

## Asthma and the elite athlete: Summary of the International Olympic Committee's Consensus Conference, Lausanne, Switzerland, January 22-24, 2008

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**Respiratory symptoms cannot be relied on to make a diagnosis of asthma and/or airways hyperresponsiveness (AHR) in elite athletes. For this reason, the diagnosis should be confirmed with bronchial provocation tests. Asthma management in elite athletes should follow established treatment guidelines (eg, Global Initiative for Asthma) and should include education, an individually tailored treatment plan, minimization of aggravating environmental factors, and appropriate drug therapy that must meet the requirements of the World Anti-Doping Agency. Asthma control can usually be achieved with inhaled corticosteroids and inhaled  $\beta_2$ -agonists to minimize exercise-induced bronchoconstriction and to treat intermittent symptoms. The rapid development of tachyphylaxis to  $\beta_2$ -agonists after regular daily use poses a dilemma for athletes. Long-term intense endurance training, particularly in unfavorable environmental conditions, appears to be associated with an increased risk of developing asthma and AHR in elite athletes. Globally, the prevalence of asthma, exercise-induced bronchoconstriction, and AHR in Olympic athletes reflects the known prevalence of asthma symptoms in each country. The policy of requiring Olympic athletes to demonstrate the presence of asthma, exercise-induced bronchoconstriction, or AHR to be approved to inhale  $\beta_2$ -agonists will continue. (J Allergy Clin Immunol 2008;122:254-60.)**

**Key words:** *Respiratory symptoms, exercise-induced bronchoconstriction, asthma,  $\beta_2$ -agonists, airway hyperresponsiveness, bronchial provocation, Olympic Games, endurance training, environment*

In response to a marked increase in the notification by athletes of use of inhaled  $\beta_2$ -agonists from 3.7% in Atlanta in 1996 to 5.6% at the 1998 Winter Games in Nagano, and to 5.7% in Sydney in 2000, the International Olympic Committee's (IOC's) Medical Commission conducted a symposium on asthma in 2001. Concerned that athletes without asthma may have been using inhaled  $\beta_2$ -agonists, the symposium recommended that to be granted permission to use inhaled  $\beta_2$ -agonists at future Games, athletes should be required to demonstrate current asthma, exercise-induced asthma, exercise-induced bronchoconstriction (EIB), or airway hyperresponsiveness (AHR). For further detail, see "Why inhaled  $\beta_2$ -agonists are prohibited and why the IOC has introduced its policy on inhaled  $\beta_2$ -agonists" in the [Online Repository at www.jacionline.org](http://www.jacionline.org). The IOC agreed with the recommendation, which was made for health and not doping reasons. Subsequent publications have reviewed the consequences of this decision at the Olympics in 2002<sup>1</sup> and in 2004<sup>2</sup> and provided an overview of  $\beta_2$ -agonists at the Olympic Games.<sup>3</sup> In 2003, the

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Anderson invented the mannitol test for Pharmaxis Ltd and is a member of the IOC Independent Asthma Panel. L.-P. Boulet has received sponsorship or funding from AstraZeneca, GlaxoSmithKline, Merck Frosst, Schering-Plough, Novartis, Alexion, AsthmaTx, Boehringer-Ingelheim, Ception, Genentech, IVAX, MedImmune, Topigen, and Wyeth. D. C. McKenzie has received research funding from the World Anti-Doping Agency and is a member of the IOC Independent Asthma Panel. V. Backer has received research funding from Pharmaxis Ltd and the Danish Lung Association and is a member of the Advisory Board of MSD, Novartis, ALK-Abelló, AstraZeneca, and GlaxoSmithKline. K. W. Rundell has delivered lectures sponsored by Merck and has received research funding from the World Anti-Doping Agency, Pharmaxis, SkyPharma, and Forest Research. P. Kippelen has received research funding from the British Olympic Association and is a member of the IOC Independent Asthma Panel. The rest of the authors have declared that they have no conflict of interest.

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*Abbreviations used*

AHR:	Airway hyperresponsiveness
ASM:	Airway smooth muscle
ATUE:	Abbreviated Therapeutic Use Exemption
BPT:	Bronchial provocation test
EIB:	Exercise-induced bronchoconstriction
EVH:	Eucapnic voluntary hyperpnea
IAAF:	International Association of Athletics Federations
ICS:	Inhaled corticosteroid
IOC:	International Olympic Committee
ISAAC:	International Study on Asthma and Allergies in Childhood
PM:	Particulate matter
WADA:	World Anti-Doping Agency

International Association of Athletics Federations (IAAF) introduced the same requirements and criteria as the IOC. At a conference in January 2008, the IOC re-examined this topic, a decision in part provoked by the World Anti-Doping Agency (WADA) seeking clarification for the differences in policy between the IOC and WADA with respect to  $\beta_2$ -agonists.

The conference examined a number of issues including the diagnosis and optimal treatment of asthma, EIB and AHR in elite athletes, past experience of  $\beta_2$ -agonists before and after the need to obtain approval, environmental and genetic aspects (see “Genetic aspects of asthma” in the [Online Repository](http://www.jacionline.org) at [www.jacionline.org](http://www.jacionline.org)), intense endurance training as a possible cause of asthma/AHR, the performance of athletes inhaling  $\beta_2$ -agonists, and the future of  $\beta_2$ -agonists at Olympic Games. This is a review of the conference proceedings and the consensus statement (see “IOC consensus statement on asthma in elite athletes” in the [Online Repository](http://www.jacionline.org) at [www.jacionline.org](http://www.jacionline.org)) prepared at the conclusion of the meeting.

## DIAGNOSIS OF ASTHMA IN ELITE ATHLETES

### Does the athlete have asthma?

Asthma is a syndrome with many clinical phenotypes.<sup>4</sup> Exercise-induced asthma is the occurrence of a transient narrowing of the airways after exercise that is reversible by inhalation of a  $\beta_2$ -agonist in an individual with asthma. When narrowing of the airways occurs only with exercise, this phenomenon is best described as EIB.<sup>5</sup> The term *EIB* is self-explanatory and is used throughout this article.

Sports activities at an elite level are often associated with symptoms that may be suggestive of asthma. These include breathlessness, wheeze, cough, chest tightness, and phlegm in relation to exercise. Of these, breathlessness is the dominant symptom, reported in almost 50% of winter athletes. In contrast, wheezing and waking with breathlessness are less prevalent in athletes than in the general population.<sup>6</sup> Epidemiologic studies suggest that self-reported and physician-diagnosed asthma are twice as common in elite Norwegian<sup>7</sup> and Finnish athletes<sup>8</sup> than in randomly selected age-matched and sex-matched control populations. The higher prevalence of asthma reported in athletes may be a result of overdiagnosis, particularly because a diagnosis of asthma is often made on the basis of the history alone.<sup>9</sup> A clinical suspicion of asthma should ideally be confirmed by demonstrating either a 12% increase in FEV<sub>1</sub> from the baseline or predicted value in response to a bronchodilator or AHR (see “Bronchial provocation tests”). In elite winter sports athletes, 2

or more symptoms suggestive of asthma had a sensitivity and specificity of 50% and 78%, respectively, for the presence of EIB assessed with a field-based exercise test.<sup>10</sup> Asthma was misdiagnosed in 21% and undiagnosed in 2.6% of athletes in the 2004 British Summer Olympic team.<sup>11</sup> In the absence of objective tests of airway function, other diagnoses such as upper airway dysfunction may be overlooked.

### Bronchial provocation tests

Bronchial provocation tests (BPTs) are used to identify AHR and to aid the diagnosis of asthma in athletes. The 2 types of BPTs are indirect and direct. The indirect tests include exercise, eucapnic voluntary hyperpnea (EVH; also known as the isocapnic hyperventilation test) and hyperosmolar aerosols such as 4.5% saline and mannitol.<sup>12</sup> These stimuli act indirectly to cause airway smooth muscle (ASM) contraction and airway narrowing by release of mediators (eg, prostaglandins, leukotrienes, and histamine) from inflammatory cells in the airways. The fall in FEV<sub>1</sub> from the baseline value used to define abnormality is the mean plus 2 SDs of the fall documented in healthy subjects without asthma in response to the maximum dose of the test stimulus. For exercise and EVH, a fall in FEV<sub>1</sub> of 10% is consistent with EIB.<sup>13,14</sup> A fall in FEV<sub>1</sub> of 15% in response to 4.5% saline or mannitol is consistent with a clinical diagnosis of asthma with or without EIB.<sup>15</sup> A positive response to indirect stimuli is consistent with airway inflammation.<sup>16</sup> After 3 to 8 weeks of treatment with inhaled corticosteroids (ICSs), 50% of subjects can expect remission of their EIB.<sup>17,18</sup> Further, drugs used acutely for the prevention of EIB, such as the leukotriene receptor antagonists, nedocromil sodium, or sodium cromoglycate and antihistamines, can also reduce the response and enhance the recovery to these provoking stimuli.<sup>19-21</sup>

Although there are laboratory protocols to investigate athletes, a field test involving sport-specific challenge was found to be more sensitive for identifying EIB.<sup>22</sup> Skating has proved a good sport-specific exercise to identify EIB.<sup>23</sup> Because it is the ventilation (rather than the heart rate) and the water content of the air inspired<sup>24</sup> that are the most important factors for identifying EIB, alternative tests were sought to encompass these factors.

The EVH test was developed as a surrogate for exercise to test for EIB.<sup>25</sup> It requires the subject to ventilate between 22 to 30 times FEV<sub>1</sub> (L; preferably 30 times) for 6 minutes while breathing dry air containing 5% carbon dioxide.<sup>14</sup> The test duration, temperature, and ventilation level can be varied to simulate the conditions of the sport. EVH has been compared with exercise and other stimuli and is now well established for assessing elite athletes.<sup>1,11,14,23,26-28</sup>

Hyperosmolar aerosols were introduced as surrogates for exercise and EVH to simulate the effects of evaporative water loss on the airways.<sup>29</sup> Hyperosmolar (4.5%) saline is inhaled during tidal breathing as a wet aerosol generated by a large-volume ultrasonic nebulizer. Alternatively, mannitol powder can be delivered from capsules by using a dry powder inhaler. The clinical efficacy and safety of mannitol to identify AHR have been established,<sup>15</sup> and the test is registered for this indication in Australia, Europe, and Korea.

The direct stimulus most often used to evaluate athletes is methacholine chloride. Methacholine stimulates acetylcholine receptors to cause smooth muscle contraction. The fall in FEV<sub>1</sub> in response to a particular concentration or dose provides an index of sensitivity of the ASM to methacholine. Because healthy people

can also respond to methacholine, it has been necessary to select an adequate dose or concentration to define hyperresponsiveness.<sup>30</sup> There are a number of different techniques and devices used to deliver methacholine, making it difficult to be precise about dose/concentration equivalents, and concentration only is used in some guidelines.<sup>13</sup> A provoking concentration to cause a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) of  $\leq 1$  mg/mL has a very high specificity for identifying clinically recognized asthma in young adults.<sup>31</sup> A PC<sub>20</sub> of  $\leq 4$  mg/mL is equivalent to a cumulative provoking dose (PD<sub>20</sub>) of 400  $\mu$ g or a noncumulative PD<sub>20</sub> of 200  $\mu$ g and identifies people with mild, moderate, and severe AHR.<sup>13,32</sup> The criteria for identifying AHR in those taking ICS are higher (a PC<sub>20</sub> of  $\leq 16$  mg/mL, or PD<sub>20</sub> of 1600  $\mu$ g and 800  $\mu$ g for cumulative and noncumulative doses, respectively).<sup>13</sup>

In elite summer athletes, the sensitivity of methacholine to identify EIB has been reported to be low and less than 40%.<sup>27,33,34</sup> This low sensitivity to identify AHR is thought to relate to the greater potency of the mediators (prostaglandins and leukotrienes) released in response to the indirect stimuli compared with methacholine in healthy fit subjects with good lung function.<sup>35,36</sup> Methacholine appears to be more sensitive to identify AHR in those exposed to cold dry environments.<sup>37</sup> AHR in these athletes may be a result of airway injury and remodeling rather than the airway inflammation of asthma, although this remains to be confirmed.<sup>38</sup>

Tests using other pharmacologic agents such as carbachol, histamine, or AMP have not been accepted by the IOC's Medical Commission.

For the 2004 Games in Athens, 3 countries had 50 or more applicants (Australia, 67; Great Britain, 54; United States, 53). Of these 174 applicants, 17% submitted results of a bronchodilator test, 59% an EVH or exercise challenge, 15% a hypertonic saline challenge, and 9% methacholine tests.<sup>39</sup>

## MANAGEMENT OF ASTHMA IN ELITE ATHLETES

### Optimal management of asthma in athletes

The goal of asthma treatment is to reduce or prevent respiratory symptoms and to optimize pulmonary function.<sup>40</sup> Management of asthma in athletes should be similar to management in nonathletes, with attention to patient education (which is often deficient in athletes),<sup>41</sup> reduction of relevant environmental exposures, treatment of associated comorbid conditions, individualized pharmacotherapy, prevention of exacerbations, and regular follow-up (Fig 1). Athletes should also be advised to avoid training when air quality is impaired and under extreme conditions of temperature and humidity. The use of a face mask attenuates EIB in athletes breathing cold air and has a synergistic effect when combined with  $\beta_2$ -agonists.<sup>42</sup> Although the high ventilation in these athletes makes these masks difficult to use during competition, use of these heat and moisture exchangers should be encouraged during training sessions. Measures to reduce chlorine derivatives in swimming pools, as well as ozone and particulate matter (PM) in indoor sports arenas, should be considered. Pharmacotherapy should aim to attenuate EIB. This is best achieved by the use of ICSs for an adequate time.<sup>18</sup> If EIB is still not controlled despite efficient inhaler technique and good compliance, the dose of ICS can be increased or treatment can be supplemented with another medication, such as a long-acting  $\beta_2$ -agonist or a leukotriene antagonist, sodium cromoglycate, or nedocromil sodium.<sup>20,21,43</sup> However, although quite effective in reducing EIB, ICS and leukotriene antagonists seem to be less effective in reducing airway

inflammation and AHR to methacholine and improving chronic respiratory symptoms in the athlete than in the nonathlete.<sup>18,44,45</sup> This may be a result of the presence of a more neutrophilic than eosinophilic airway inflammation in the athlete.<sup>46-49</sup> Criteria for good asthma control include no or minimal daytime symptoms, no limitations of activity, no nocturnal symptoms, no or minimal need for rescue medication, normal lung function, and no or mild infrequent exacerbations. Difficult-to-control asthma may be a result of an inadequate diagnosis, undertreatment (usually from underestimation of severity), poor adherence to the treatment, exacerbating factors such as allergen or pollutant exposures, or comorbidities, or a more severe phenotype of asthma that is less responsive to therapy.

### Benefits and dangers of $\beta_2$ -agonists

Athletes with asthma will need a fast-acting bronchodilator. Inhaled  $\beta_2$ -agonists are the most effective bronchodilators for the relief of asthma symptoms and for pretreatment of EIB.<sup>50</sup> In addition, long-acting  $\beta_2$ -agonists are often combined with inhaled corticosteroids to improve asthma control.<sup>50</sup>

Unfortunately, studies show that regular treatment with  $\beta_2$ -agonists increases the sensitivity of the airways to bronchoconstrictive stimuli including exercise and allergens (see this article's Fig E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Athletes who have been using  $\beta_2$ -agonists regularly or frequently are likely to experience worsening of EIB if they do not take them before exercise. In addition, both the bronchodilator and the bronchoprotective effects of  $\beta_2$ -agonists diminish after a few days of regular use. Hence athletes using regular or frequent  $\beta_2$ -agonists will have reduced protection against EIB even if they take them immediately before exercise.<sup>51-54</sup> They are also likely to have a suboptimal response to rescue  $\beta_2$ -agonists taken to relieve exercise-induced symptoms.<sup>55-57</sup>

These effects are probably a result of downregulation of  $\beta_2$ -receptors on ASM and inflammatory cells such as mast cells induced by chronic exposure to agonist. Although tolerance (or tachyphylaxis) is usually only partial, it may present a management dilemma for athletes who use  $\beta_2$ -agonists to prevent EIB. Ideally athletes should use  $\beta_2$ -agonists infrequently, but this may not be appropriate for those who train every day. Other than avoiding frequent  $\beta_2$ -agonist use, there are no known ways to prevent tolerance. It occurs with both long-acting and short-acting  $\beta_2$ -agonists. Tolerance is neither prevented by inhaled corticosteroid treatment<sup>51,57-60</sup> nor overcome by using a higher dose of  $\beta_2$ -agonist.<sup>61,62</sup> However, adequate anti-inflammatory treatment may help to reduce the severity of EIB and thereby reduce the need for additional  $\beta_2$ -agonist.<sup>63</sup> Alternative bronchodilators such as the anticholinergics (eg, ipratropium bromide) do not prevent EIB in most patients with asthma.<sup>64</sup> In keeping with standard guidelines,<sup>50</sup> it is not recommended that either long-acting  $\beta_2$ -agonists or regular/frequent use of short-acting  $\beta_2$ -agonists is relied on as sole therapy for athletes with asthma.

## EXPERIENCE OF ATHLETES HAVING TO DEMONSTRATE THE NEED TO INHALE

### $\beta_2$ -AGONISTS

#### $\beta_2$ -Agonists experience at Olympic Games

In 2004, requiring Olympic athletes to demonstrate evidence of asthma or AHR to inhale  $\beta_2$ -agonists resulted in a 27% reduction

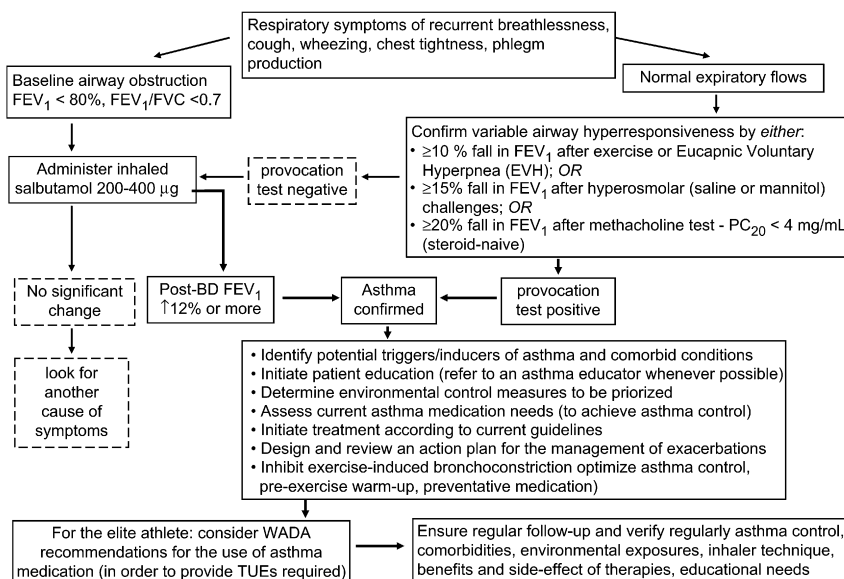


FIG 1. Asthma management for the athlete. BD, Bronchodilator; FVC, forced vital capacity.

in their use from the 2000 Olympics, when notification only was accepted.<sup>2</sup> Identified in 2001, the markedly skewed prevalence of  $\beta_2$ -agonist notifications was confirmed after use of  $\beta_2$ -agonists had to be approved in 2002. A higher percentage of  $\beta_2$ -agonist notifications/approved applications was observed in summer sports with a major endurance component in competition and/or in training (see this article's Fig E2 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). A similar trend was evident in winter sports with the mean percentage  $\beta_2$ -agonists notified/approved from 1998 to 2006 greatest in cross-country skiing (16.3%), speed skating (14.2%), and Nordic combined (12.9%), in contrast with ice hockey (2.9%), luge (1.8%), and ski jumping (1.7%). The 7-fold difference between ski jumping and Nordic combined is the most striking example of the difference between endurance and nonendurance competitors' use of  $\beta_2$ -agonists. In the latter event, athletes participate in a 15-km cross-country ski race in addition to ski jumping.

The percentage of  $\beta_2$ -agonists notified/approved over 3 Summer Games, 1996 to 2004, for each country closely correlates with the reported prevalence of asthma symptoms in the International Study on Asthma and Allergies in Childhood (ISAAC) study<sup>65</sup> and the European Community Respiratory Health Survey.<sup>66-68</sup> The principal exceptions were countries in South and Central America. Brazil, with more than 200 athletes at each of these Games and rated eighth by ISAAC, had mean  $\beta_2$ -agonist notifications/approved applications of 0.7% over the 3 Games. No reason for this has been identified.

In contrast, large countries ranking lowest on ISAAC ratings—Russia (a total of 1277 athletes), China (977 athletes), and Korea (864 athletes)—had no athlete inhaling  $\beta_2$ -agonists at any Summer Games between 1996 and 2004. A similar correlation was observed between the proportion of winter sports athletes using  $\beta_2$ -agonist and the prevalence of asthma symptoms in the ISAAC study.

In 2001, inhaled corticosteroids were believed to be underused by athletes, and this appears to have been rectified. The percentage of athletes approved to use inhaled  $\beta_2$ -agonists who also inhaled corticosteroids was 46.1% in 1996, 69.4% in 2004, and

77.2% in 2006. Notification for use of inhaled corticosteroids was unnecessary at the Games of 1998, 2000, and 2002.

### IAAF $\beta_2$ -agonist experience

The IAAF introduced the Abbreviated Therapeutic Use Exemption (ATUE) requirement for  $\beta_2$ -agonists at the 2003 World Championships. Since 2003, a total of 3174 Therapeutic Use Exemption applications have been received, 868 of which were for the use of  $\beta_2$ -agonists—either alone or in combination with inhaled steroids—of which 690 (79.5%) were approved. Geographically, 85% of all applications were submitted by only 23 of the 212 IAAF Member Federations. Again, the percentage of  $\beta_2$ -agonists applications seems to reflect the prevalence of asthma of the relevant countries. In the last 2 IAAF World Championships in Athletics in Helsinki (2005) and Osaka (2007), a total of 2749 different athletes participated. Of these, 115 (4.2%) were granted approval to use a  $\beta_2$ -agonist. When related to exercise intensity and total number of athletes within each category, the frequency of approvals was 4.7% in endurance running and race walking; 3.7% in sprinting, jumping, and throwing; and 7.9% in combined events.

### ENVIRONMENTAL ASPECTS OF ASTHMA IN ELITE ATHLETES

Airway function can be affected by exposure to seasonal and perennial allergens in sensitized individuals, dry/cold air, and poor quality air containing pollutants such as chlorine derivatives in swimming pools, ozone and oxides of nitrogen, and fine and ultrafine PM derived from combustion.<sup>69</sup> The effects may be greater in subjects with asthma than without asthma. Because of the high minute ventilation during exercise, the effects of these exposures may be more marked in athletes than in nonathletes with the development of nonallergic asthma symptoms and bronchoconstriction during or after exercise. A significant part of variability in reported prevalence of EIB between sports is likely a result of environmental influence. The 30% to 50% prevalence of AHR<sup>10,70-72</sup> in cross-country skiers has been attributed to the

high minute ventilations achieved and sustained during training and racing in cold/dry ambient conditions.<sup>73</sup>

Recently, attention has been given to the effect of environmental pollutants on asthma and EIB. The high prevalence of EIB identified in the ice rink athletes has been related to inhalation of exhaust fumes from ice resurfacing equipment during training and competition.<sup>74,75</sup> Current information suggests other associations of exposure to exhaust emissions with changes in allergy prevalence,<sup>76,77</sup> asthma exacerbations, and increase in the severity of asthma symptoms and medication usage.<sup>69</sup> A likely mechanism for PM inhalation-induced bronchoconstriction involves increased production of reactive oxygen species that activate 5-lipoxygenase and increase production of leukotrienes.<sup>78,79</sup> Pulmonary hypertension has been associated with exposure to fine PM (PM<sub>2.5</sub>)<sup>80</sup> and may be related to the observed decrease in exercise performance in high-emission pollution air.<sup>81</sup> Bronchoconstriction from inhalation of combustion derived particles has been shown to be strongly associated with leukotrienes in human beings<sup>75</sup> with significant falls in FEV<sub>1</sub> after 30 minutes of high-intensity exercise while breathing air with a high concentration of ultrafine PM (PM<sub>1</sub>).<sup>82</sup>

## TRAINING AS A CAUSE OF ASTHMA

The prevalences of asthma, EIB, and AHR are increased in elite athletes.<sup>6,47,83</sup> For swimmers, this has been attributed to the frequent recommendation for patients with asthma to engage in this sport. However, the proportion of elite swimmers who commence swimming because of asthma compared with those who develop asthma and/or AHR after years of intense training is unknown. Several studies in the last decade have suggested that long-term intense endurance training may promote the development of asthma and AHR.<sup>38,47,70,73,84</sup>

Environmental conditions together with the high ventilation required by the intense effort may contribute to this phenomenon. Exposure to chlorinated pools, cold air, allergens, or high levels of pollutants may irritate or sensitize the airways. The mechanical stress of extreme breathing on airway epithelial cells may cause release of mediators. The effects of these mediators may be to initiate or increase inflammatory processes in the airways, leading to airway remodeling, variable airway obstruction, and AHR.<sup>46,49,70,73,85,86</sup>

The changes in lung function and airway responsiveness may be at least partly reversible after cessation of long-term endurance training.<sup>87,88</sup> More research is needed on how to prevent or minimize the adverse effects of long-term training on the airways, particularly the effects of environmental exposure on airway structure and function.

## WHY ARE PATIENTS WITH ASTHMA SUCCESSFUL AT THE OLYMPIC GAMES?

Athletes who notified  $\beta_2$ -agonist use in Sydney and were approved to inhale  $\beta_2$ -agonists in Salt Lake City, Athens, and Torino won more individual Olympic medals than their counterparts without asthma at each Games (see this article's Fig E3 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

The differences were greater in winter athletes than in summer athletes because a greater percentage of winter competitions can be classed as endurance events. Of the 28 summer sports, 6—boxing, wrestling, gymnastics, judo, shooting, and

weightlifting—award 42% of all individual medals, and none of these can be classed as an endurance sport. This raises the intriguing question whether some endurance athletes develop asthma or AHR after achieving success as an elite athlete. There is some evidence that the age of onset of asthma/AHR is unusually high in endurance winter athletes.<sup>3</sup> In addition, the psychology of having a chronic disease and competing at this level may represent an additional training stimulus for the elite athlete. Inhaled  $\beta_2$ -agonists are not considered to enhance endurance performance,<sup>89,90</sup> although oral salbutamol does increase strength.<sup>91</sup> Every medalist is drug-tested after the event, and oral salbutamol is distinguishable from inhaled,<sup>92</sup> a test introduced before the 2000 Olympics. For further details see "The effects of inhaled  $\beta_2$ -agonists on endurance performance: Olympic medalists inhaling  $\beta_2$ -agonists" in the Online Repository at [www.jacionline.org](http://www.jacionline.org).

## Conclusion

Elite endurance athletes may develop respiratory symptoms, AHR, and/or asthma as a consequence of their training. To reduce the risk of developing these conditions, athletes and their medical advisors should address specific aspects such as frequency of intense training, especially under adverse environmental and ambient conditions. Elite athletes with asthma and AHR and their medical advisors must adhere to WADA regulations and should be aware of the high likelihood of developing tolerance/tachyphylaxis to  $\beta_2$ -agonists with regular use. Nevertheless, the treatment of asthma, EIB, and AHR in elite athletes should follow the currently accepted guidelines for these conditions in nonathletes. The conference reaffirmed that athletes should continue to be required to demonstrate the presence of asthma and EIB or AHR to be approved to inhale  $\beta_2$ -agonists at the Olympic Games.

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## WHY INHALED $\beta_2$ -AGONISTS ARE PROHIBITED AND WHY THE IOC HAS INTRODUCED ITS POLICY ON INHALED $\beta_2$ -AGONISTS

In 1967, the IOC established a Medical Commission (IOC-MC) to fight doping at the Olympic Games. It published a List of Prohibited Drugs and Prohibited Methods (“the List”), which soon became accepted by the majority but not all major sporting bodies. Inhaled  $\beta_2$ -agonists were first considered by the IOC-MC at the 1972 Games, and their subsequent variable status has been detailed.<sup>E1</sup>

The WADA was inaugurated in 1999 and soon assumed from the IOC the global responsibility of determining which drugs are prohibited in sport. WADA developed a World Anti-Doping Code (“the Code”),<sup>E2</sup> of which the List<sup>E3</sup> is an international standard.

The Code has a minimum 2 of 3 criteria that must be met before a drug or a method can be considered for inclusion on the List:

1. The substance or method can be performance enhancing
2. The use of the substance or the method can endanger the athlete’s health
3. The use of the substance or method is against the spirit of sport

Not one of the criteria is compulsory, meaning that a substance or a method can be listed without being performance-enhancing. At the Olympic Games, the IOC, like every other sporting body that adheres to the Code, must institute measures to be compliant with the Code.

For inhaled  $\beta_2$ -agonists, the IOC complies via the ATUE process.<sup>E4</sup> When WADA assumed from the IOC the global responsibility of antidoping policy, the IOC switched its focus from doping to the health and well being of athletes. In 2001, the IOC-MC reviewed the use of inhaled  $\beta_2$ -agonists at the 2000 Olympic Games and was concerned that some athletes without asthma may have been using these drugs and resolved to ensure that use of inhaled  $\beta_2$ -agonists at future Games was fully justified. Thus, it was for health and not doping reasons that the IOC introduced its  $\beta_2$ -agonists policy before the 2002 Olympic Winter Games in Salt Lake City. This required a doctor to provide evidence via either a bronchodilator response or 1 of several BPTs<sup>E5</sup> before approval was given to an athlete to inhale a  $\beta_2$ -agonists.

As to health issues, the IOC considers that inhaling a  $\beta_2$ -agonist without need is unacceptable. For more than 3 decades,  $\beta_2$ -agonists have been in the spotlight because of side effects, and recent issues with regulatory bodies including the US Food and Drug Administration and particularly salmeterol reactivate and re-enforce these concerns. Martinez<sup>E6</sup> and others<sup>E7-E9</sup> have demonstrated significant unwanted effects of  $\beta_2$ -agonists. The fact that only 445 athletes at the Olympic Games in Athens<sup>E10</sup> demonstrated the need to inhale  $\beta_2$ -agonists compared with 607 4 years earlier in Sydney when doctors notified intended use but did not provide any justification suggests that some Olympic athletes in Sydney may have inhaled  $\beta_2$ -agonists without the clinical need. The IOC considers that it is important that athletes justify the use of drugs such as inhaled  $\beta_2$ -agonists. The media constantly re-enforce the concept that elite athletes are role models in society, and for elite athletes without asthma to be inhaling  $\beta_2$ -agonists cannot be justified or condoned.

It should be mentioned that currently and independently of the IOC, WADA is proposing to introduce the IOC’s policy on inhaled  $\beta_2$ -agonists in 2009, but only for elite athletes in each country and each sport.

Regarding inhaled glucocorticosteroids (GCSs), the IOC considers them the gold standard treatment for asthma and exercise-induced asthma/EIB. The IOC removed the necessity to notify the use of these substances after the 1996 Olympic Games in Atlanta. However, in 2004, WADA required all nonsystemic preparations of corticosteroids to be notified via an ATUE. It did so because it was aware that oral and other systemic routes of administration were being misused by athletes to enhance performance. Currently there is no analytical test to distinguish systemic from nonsystemic administration of GCS.

Because of the WADA Code, in 2004 the IOC was compelled to reintroduce the requirement for athletes to notify the use of inhaled and all other administrations of GCS at the Athens Games via the ATUE process. Although many nonsystemic routes of administration (including nasal) of GCS have been permitted since 2005, currently WADA requires an ATUE for inhaled and injected administrations. However, the IOC does not require athletes to provide any justification to inhale a GCS, although the majority do because inhaled GCSs are mostly taken in conjunction with  $\beta_2$ -agonists.

### The effect of inhaled $\beta_2$ -agonists on endurance performance: Olympic medalists inhaling $\beta_2$ -agonists

In a European Respiratory Society Monograph in 2005, Larson et al<sup>E11</sup> reviewed 21 studies involving  $\beta_2$ -agonists and endurance performance, of which 16 were double-blind and involved inhaled salbutamol. In 13 of the 16, there was no difference between placebo and salbutamol; in 1, placebo was superior, and in 2, salbutamol was superior. One of the latter 2 articles, by Bedi et al,<sup>E12</sup> has been repeatedly criticized for including 2 aberrant subjects whose results skewed the outcome, and the other, by Signorile et al,<sup>E13</sup> found enhancement for only peak power via a 15-second supramaximal effort on a cycle ergometer. In contrast with van Baak et al,<sup>E14</sup> Sporer et al<sup>E15</sup> in 2008 found no difference in performance in elite cyclists without asthma after inhaling placebo and 200, 400, and 800  $\mu$ g salbutamol. Significantly, to exclude athletes who may have unrecognized asthma or bronchial hyperresponsiveness, Sporer et al<sup>E15</sup> required all subjects to undertake a EVH test, and 19% of subjects were positive and excluded from the study.

After Martineau et al<sup>E16</sup> (1992) demonstrated that oral salbutamol had the capacity to increase strength, the IOC funded research studies that resulted in the ability to distinguish oral from inhaled salbutamol.<sup>E17</sup> The distinction involves a urinary concentration upper threshold of 1000 ng/mL salbutamol (free plus gluconuride) and the ratio of the S+ and R- enantiomers. This test was available at Sydney and all subsequent Games. Every athlete who wins a medal is required to undertake a postevent doping test, and at each of the 4 Games from 2000 to 2006, between 7 and 14 athletes have been identified with a urinary concentration of salbutamol exceeding 100 ng/mL, the reporting threshold. The vast majority of athletes have concentrations of less than 100 ng/mL; for instance, in Torino 2006, 7 athletes had a urinary salbutamol >100 ng/mL in addition to 34 athletes who were noted by the laboratory to have taken salbutamol but their urinary concentration was <100 ng/mL. The highest urinary concentration at these 4 Games was less than 350 ng/mL, well below the upper threshold of 1000 ng/mL. Thus, the IOC is confident that no athlete with asthma who won a medal used oral salbutamol.



## Genetic aspects of asthma

The prominence of family history among asthma risk factors has long suggested an important role for genetics. However, asthma has no clear pattern of inheritance, and heritability estimates of asthma vary between 36% and 79%.<sup>E18-E20</sup> The search for specific genes involved in predisposition to asthma has been challenging, in part because of the complex nature and pathogenesis of the disease. Moreover, the marked differences in prevalence of asthma between countries that are reflected in populations of elite athletes clearly support the idea that asthma results not only from genetic predisposition but also from complex interactions between genetic and environmental factors.

Several candidate genes for asthma risk factors are found in chromosomal areas that have also been identified by asthma linkage studies. On chromosome 11q13 can be found the high-affinity IgE receptor, the Clara cell protein, and glutathione-S-transferase P1 (*GSTP1*), a candidate gene because of its role in protection against oxidative stress. In human lung epithelium, the *GSTP1* gene contributes more than 90% of GST-derived enzyme activity.<sup>E21</sup> Variation in *GSTP1* genes has previously been associated with asthma risk.<sup>E21-E23</sup> Moreover, recent results suggest that *GSTP1* Ile105Val genotype strongly determines the progression of AHR to physician-diagnosed asthma in the general population.<sup>E24</sup> On the other hand, Lee et al<sup>E25</sup> showed that homozygosity for 105Ile represents a risk factor for asthma in children only in areas with high outdoor air pollution. This result suggests that outdoor air pollution may play a crucial interactive role in determining whether susceptible individuals develop asthma. Glutathione S transferase M 1 (*GSTM1*), another gene from the GST family, has been shown to act as a modifier of the lung response to ozone.<sup>E26</sup> Moreover, in children with asthma, the deletion of the *GSTM1* gene could increase the susceptibility to the deleterious effects of ozone on small airways.<sup>E27</sup>

The ability of acute physical activity to alter gene expression has also been reported recently. An upregulation in genes (*ALOX5* and *ALOX5AP*) coding for the 5-lipoxygenase pathway has been demonstrated after endurance exercise in healthy subjects without asthma.<sup>E28</sup> Because 5-lipoxygenase is a central enzyme in the leukotrienes (LTs) pathway and the release of cysteinyl LTs appears to be involved pathogenesis of EIB,<sup>E29, E30</sup> exercise could possibly trigger EIB via LT release if a predisposition is present.<sup>E31</sup> Moreover, recent results showing that brief heavy exercise leads to alteration in the expression of a subset of neutrophil genes that are also linked to asthma.<sup>E32</sup> These observations give further support to the idea that strenuous physical activity might be a trigger for asthma. Conversely, some results suggest that exercise—if performed at moderate intensity—could have a beneficial effect on atopic asthma by attenuating airway inflammation via modulation of the transcription factor nuclear factor- $\kappa$ B.<sup>E33</sup>

Finally, pharmacologic and pharmacogenetics studies that have looked at specific genes related to specific therapeutic agents generally have been performed in nonathletes.<sup>E34, E35</sup> Several genetic polymorphisms have been shown to influence responses to all 3 main treatments for asthma:  $\beta_2$ -agonists, glucocorticosteroids, and LT modifiers. Gene mutations that appear to alter the response to asthma therapy include Arg/Arg at position 16 of the  $\beta_2$ -receptor, and mutations of leukotriene C4 synthase (*LTC4S*), *ALOX5*, and glucocorticoid receptor (*GR*).<sup>E36</sup> Some of the effects associated with these mutations are increased/decreased response to therapy, glucocorticoid resistance, and

increased bronchoconstriction. Whether elite athletes respond differently to asthma medications because of exercise-induced alteration in genes expression remains to be established. Consequently, treatment guidelines for asthma in athletes do not currently differ from the general recommendation.<sup>E36-E38</sup>

## IOC CONSENSUS STATEMENT ON ASTHMA IN ELITE ATHLETES

### Diagnosis of asthma in elite athletes

Respiratory symptoms such as recurrent breathlessness, cough, wheezing, chest tightness, and excessive mucous production are common in athletes and may be suggestive of asthma. Because these symptoms alone cannot be relied on to make a diagnosis of asthma in an athlete and clinical examination may be normal, objective tests are required to confirm the diagnosis. These tests would include spirometry (FEV<sub>1</sub>). Because athletes may have an FEV<sub>1</sub> above the normal range, normal spirometry does not exclude variable airway obstruction. If airway obstruction is present, spirometry should be repeated after inhalation of a bronchodilator to test for reversibility. In the absence of airflow limitation, a bronchial provocation test, to establish the presence of airway hyperresponsiveness, is required. If the results of these tests are negative, other disorders should be considered.

### Management of asthma in elite athletes

The management of the athlete with asthma should follow current national or international guidelines (eg, Global Initiative for Asthma). Currently, there is no evidence that management of asthma in athletes should differ from that in nonathletes. However, some specific issues need to be considered for the high-level athlete.

The prevention and management of EIB is a key issue in athletes. They may also be exposed to high levels of allergens and environmental irritants during training and competition. Dry/cold air may be a particular problem for some athletes.

The nonpharmacologic management of asthma in athletes is important. This includes identifying and reducing exposure to asthma triggers whenever possible and especially during training. Warm-up may help to reduce EIB.

Drug treatment of asthma in elite athletes should follow standard guidelines with treatment individualized to achieve asthma control and the effects of treatment monitored. Any medications prescribed must comply with WADA regulations. All  $\beta_2$ -adrenoceptor agonists ( $\beta_2$ -agonists) and in particular oral preparations are prohibited. Inhaled corticosteroids and some inhaled  $\beta_2$ -agonists can be used in accordance with the relevant section of the International Standard for Therapeutic Use Exemptions (TUE). Systemic corticosteroids are prohibited and require a Standard TUE.

Inhaled corticosteroids are the most effective drugs for long-term control of asthma and prevention of EIB. Inhaled  $\beta_2$ -agonists are the most effective drugs for immediate inhibition of EIB and for relieving intermittent symptoms of asthma. However, when used frequently, tolerance (or tachyphylaxis) to these effects develops rapidly. Athletes who use either short-acting or long-acting  $\beta_2$ -agonists on a daily basis should be advised that their effectiveness to prevent EIB will partially diminish. Frequent use of  $\beta_2$ -agonists may also increase the bronchoconstrictor response to exercise and allergens. Strategies to avoid these

problems could include restricting  $\beta_2$ -agonists to infrequent use, using alternative treatments for preventing EIB, and ensuring adequate treatment of underlying asthma with inhaled corticosteroids. Long-acting  $\beta_2$ -agonists should not be used as monotherapy.

Athletes should be offered asthma education to develop self-management skills and ensure appropriate use of medication, including inhaler technique. Individualized action plans for the management of exacerbations, asthma monitoring, and follow-up are important.

### Environmental aspects of asthma in elite athletes

The major environmental factors which could influence airway function in elite athletes are allergens and ambient conditions such as temperature, humidity, and air quality. Exposures of importance to the athlete include seasonal and perennial allergens, dry/cold air, chlorine derivatives in swimming pools, and ozone and combustion-derived pollutants such as oxides of nitrogen and particulate matter. Because of the high minute ventilation during exercise, the effects of these exposures may be more marked in athletes than in nonathletes.

### Training as a cause of asthma in elite athletes

Long-term intense endurance training may be associated with an increased risk of development of AHR and asthma in the elite athlete. Environmental factors, such as allergens, chlorine derivatives, pollutants, or cold air exposure may contribute to the development of airway inflammation and functional changes. Their penetration into the airways will be enhanced by the high ventilation required during intense exercise. The changes in lung function and airway responsiveness may be at least partly reversible after cessation of long-term endurance training.

More research is necessary on how to prevent or minimize the adverse effects of long-term training on the airways, particularly the effects of environmental exposure on airway structure and function.

### Past experience of $\beta_2$ -agonist use in elite athletes

Data are now available on athletes who seek approval to use inhaled  $\beta_2$ -agonists. These data arise from the recent Winter and Summer Olympic Games and from the IAAF world championships in athletics. Although most applications for the Games came from those competing in endurance sports, this was not a universal finding in athletics. The geographic distribution of the applications closely relates to the reported prevalence of asthma in those countries. Over the last 5 years, there has been a significant increase in the proportion of athletes using inhaled corticosteroids in conjunction with a  $\beta_2$ -agonist. A minority of athletes is now relying on a  $\beta_2$ -agonist alone to manage the condition.

### Future of $\beta_2$ -agonists in elite athletes

$\beta_2$ -Agonists are likely to remain the most effective bronchodilators available in the foreseeable future. However, they may have a less important role in the management of asthma in athletes because EIB should be better controlled by use of other therapies. Such therapies are likely to target the production, release, and effects of the mediators of bronchoconstriction. Ideally,  $\beta_2$ -agonists should be reserved for occasional use and breakthrough symptoms.

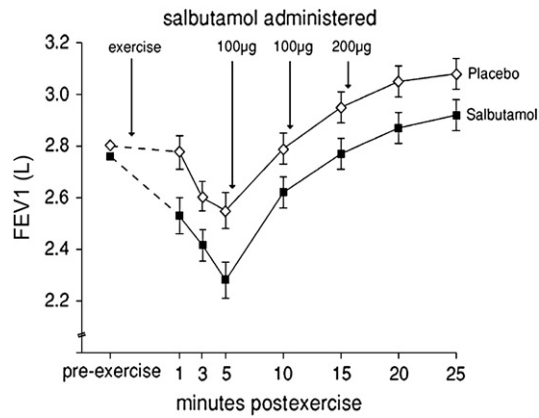
Because of the widespread use and potential for misuse of inhaled  $\beta_2$ -agonists by athletes, there was consensus to continue the strict control of the use of this class of drugs in sport.

Better strategies need to be developed to avoid the development of tolerance to  $\beta_2$ -agonists.

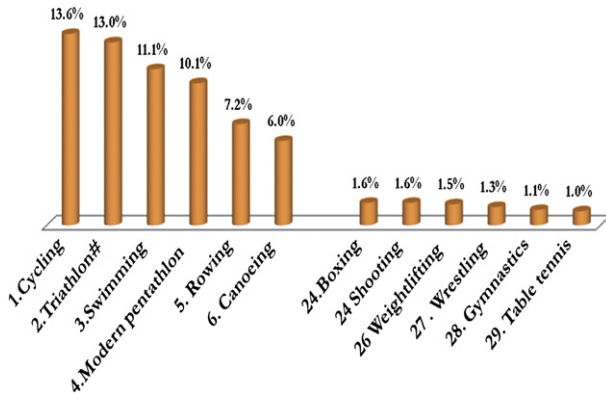
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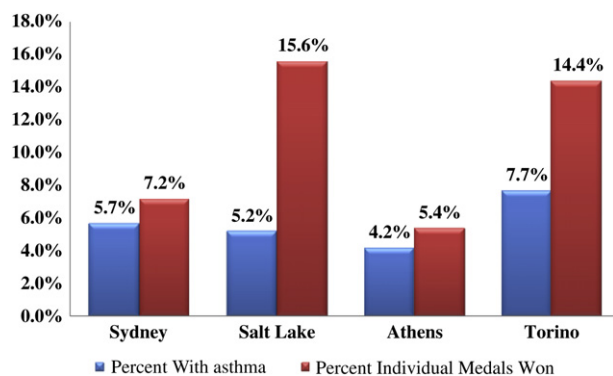
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**FIG E1.** FEV<sub>1</sub> changes before and after exercise challenge and after salbutamol following 1 week of salbutamol or placebo treatment. Error bars represent 95% CIs. The mean FEV<sub>1</sub> is lower after exercise and during the salbutamol response curve in the salbutamol arm ( $P < .001$ ). Adapted with permission from Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. *Am J Respir Crit Care Med* 2002;165:1068-70.<sup>E39</sup>



**FIG E2.** Endurance versus nonendurance Olympic Summer Sports 1996 to 2004 mean percentage  $\beta_2$ -agonists notified/approved. #Triathlon, estimate because did not participate in 1996; 29 sports because swimming and synchronized swimming classed separately from diving and water polo.



**FIG E3.** Percentage of athletes notifying (Sydney) or approved (Salt Lake City, Athens, Torino) for  $\beta_2$ -agonist use and the percentage of individual medals won by these athletes at the 2000 to 2006 Olympic Games.