

Responses to bronchial challenge submitted for approval to use inhaled β_2 -agonists before an event at the 2002 Winter Olympics

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Background: There has been an increase in the number and percentage of athletes competing in Olympic Games notifying use of β_2 -agonists, from 1.7% at Los Angeles (1984) to 5.5% at Sydney (2000). For Salt Lake City (2002), the International Olympic Committee requested objective evidence to use β_2 -agonists for asthma or exercise-induced asthma (EIA).

Objective: The objective of this study was to evaluate the evidence submitted for approval to use a β_2 -agonist.

Methods: Objective evidence for asthma or EIA included (1) an increase of 12% or more of the predicted FEV₁ in response to bronchodilator, (2) a reduction in FEV₁ of 10% or greater from baseline in response to exercise or eucapnic voluntary hyperpnea, (3) a PD₂₀ FEV₁ to methacholine or histamine at a dose of less than 200 μ g (2 mg/mL) or less than 1320 μ g (13.2 mg/mL) for those taking inhaled corticosteroids for 3 months. **Results:** There were 165 applications. Of these, 147 (89%) included evidence of a challenge, bronchodilator response, or both, and 163 test results were submitted. One hundred thirty (5.2%) applications were approved. For those with positive responses, the median value (1) was 16.2% of predicted FEV₁ for response to a bronchodilator (n = 13), (2) was a 15.9% decrease in FEV₁ for response to a physical challenge (n = 36), and, (3) for PD₂₀ FEV₁, was 173 μ g for response to a pharmacologic challenge (n = 45).

Conclusion: The analysis demonstrated that it is feasible to request objective evidence to justify use of β_2 -agonists on the

medical grounds of asthma or EIA. (*J Allergy Clin Immunol* 2003;111:45-50.)

Key words: β_2 -Agonists, sport, elite athletes, exercise-induced asthma, asthma, Olympic Games

β_2 -Adrenoceptor agonists are sympathomimetic agents and are given by means of inhalation to induce relaxation of bronchial smooth muscle. Although indicated for prevention of exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB),¹ the use of inhaled β_2 -adrenoceptor agonists (IBAs) by athletes was prohibited at the Olympic Games in 1972. This ban was lifted in 1976, and IBAs were permitted if a respiratory or team physician had submitted prior written notification that the athlete had asthma, EIA, or both. Between 1986 and 1993, notification was unnecessary but was reintroduced in 1994 and remained effective until 2001.

In May 2001, a workshop was convened in Lausanne by the International Olympic Committee–Medical Commission (IOC-MC) to examine the use of IBAs at the Olympic Games. This revealed a trend toward an increasing frequency of notification of use of IBAs, from 1.7% of athletes at the Los Angeles Games (1984) to 3.6% at Atlanta (1996), 5.6% in Nagano (1998), and 5.5% in Sydney (2000). Furthermore, the use of IBAs was more common in athletes competing in endurance sports, with, for example, notification of 17.9% by cross-country skiers in Nagano and by 17.3% of cyclists and 20% of triathletes in Sydney. The frequency of notification correlated well with the reported national prevalences of asthma symptoms^{2,3} and is consistent with studies reporting a high prevalence of asthma symptoms in elite athletes.⁴⁻⁷

Recent studies report that athletes' asthma symptoms are poor predictors of EIB.^{8,9} Furthermore, the inflammatory cell profiles in bronchoalveolar lavage fluid and endobronchial biopsy specimens from athletes training and competing in subzero temperatures and with asthma symptoms are different from those obtained from asthmatic patients.¹⁰⁻¹²

The workshop recommended that, in addition to notification, the IOC-MC seek objective evidence to justify,

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Abbreviations used

AHR:	Airway hyperresponsiveness
EIA:	Exercise-induced asthma
EIB:	Exercise-induced bronchoconstriction
EVH:	Eucapnic voluntary hyperpnea
IBA:	Inhaled β_2 -adrenoceptor agonist
IOC-MC:	International Olympic Committee–Medical Commission

on medical grounds, the use of IBAs before an event. Although β_2 -agonists do not seem to enhance exercise performance when given in doses required to relieve bronchospasm or prevent EIB,¹³⁻¹⁵ they might do so when administered orally.^{16,17}

An independent panel (the authors) was convened in October 2001 to advise the IOC-MC and to establish objective criteria for an athlete to be granted permission to use IBAs from the current list of approved preparations at the 2002 Winter Olympic Games. In addition to history, clinical indicators, details of current daily medications, and details of other medications in the last 3 months, the athletes were also required to document the presence of variable airflow obstruction since the last winter Olympiad (ie, in the last 4 years). The panel proposed tests that are internationally recognized for the assessment of asthma or EIB.^{18,19} These tests, which were placed on the IOC Web site with appropriate forms and references, included the following.

For bronchodilator testing, a positive response was defined as an increase in FEV₁ of at least 12% of the predicted value²⁰ after the administration of a permitted IBA (formoterol, salbutamol, salmeterol, or terbutaline). This value was chosen because it has been defined as “an unequivocal response to a bronchodilator”²⁰ and is a more lenient value for those with a baseline FEV₁ higher than predicted. The predicted values used were chosen by the testing laboratories, although a set of predicted values was provided at the IOC Web site if one was needed. Graphic evidence (spirometry or flow volume tracings) was requested but not required. Submission of peak expiratory flows in response to bronchodilator was not acceptable.

For bronchial provocation testing, tests acceptable to identify EIB or EIA were physical stimuli, such as exercise in the field^{21,22} or laboratory^{18,19,23} or a eucapnic voluntary hyperpnea (EVH) test with dry air.²⁴⁻²⁶ Airway hyperresponsiveness (AHR) consistent with EIB was confirmed if there was a decrease of 10% or greater in FEV₁ after the challenge. The value of 10% is widely used and is the value generally recommended in guidelines from the United States and Europe for exercise and EVH.^{18,19,25,27} A form with the relevant questions and equations to calculate the indices was provided at the Web site and was required to be completed and returned.

Pharmacologic challenge was also acceptable^{18,19} for bronchial provocation, and methacholine was recommended because it is the only agent commercially available for this use. The criteria for a positive test result are as follows. For those not taking inhaled steroids, the val-

ues for PD₂₀ were required to be less than 1 μ mol (ie, 200 μ g), and the values for PC₂₀ were required to be less than 2 mg/mL. For those taking steroids, the PD₂₀ was required to be equal to or less than 6.6 μ mol (ie, 1320 μ g) or less than 13.2 mg/mL (inadvertently listed as 4 mg/mL on the IOC Web site).

Inability or failure to provide any confirmatory evidence for EIB-EIA or, in the case of methacholine challenge, values for PC₂₀ or PD₂₀ that did not meet the criteria above would result in the need for testing in Salt Lake City before the games.

The findings of the bronchial challenge tests submitted form the basis of this report. The objective is to discuss these findings in relation to the suitability of these tests to identify those who are justified, on medical grounds, in taking IBAs before a sporting event.

METHODS

References were provided for methodologies to perform the various bronchial provocation tests.^{18,19,21-23,26,28,29} The actual measurements of FEV₁ before and after challenge and after bronchodilator use had to be provided to the panel with the source of the predicted values used.

Comparisons between the groups who had positive and negative results to each test were made by using the F test or the variance ratio test.³⁰

RESULTS

There were 2517 athletes at Salt Lake City, and of these, 36.3% were women. There were 165 individual applications for use of IBAs (6.6% of all participants), and these included 105 men and 60 (36.7%) women. Of these 165, 147 (89%) athletes submitted sufficient data to permit inclusion in the analysis of challenge tests. Some athletes submitted more than one result (ie, the results of methacholine and exercise or the results of methacholine and bronchodilator challenge), and in all, 163 tests were performed on these 147 athletes. These are summarized in Table I and Figs 1 and 2. Ninety percent of the athletes documented symptoms normally associated with asthma, such as wheeze, shortness of breath, chest tightness, and cough.

Thirty-eight athletes had tests performed in Salt Lake City before or during the Olympics. Ten athletes performed prebronchodilator and postbronchodilator tests, 12 performed EVH tests, and 16 performed event-specific exercise. The number of test results submitted to the IOC is unknown because the final reports were given to the team physician, who might or might not have submitted them to the IOC.

Types of challenge

The types of challenges were as follows: bronchodilator response (n = 28), exercise (n = 40), EVH (n = 17), and methacholine (n = 57). A number of applicants ignored the request to use the suggested tests and reported bronchial provocation with either histamine (n = 14), carbachol (n = 4), or hypertonic saline (n = 3). Because of the lateness of the information going onto the Web site, these alternative challenges were accepted by the panel.

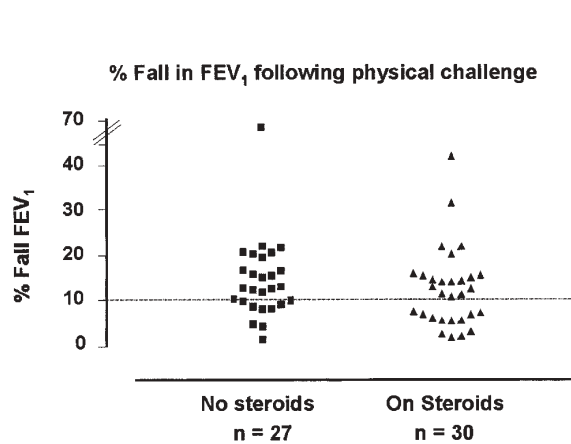


FIG 1. Individual values for the decrease in FEV₁ after exercise (n = 40) or EVH (n = 17) in 57 athletes expressed as a percentage of the prechallenge value (percentage decrease in FEV₁). Thirty-six athletes had a decrease in FEV₁ of 10% or greater, the value considered as the cutoff point for a positive response. Nineteen of these 36 were taking inhaled steroids. Of the 21 athletes who had negative results, 12 were taking inhaled steroids.

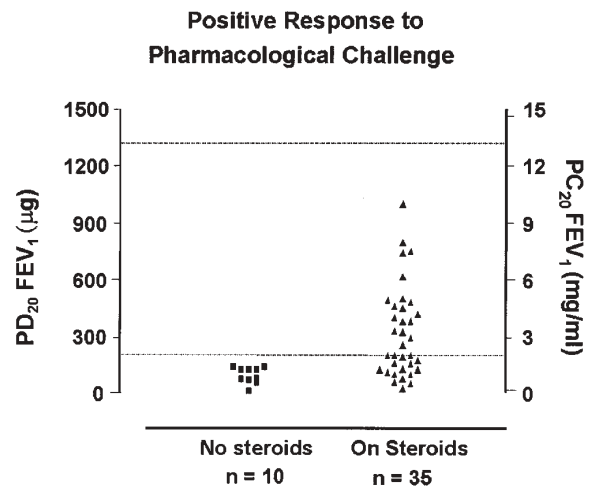


FIG 2. Individual values for the dose of methacholine (n = 40) or histamine (n = 5) required to provoke a 20% decrease in FEV₁ (PD₂₀ FEV₁) in those athletes with a positive response. Broken lines represent the acceptable values for PD₂₀ for those not taking (lower line) and those taking (upper line) inhaled steroids. The equivalence values for the provoking concentration of agent are also given. Thirty-five subjects submitted PD₂₀ values, and 10 submitted PC₂₀ values.

Asthma, rhinitis,
other respiratory
diseases

TABLE I. Mean values for spirometry at baseline and the decrease in FEV₁ expressed as a percentage of baseline after (1) physical challenge with exercise or EVH or (2) challenge with either methacholine or histamine

	FEV ₁	FEV ₁ (% predicted)	FVC	FVC (% predicted)	Baseline FEV ₁ /FVC	% Decrease in FEV ₁	Range
Physical, positive	4.5	112.1	5.39	112.5	83.9	18.3	10.2 to 68.0
SD	0.8	15.7	1.0	14.3	6	10.6	
n	36	31	36	30	36	36	
Physical, negative	4.2	104	5.05	105.70	83.5	5.9	1.3 to 9.9
SD	0.81	11.1	1.0	11.7	6.3	7.5	
n	21	20	21	20	21	21	
Pharmacologic, positive	4.11	102.34	5.28	106.55	79.40	32.2	20.1 to 54.7
SD	0.8	15.8	0.9	12.7	9.3	9.8	
n	45	43	38	37	39	45	
Pharmacologic, negative	4.16	104.4	5.1	106.8	79.6	18.6	-0.2 to 45.2
SD	0.8	13.7	0.9	9.4	8.0	10.5	
n	26	25	19	18	19	26	
Bronchodilator, positive	4.2	93	5.4	99.8	80.1	+18.7*	12.4 to 38.9
SD	0.7	11.1	1.1	14.9	6.8	7.3*	
n	13	13	13	13	13	13	
Bronchodilator, negative	4.2	95.7	5.6	107.6	75.2	+7.5*	1.2 to 11.8
SD	0.92	13.77	1.46	14.96	7.21	3.41*	
n	15	15	15	15	15	15	

The response to bronchodilator was the increase in FEV₁ of greater than baseline expressed as a percentage of the predicted value. The number of tests exceeds the total number of athletes because some athletes submitted results from more than one test.

FVC, Forced vital capacity.

*Increases in FEV₁ percent predicted.

Analysis

The submissions were analyzed according to the definitions for a positive response set out above and given at the IOC Web site. Ninety-one (65%) of 139 athletes had a positive response to either a bronchodilator, a physical challenge, or a pharmacologic challenge with methacholine or histamine; 62% were taking inhaled corticosteroids. Forty-eight athletes did not meet the

challenge criteria, and 64% of these were taking inhaled corticosteroids.

Five additional athletes had a positive response to challenge with either another pharmacologic agent, carbachol, or hypertonic (4.5%) saline, but they are not included in Table I.

Response to bronchodilator

The mean values for spirometry before bronchodilator

use are within the normal range defined as the predicted value for sex, height, and age minus 1.64 SDs.²⁸ There were no significant differences between baseline values for FEV₁ or forced vital capacity for those who had positive results compared with those who had negative results.

Response to the provocation tests

Exercise and EVH challenges. Fifty-seven subjects performed either exercise in the laboratory (n = 30) or field (n = 10) or EVH (n = 17). The data for prechallenge lung function and the percentage decrease after challenge are given in Table I. Individual responses are given in Fig 1. Seven (5 from the same country) athletes with negative exercise or EVH test results also submitted a methacholine challenge.

Pharmacologic challenge tests. Those who performed bronchial provocation with either methacholine or histamine were grouped with the pharmacologic challenge group because previous studies have shown little or no difference in potency for doses of histamine dihydrochloride (molecular weight, 184) and methacholine chloride (molecular weight, 196).³¹ For the analysis, all PD₂₀ values were expressed in micrograms. For the analysis, 1 μ mol was taken to equal 200 μ g, 1 mg was taken to equal 1000 μ g, and 1 mg/mL PC₂₀ was taken to equal 100 μ g.³² The carbachol data proved difficult to convert to micrograms, and the data for these 4 athletes were not included in the analysis.

Full data were available for analysis of the pharmacologic challenges in 71 subjects. Of these, 45 (63%) had positive results, and of these, 35 (77%) were taking steroids (Fig 2). Of the 26 athletes who had negative results, 15 (57%) were taking inhaled steroids. Three who had negative results to pharmacologic challenge went on to submit positive results to exercise or EVH challenge.

The median dose of the pharmacologic agent required to provoke a 20% decrease in FEV₁ was 173 μ g (0.86 μ mol [<1.7 mg/mL]). These data included those taking steroids (n = 35) and those not taking steroids (n = 10, Fig 2). These values are in keeping with the AHR of asthma.³²

The mean dose of methacholine administered to the 17 athletes with negative pharmacologic challenge results who were taking inhaled steroids was 2174 μ g (11.1 μ mol or 2.2 mg, >21.7 mg/mL), and for the 9 with negative results who were not taking inhaled steroids, it was 1142 μ g (5.5 μ mol or 1.1 mg, >11.4 mg/mL). These values would be accepted internationally as being outside the range of hyperresponsiveness³³ or for specifically identifying asthma.³⁴ Asthmatic patients taking inhaled steroids, even for prolonged periods, would normally remain responsive to these high doses of pharmacologic agent.^{35,36}

DISCUSSION

The majority (89%) of applicants were able to meet the requirements of performing or providing test results for a bronchial challenge with 3 months' notice.

Although the response to a bronchodilator would nor-

mally be the simplest challenge to confirm the AHR of asthma, only 17% of the applicants submitted an acute response to a bronchodilator. No athlete was unfairly excluded from using IBAs because the value of 12% or more of predicted FEV₁ was used for a positive bronchodilator test result rather than the more common clinical criterion of a 15% increase over baseline FEV₁.

Because most common complaints for athletes are symptoms relating to exercise,^{8,9} it would have been most appropriate to submit data relating to the exercise that provokes their symptoms. In spite of the freedom to do this, only 10 tests were stated on the form to have been performed in the field. A further 30 athletes performed laboratory exercise testing, even though the laboratory might not always be the optimal environment to demonstrate EIB in winter athletes.²¹ EVH with dry air was nominated as the optimal laboratory test simply because the ventilation achieved and sustained for 6 minutes is usually higher than can be achieved with exercise,⁹ and EVH is considered to be a sensitive test for identifying people with EIB.^{22,24,28,37} In addition, the conditions under which the athlete exercises can be simulated by altering the duration and intensity of the EVH test and the temperature of the inspired air. Although most exercise laboratories could modify their set up to perform EVH as recommended,²⁶ the time to do so was short, and testing was offered in Salt Lake City.

The advantage in using bronchodilator response, exercise, or EVH is that these tests are specific for identifying people with EIA-EIB. The advantage in using a physical stimulus for bronchial provocation is that it is likely to involve a wide variety of mediators of bronchoconstriction (histamine, leukotrienes, and prostaglandins), thus improving the chances of a positive response. By contrast, challenges with pharmacologic agents involve the inhalation of a single agonist and, for this reason, might not be the challenge of choice to demonstrate the need for IBA in the elite athlete community. Furthermore, a positive³⁸ response to a pharmacologic agent does not necessarily identify a person with EIA-EIB, and a negative response does not exclude a person with EIA-EIB.⁹ For example, there are a number of studies reporting persons with EIB who have negative challenge results to methacholine or histamine.^{9,39,40} In one study⁹ methacholine had a sensitivity of only 36% for identifying athletes with EIB. It is possible that the more potent mast cell mediators, prostaglandins and leukotrienes, are causing the EIB in these athletes who, like asthmatic patients, are likely to have mast cells near the smooth muscle.⁴¹ Furthermore, a positive test result to a pharmacologic challenge is less specific than a physical test result for the diagnosis of asthma because healthy persons with no symptoms or history of asthma can respond to these agents.^{42,43}

It is unlikely that athletes were unjustly excluded from using IBAs on the basis of their response to a pharmacologic agent. For those who had negative results and were not taking inhaled steroids, the mean dose of pharmacologic agent was 4 times that of the group with positive results. The mean value for PD₂₀ in those taking inhaled

steroids (2174 μg) who did not fulfill the criteria for a positive methacholine challenge result was 8 times the dose of those who did fulfill the criteria, many of whom were also taking inhaled steroids. This value of 8 times for PD_{20} is much higher than the 2 to 3 times increase normally reported for pharmacologic challenges before and after treatment with steroids.^{35,36,44} It should be noted that the cutoff point for defining AHR in the European Community Respiratory Health Survey is a PD_{20} of 1000 μg or less (ie, 1 mg or equivalent to a PC_{20} of 10 mg/mL).³ The value of 13.2 mg/mL used by the panel was well above this but within the range 8 to 16 mg/mL, which is considered to be borderline.

The error of 4 mg/mL instead of 13.2 mg/mL posted at the Web site did not present a problem. Only 14 submissions involved PC_{20} , and all but one was less than 3.0 mg/mL; the remaining submission had a PC_{20} of 5.13 mg/mL and was approved. Moreover, a total of 33 athletes who did not meet the strict criteria were approved by the panel for a variety of reasons. For example, some were approved on the basis of borderline challenge test results (bronchodilator response of >11% predicted, decrease on exercise or EVH challenge of >9%, or decrease on methacholine challenge of >19% at the dose set by the criteria) or a combination of medical history, borderline response, and use of medications over a long period.

Pharmacologic agents might not be the challenge of choice to demonstrate the need for IBAs in the elite athlete community. In addition to not clearly identifying persons with EIB,⁹ AHR to methacholine in cold-weather athletes³⁸ might arise from airway injury caused by conditioning large volumes of cold dry air in a relatively short time period rather than being an indicator of the airway inflammation of asthma.¹² Furthermore, there is no common operating procedure for administration and calculation of the delivered dose with a pharmacologic agent. Despite these limitations, the panel considered that they used appropriate equivalence for doses and concentrations, and they were liberal in the choice of cutoff points. In the interest of fair play, however, it should be deliberated as to whether AHR to direct-acting pharmacologic agents should be acceptable as evidence of EIB or asthma in the elite athlete in future Olympiads.

The results for the physical challenges demonstrate that half the athletes had their symptoms controlled while taking their steroids, and the other half remained hyperresponsive. These findings are in keeping with other published data.^{23,45} Athletes were not required to notify use of other medications commonly used in the control of EIB (eg, nedocromil sodium, sodium cromoglycate, and montelukast), and therefore the prevalence of EIB in those not applying to use β -agonists is not known.

There was a remarkable difference in the use of β_2 -agonists by the athletes performing different disciplines. For example, in Salt Lake City, 14.6% of the cross-country athletes used β -agonists, whereas only 2.6% of the ski jumpers did so. This difference suggests that exercise associated with high ventilation of cold air over prolonged periods might lead to more "asthma" symptoms

and more frequent use of β_2 -agonists than low-intensity exercise. The prevalence rate of EIB among skaters and cross-country skiers has been reported to be high,⁴⁶ and in keeping with this, 70% of the applications were made by those who skated or skied.

In summary, 163 sets of data on 147 subjects were submitted in support of variable airflow obstruction. Adhering to the criteria set out by the IOC, which were based on published criteria for a positive test result, 91 athletes had positive results to challenge with either a bronchodilator, a physical stimulus, or a pharmacologic stimulus. These athletes would be considered to have a medical indication to justify their use of IBAs before an event on the basis of their reversibility or their EIB or AHR consistent with a diagnosis of asthma. Five more athletes qualified with carbachol and saline provocation, bringing to 96 the number approved on the basis of objective evidence of AHR.

In all, 130 applications (5.2% of athletes) were approved, and 29 applications were rejected. This group of 29 athletes won 2 individual and 6 team medals. Athletes were tested according to standard Olympic Games selection processes. Medalists and random selections in both teams and individual events were subjected to doping controls. In all, 12 athletes had positive test results for salbutamol, with urinary levels of between 150 and 280 ng/mL. Levels less than 100 ng/mL are not reported. All 12 had received approval to inhale salbutamol.

Of relevance, after Sweden commenced a program of education of their athletes on asthma and its correct management, the percentage of Swedish Olympic athletes requesting permission to use IBAs decreased significantly in both Sydney 2000 and Salt Lake City 2002. There is a need for universal availability of similar educational programs for athletes and team physicians.

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