelial cells are sensitive to increases in osmolality,^{65,66} whereas cultures of isolated nerve cells have been shown to release neuropeptides in response to increased osmolality.⁶⁷ In the animal model these neuropeptides increase microvascular permeability.⁶⁸ Similarly, cul-

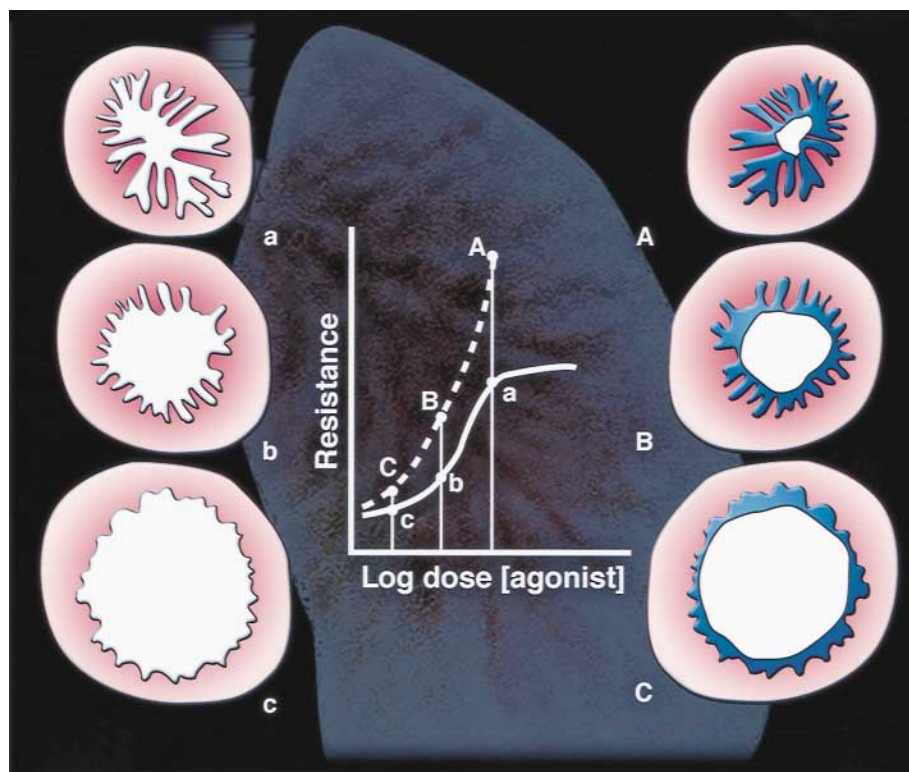


FIG 4. The effects of increasing degree of airway smooth muscle contraction on luminal cross-sectional area are shown schematically, and a plot of airflow resistance as a function of dose of agonist is presented for the case of no airway luminal liquid (*a, b, c*; solid line) and in the presence of liquid-filled interstices (*a', b', c'*; dashed line). (Reprinted with permission from *Am Rev Respir Dis* 1991;143[Suppl]:S52-4.)

tures of submucosal gland cells have shown a 4.5-fold increase in secretion of mucus glycoconjugates after transient exposure to a small increase in osmolarity (30 mOsm).⁶⁹ Additionally, vasodilation in both the upper and lower airways occurs in response to hyperosmolarity.^{70,71} Release of the arachidonic acid product 15-hydroxy-eicosatetraenoic acid into nasal lavage fluid has also been documented in response to an osmotic stimulus in people with allergic rhinitis, and the epithelial cell is the likely source.⁷² These events are all thought to be cellular defense mechanisms in response to the increased osmolarity that occurs with exercise.

Pathologic changes from dehydration have also been observed in the lower airways of animals and human subjects after dry air challenge and mechanical ventilation. These include epithelial desquamation, leukocyte infiltration, increased vascular leakage, and mast cell degranulation.⁷³⁻⁷⁸ The fact that airway narrowing and pathologic changes occur in response to dry air hyperpnea challenge in animals suggests that preexisting airway inflammation is not a prerequisite for dehydration injury. In asthmatic subjects it is highly likely that the normal airway narrowing in response to dehydration is exaggerated in the presence of inflammatory cells and their mediators because treatment with steroids reduces severity of EIA (Fig 3).

CONSEQUENCES OF TRANSIENT CELLULAR DEHYDRATION

There are a number of cellular events that could explain both the respiratory symptoms and increased airway responsiveness to exercise. For example, cough may be caused by either stimulation of airway sensory nerves in response to dehydration and release of neuropeptides or excessive mucus production in the presence or absence of significant airway narrowing. In nonasthmatic subjects cough frequency is greatest when the air inspired is dry, and cough is almost entirely suppressed if exercise is performed while breathing warm humid air.⁷⁹

We have previously proposed¹³ that the recruitment of the small airways into the humidifying process may result in their injury, which is manifested as airway edema. In the presence of edema and/or excessive airway mucus (particularly in the small airways) the airway narrowing caused by "physiologic" amounts of smooth muscle shortening could be amplified sufficiently to achieve a value for reduction in FEV₁ diagnostic for EIA. Such amplification of airway narrowing has been predicted for increased wall thickening in the peripheral airways of asthmatic subjects.⁸⁰ For example, the normal response to exercise of a fall in FEV₁ of 3% to 4% may be amplified to 10% or more in the presence of mucus or edema

Effects of Pharmacological agents on exercise-induced asthma

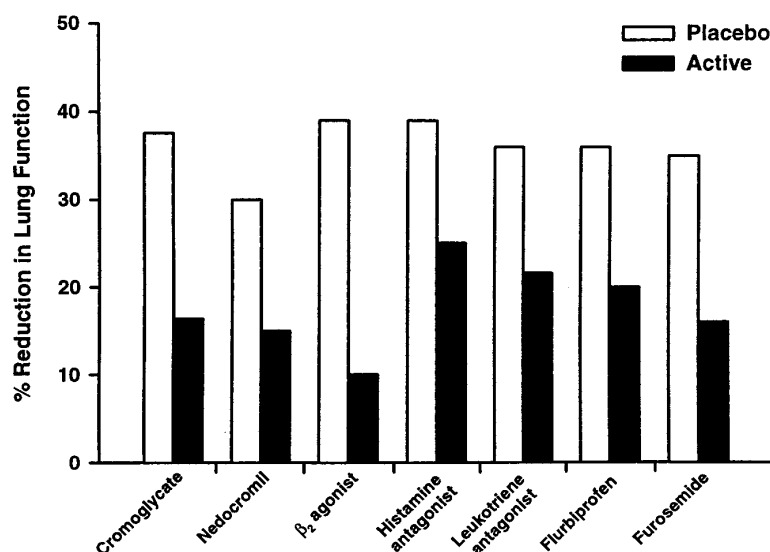


FIG 5. Mean value for the percentage change in lung function usually measured as percentage fall in FEV₁ or peak expiratory flow after exercise in the presence of a placebo or the active agent.

arising from dehydration injury. A similar mechanism is illustrated in Fig 4, where it is the fluid in the interstices that acts to amplify airway narrowing.⁸¹

If the airway narrowing measured in elite athletes and other healthy subjects is simply amplified as a consequence of airway dehydration and injury, it would seem inadvisable to diagnose classical EIA. Before such a diagnosis could be made, it would seem important to determine that the airway narrowing after exercise is a result of abnormal smooth muscle contraction, as it is in subjects with documented asthma.

Just as cough and mucus are normal defense mechanisms against airway dehydration, so may transient airway narrowing be a normal defense mechanism to protect the lower airways from desiccation, as suggested by Freed.⁸² This may explain why dry air hyperpnea provokes an increase in airway resistance in a wide range of animals.^{82,83}

CAUSE OF AIRWAY NARROWING FROM AIRWAY DRYING AND HYPEROSMOLARITY IN SUBJECTS WITH CLINICALLY RECOGNIZED ASTHMA

There are many studies in asthmatic subjects demonstrating that histamine antagonists, leukotriene antagonists, and cyclooxygenase inhibitors modify the airway response to both exercise and known hyperosmolar stimuli (Fig 5).⁸⁴⁻⁸⁹ None of these specific antagonists completely inhibits EIA, but given in combination, the inhibition is greater, suggesting that more than one mediator is involved.⁸⁴ Thus significant increases in the urine of asthmatic subjects of 9α11β PGF₂, the initial metabolite of

PGD₂, and leukotriene E₄ occur in both children^{28,90} and adults^{26,27} after EIA. Some studies have demonstrated, in some but not all asthmatic subjects, that there is an increase in histamine concentration in plasma at the time of maximum airway narrowing in response to exercise.^{25,29}

Although β-agonists are well recognized as effective inhibitors of EIA and hyperosmolar stimuli,^{91,92} their functional antagonism of bronchial smooth muscle contraction makes them less useful for inferring mechanism. When given by inhalation, however, they are likely to reach sufficient concentration to inhibit release of mediators from a wide variety of cells.

Sodium cromoglycate and nedocromil sodium are very effective in inhibiting EIA (Fig 5) and the airway response to hyperosmolar aerosols.^{53,54,93-95} The precise site of action of these drugs is not known, but studies suggest that there is potential for mast cells, sensory nerves, epithelial cells, and inflammatory cells to be affected.^{64,96-98} Their ubiquitous action is in keeping with the suggestion that they may act on the ion channels involved in cell volume regulation and thereby could inhibit mediator release.^{54,99,100} This suggestion is also supported by the finding that furosemide, an inhibitor of Na⁺K⁺2Cl⁻ transport, is also effective against airway narrowing provoked by exercise (Fig 5)¹⁰¹ and hyperosmolar aerosols.⁵⁸

When treated chronically over 4 to 8 weeks with inhaled steroids, 50% of asthmatic subjects will no longer demonstrate EIA or airway narrowing to hyperosmolar stimuli.^{53,102} A reduction in the number of mast cells and eosinophils together with improved integrity of the epithelial cell layer^{103,104} probably accounts for these findings.

INFLAMMATORY CYTOKINES, EIA, AND HYPEROSMOLAR STIMULI

The possibility exists that repetitive exercise itself may contribute to the development of EIA by the release of inflammatory cytokines.⁷⁷ One of the potential sources of cytokines are the circulating cells. An increase in microvascular permeability in response to cell injury could account for the presence of proinflammatory cells in the airways, particularly in atopic subjects.

There are other possible sources of cytokines, and the airway epithelium is one such example. It has been reported that a hyperosmolar stimulus of only 10 minutes' duration can cause an increase in expression of IL-8 in human epithelial cells, and this occurs through p38-MAP kinase.¹⁰⁵ IL-8 is thought to be the neutrophil chemotactic factor released during exercise in asthmatic subjects, as described by Lee et al¹⁰⁶ in the 1980s. At that time, considerable attention was given to the measurement of neutrophil chemotactic activity (NCA) mediated by means of neutrophil chemotactic factor. Lee et al^{107,108} showed that 29 (75%) of 39 asthmatic subjects with EIA had an increase in NCA after exercise, and this rise could be blocked when sodium cromoglycate was used to prevent EIA. A rise in NCA also occurred in response to inhaling hyperosmolar saline, but it did not occur when airway narrowing was provoked by inhaling methacholine.

Helenius et al¹⁰⁹ found an increase in neutrophils in the sputum of elite swimmers after training. It is possible that IL-8 production was stimulated by airway dehydration, and the increased numbers of neutrophils in the sputum were a consequence of this. Neutrophil numbers increase 2 and 4 hours after heavy, but not moderate, exercise training in athletes, and this was accompanied by an increase in serum myeloperoxidase.¹¹⁰ Similarly, there is an increase in serum eosinophil cationic protein levels, but the numbers of eosinophils are not increased. Larsson et al¹¹¹ found that a short (2 hour) exposure to cold air while running induced an increase in the number of granulocytes and macrophages, but not lymphocytes, in the bronchial lavage fluid of healthy subjects. However, they were not able to demonstrate any involvement of other inflammatory indices, such as plasma leakage (albumin) cytokines (IL-6, IL-8, and TNF- α) or cellular activation (eosinophil cationic protein).

Longphre et al¹¹² have recently reported that allergen-induced IL-9 stimulates mucin production in respiratory airway epithelial cells. This is important because this implicates IL-9 and its receptor in allergic mucus hypersecretion. The cellular provenance of IL-9 in this model is thought to be the T_H2 lymphocyte. The significance of this in the elite athletes is the finding in bronchial biopsy specimens of lymphoid aggregates (>50 cells) in 65% of cross-country skiers compared with 25% of control subjects.¹¹³

BRONCHIAL HYPERRESPONSIVENESS TO PHARMACOLOGIC AGENTS

There are a number of studies performed in elite athletes from a range of sports reporting an abnormal preva-

TABLE I. Airway responsiveness measured by exercise and inhaled histamine in two epidemiologic studies of children

Exercise		Histamine	
% Fall FEV ₁	n	Positive	Negative
>15*	27	77%	33%
10-14.9*	50	22%	78%
<10*	387	12%	88%
>15†	40	55%	45%
<10†	161	12%	88%

*Reference 8.

†Reference 5.

lence of BHR to agents, such as methacholine and histamine.^{45-47,114} In a recent study performed on 100 elite athletes from a variety of different sports, there was a 49% prevalence of BHR to methacholine (PC₂₀ <16 mg/mL), and in the subgroup of swimmers, BHR was 76%.⁴⁷ The reason for the increase in BHR in these athletes is unclear, but the investigators concluded that the nature and content of the inhaled air was important. The increased BHR in athletes may be due to repetitive injury of the airway epithelium with exercise and consequent remodeling. Support for this concept comes from Karjalainen et al,¹¹⁵ who found that the expression of extracellular matrix protein, tenascin, was markedly increased in skiers compared with control subjects and similar to that found in asthmatic subjects.

The higher prevalence of BHR in elite athletes, compared with the healthy population, has led some authors to suggest that air quality may be an important factor in "turning on" the airways. It is well known that swimmers are exposed to the products of chlorine in amounts exceeding recommendations by the World Health Organization.¹¹⁶ Skaters are also exposed to the oxides of nitrogen,¹¹⁷ cross-country skiers to cold dry air,⁴⁶ and outdoor athletes to inhaled allergens, motor emissions, and particulate matter. Exercise would thus result in an increased deposition of airborne materials into the airways of athletes, many of whom are atopic.

Importantly, BHR measured in response to pharmacologic agents is different to BHR measured in response to physical stimuli, such as exercise and osmotic agents. Unlike the physical challenges, positive airway responses to histamine and methacholine do not infer the presence of inflammatory cells or their mediators, and negative responses do not exclude EIA (Table I). The prevalence of BHR to histamine or methacholine in a population of schoolchildren has been reported to be between 15.9% and 22%,^{8,118-120} and in adults it was 11%.¹²¹ In these studies between 30% and 50% of people with BHR to histamine or methacholine had no asthma symptoms past or present. Furthermore, 30% to 45% of people with demonstrable EIA in the field had negative responses to inhaled histamine.^{5,8} Thus it is essential in the diagnosis of EIA that we measure BHR to exercise or surrogates for exercise challenge and not histamine or methacholine.

CONCLUSION

The hallmarks of classical EIA, as documented in subjects with recognized asthma, are as follows: the presence of inflammatory cells, airway hyperresponsiveness to hyperosmolar aerosols, the release of a variety of mediators in response to airway dehydration and increased osmolarity, the hypersensitivity of the bronchial smooth muscle to these mediators, and the rapid reversal of airway narrowing with a β -agonist. These features need to be established in the airway narrowing of healthy subjects before classical EIA can be diagnosed.

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