

Bronchial challenges in athletes applying to inhale a β_2 -agonist at the 2004 Summer Olympics

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Background: The International Olympic Committee Medical Commission required a medical justification for athletes to inhale a β_2 -agonist before an event at the Summer Games in Athens in 2004.

Objective: We sought to establish the percentage of athletes applying to use an inhaled β_2 -agonist on the basis of the results of objective tests to establish a diagnosis of asthma or exercise-induced bronchoconstriction. We also sought to compare this percentage with the percentage of athletes simply notifying the intention to use a β_2 -agonist at the previous Summer Games in Sydney in 2000.

Methods: An analysis was made of tests that measured the change in FEV₁ in response to a bronchodilator or in response to a provoking stimulus, such as exercise, eucapnic voluntary hyperpnea, hypertonic saline, or methacholine.

Results: Ten thousand six hundred fifty-three athletes competed in Athens; 4.2% were approved to use a β_2 -agonist, and 0.4% were rejected. This approval rate was 26% less than the notifications in 2000 in Sydney (5.7%). Compared with Sydney 2000, there was a significant reduction of submissions and approvals for athletes from the United States, New Zealand, Australia, and Canada and in triathlon and swimming sports.

Conclusion: The need to provide objective testing has resulted in a reduction in the number of athletes seeking approval to use an inhaled β_2 -agonist. Objective evidence has provided information for the doctor that is likely to improve the health of

the athlete because many athletes appeared to be undertreated at the time of testing.

Clinical implications: We show that documentation of airway narrowing in athletes, particularly in response to exercise or surrogate stimuli for exercise, aids in the diagnosis and management of asthma by providing evidence of bronchial hyperresponsiveness that will respond to treatment with inhaled corticosteroids and is usually associated with a reduction in respiratory symptoms on exercise. (*J Allergy Clin Immunol* 2006;117:767-73.)

Key words: Athletes, asthma, β_2 -agonist, bronchial provocation, exercise, eucapnic hyperpnea, methacholine

Objective documentation of asthma or exercise-induced bronchoconstriction (EIB) as a prerequisite for permission to use an inhaled β_2 -adrenoceptor agonist (IBA) was first introduced at the 2002 Winter Olympic Games in Salt Lake City. This policy was developed after a workshop convened in May 2001 by the International Olympic Committee Medical Commission (IOC-MC) to examine asthma, use of IBAs, and the Olympic Games. Although there is no scientific evidence to confirm that therapeutic doses of IBAs enhance athletic performance, the workshop concluded that notifications to use IBAs had increased by more than 3-fold in the Sydney Games in 2000 (5.7% of athletes) compared with the Los Angeles Games in 1984 (1.7% of athletes). With the advent of the World Anti-Doping Agency in 2000, there has been more focus by the International Olympic Committee (IOC) on the protection of the health of athletes. It is possible that some athletes receiving treatment with IBAs might have received misdiagnoses. Recent studies have suggested that exercise-related respiratory symptoms reported by elite athletes are poor predictors of EIB and therefore should not be the sole basis for prescribing medication.^{1,2} In addition, the daily use of these drugs could contribute to the development of airway hyperresponsiveness (AHR) in individuals without asthma.³ In contrast, inhaled corticosteroids might be underused in asthmatic athletes who provided notification of their intention to use an IBA at previous Olympic Games. Together with the reported development of tolerance to the protective effects of the IBAs observed in asthmatic subjects,⁴ the effects of suboptimal treatment of asthma might be potentiated.

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Abbreviations used

AHR:	Airway hyperresponsiveness
EIB:	Exercise-induced bronchoconstriction
EVH:	Eucapnic voluntary hyperpnea
FVC:	Forced vital capacity
GM:	Geometric mean
IBA:	Inhaled β_2 -adrenoceptor agonist
ICS:	Inhaled glucocorticosteroid
IOC:	International Olympic Committee
IOC-MC:	International Olympic Committee Medical Commission

In Salt Lake City the policy of objective documentation required submission of bronchial provocation test results to exercise, eucapnic voluntary hyperpnea (EVH), or methacholine or the response to a bronchodilator. The outcome was a stabilization of the notification rate, with 5.2% of athletes seeking approval compared with 5.6% and 5.7% of athletes for the 1998 Winter Games in Nagano and the 2000 Summer Games in Sydney, respectively.⁵ A similar policy was implemented by the International Amateur Athletic Federation before the 2003 World Championships in Paris.

In 2003, the IOC resolved to continue this policy for the Summer Games in Athens in 2004. The permissible bronchial provocation tests were expanded to include hypertonic saline. In this article we report the findings for the test results of the competitors who requested approval to use an IBA at the 2004 Summer Olympic Games in Athens and on the submission and approval rates relative to the notification rate at the previous Summer Olympic Games in Sydney in 2000.

METHODS

Each athlete was required to complete the mandatory application form with details about the athlete's National Olympic Committee, sport, age of onset of asthma, and current medications and known allergies, as well as data on response to bronchodilator, bronchial provocation test results, or both.

For bronchodilator testing, a positive response was defined as an increase in FEV₁ of at least 15% above the baseline value after inhalation of a permitted IBA (formoterol, salbutamol, salmeterol, or terbutaline). Details concerning the drug administered, dose, and inhalation device were compulsory, and submission of flow-volume curves was encouraged. Evidence of an increase in peak expiratory flow or forced expiratory flow through the midportion of vital capacity in response to a bronchodilator was not accepted. Although equations for predicted values were available on the IOC Web site,⁶ the testing laboratories were free to choose the predicted values, but they were asked to identify whose equations they had used.

The bronchial provocation tests recommended were as follows: exercise in the field or laboratory,⁷ EVH with dry air,⁸ hypertonic (4.5%) saline,⁹ or methacholine.^{10,11} The references for the methodology were posted on the IOC Web site in July 2003 (http://multimedia.olympic.org/pdf/en_report_732.pdf; accessed January 21, 2005).

EIB was considered to be confirmed if there was a decrease in FEV₁ of at least 10% from baseline value in response to exercise and EVH. This magnitude of change is generally recommended in guidelines from the United States¹¹ and Europe.¹⁰ The corresponding

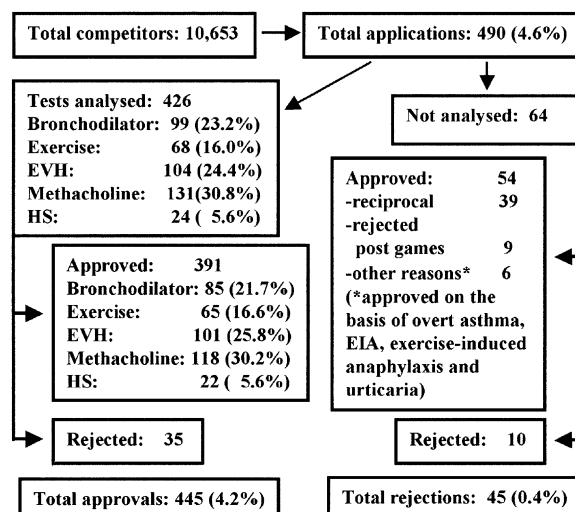


FIG 1. The total number of competitors and applications received for the Summer Games in Athens, the bronchial provocation tests performed, and the numbers approved and rejected. HS, Hypertonic (4.5%) saline; EIA, exercise-induced asthma.

value for the airway response to saline was a 15% decrease in FEV₁ after a delivered dose of 22.5 mL or less of 4.5% saline.⁹ Although encouraged, submission of graphic evidence of flow-volume curves was not made essential for these tests because it was recognized that some might have been performed in the field.

Methacholine was recommended because it is the only commercially available pharmacologic agent that has been approved by regulatory authorities for use by means of inhalation in human subjects. The criteria for a positive test response was as follows: for those taking inhaled glucocorticosteroids (ICSs), the provoking dose of methacholine to provoke a 20% reduction in FEV₁ (PD₂₀) was required to be 1320 μ g or less or 6.6 μ mol, or the provoking concentration of methacholine (PC₂₀) was required to be 13.2 mg/mL or less. For those not taking ICSs, the PD₂₀ was required to be 200 μ g or less or 1 μ mol, or the PC₂₀ was required to be 2 mg/mL or less. Graphic evidence of flow-volume curves was mandatory for this test.

Because not all forms were complete, only applications containing sufficient information for the test performed were included in the statistical analysis. Data on medication use, AHR-bronchodilator tests, and baseline spirometry were analyzed in 490 (100%), 426 (87%), and 391 (80%) applications, respectively. For tests of AHR, only applications containing results of recommended tests as posted on the IOC Web site were included in the statistical analysis. There were 64 applications that were excluded from the statistical analysis for reasons reported in the Results section of this article.

Baseline FEV₁ values are reported as percent predicted, as stated on the application form. Spirometric data and percentage change in FEV₁ in response to bronchodilator or physical challenges are reported as mean (SD) values, with the FEV₁ and forced vital capacity (FVC) presented in liters. All but a few methacholine tests were reported as either PD₂₀ in micrograms or PC₂₀ in milligrams per milliliter, and therefore for analysis, the PC₂₀ was converted to PD₂₀ in accordance with the equivalence values cited above. The values are reported as geometric means (GMs) and 95% CIs. Comparisons between the groups were made with the F test or the variance ratio test.¹² Differences in applications and approvals for use of IBAs for the Athens Games and notifications for the Sydney Games were analyzed for statistical significance in a contingency table by using the χ^2 test (2-sided *P* value, Fisher exact test when appropriate). A *P* value of .05 or less was considered statistically significant.

TABLE I. Use of inhaled β_2 -agonists and ICSs by the 490 applicants who applied to use inhaled β_2 -agonists

Concomitant use of ICSs		Inhaled β_2 -agonist			
		SABA only	LABA only	SABA + LABA	Not stated
No	168 (34.3%)	236 (48.2%)	59 (12.0%)	187 (38.2%)	8 (1.6%)
Yes	322 (65.7%)	129 (26.3%)	11 (2.2%)	22 (4.5%)	6 (1.2%)
		107 (21.8%)	48 (9.8%)	165 (33.7%)	2 (0.4%)

SABA, Short-acting β_2 -agonist; LABA, long-acting β_2 -agonist.

TABLE II. Spirometric values at baseline and percentage change in FEV₁ for applicants approved to inhale a β_2 -agonist on the basis of a test result submitted for the Athens Games

Spirometric variables	Physical*		Hypertonic NaCl		Methacholine		Bronchodilator test	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
FEV ₁ (% predicted)	164	104.6 (14.2)	22	105.3 (16.0)	111	106.3 (16.0)	85	92.6 (16.0)
FVC (% predicted)	161	114.0 (30.5)	22	114.3 (13.6)	105	110.9 (19.9)	83	109.4 (17.7)
FEF ₂₅₋₇₅ (% predicted)	105	85.7 (22.7)	21	84.6 (23.0)	75	88.0 (24.3)	66	67.8 (24.0)
FEV ₁ /FVC	159	80 (9)	22	78 (8)	110	81 (7)	82	72.4 (9.1)
% Decrease in FEV ₁	166	21.7 (12.3)	22	22.7 (8.9)	118	28.7 (8.8)	85	21.0† (8.7)

Data are presented as means $\pm$ SD (N = number of applications). Postchallenge decrease and postbronchodilator increase in FEV₁ are expressed as a percentage of the baseline FEV₁. FEF₂₅₋₇₅, Forced expiratory flow through the midportion of vital capacity.

*Exercise and EVH.

†Percentage increase in FEV₁.

RESULTS

Data on the total number of competitors and applications for permission to use IBAs, together with the distribution of bronchodilator and bronchial provocation tests and outcomes of applications are presented in Fig 1.

Outcome of applications

Approval of the use of IBAs was granted to 445 (90.8%) applicants. Of the applications not included in the statistical analysis, 39 athletes were approved without submission of tests on the basis of previous approval to use IBAs by the International Amateur Athletic Federation. Nine applications that were approved on the basis of positive bronchoprovocation test results were excluded from analysis after a careful post-Olympics analysis revealed inconsistencies with the submitted flow-volume loops suggestive of an inadequate spirometric technique. The various laboratories were advised of this problem. A further 6 applications were approved on the basis of overt asthma, exercise-induced anaphylaxis, and urticaria.

Among the rejected applications, there were 14 athletes who used ICSs concomitantly. Of the nonanalyzed applications, 6 were rejected on the basis of submission of a nonapproved test result, and 4 did not contain enough information to permit a proper assessment.

Antiasthmatic medication use

The prevalence of use of IBAs and ICSs in the applications is summarized in Table I. Inhaled corticosteroid therapy was used by 66% of the applicants, and 50% of these applicants were receiving combination therapy

with inhaled corticosteroids and long-acting β_2 -agonists. Of the applications approved on the basis of bronchodilator results, physical challenge, and methacholine challenge, 59%, 60%, and 76%, respectively, were taking ICSs.

Spirometry

Baseline lung function of athletes given approval for use of IBAs was good and well over the lower limit of normal for FEV₁ (>80% of predicted value), FEV₁/FVC ratio (>70%), and forced expiratory flow through the midportion of vital capacity (>67% of predicted value, Table II). The lowest values for these variables were seen in athletes submitting a response to a bronchodilator. Spirometric values and demographics in those who were approved were not different from values of those who were rejected.

Bronchial provocation tests

The stimulus of hyperpnea to provide evidence of EIB for approval was used by 40.4% of subjects, and 70% of the exercise or EVH tests were done in a laboratory. The percentage decrease in FEV₁ on physical challenges is presented in Fig 2.

The GM PD₂₀ FEV₁ for methacholine for all (n = 118) who were approved was 111 μ g (95% CI, 77-161), with a median PD₂₀ value of 147 μ g. Of these, 90 athletes were taking ICSs. The GM and median values for PD₂₀ FEV₁ in this group of 90 (GM, 145 μ g [95% CI, 103-205]; median, 168 μ g) was not significantly different ($P > .06$) from those of those athletes not taking ICSs (GM, 48 μ g [95% CI, 16-139]; median, 96 μ g; Fig 3).

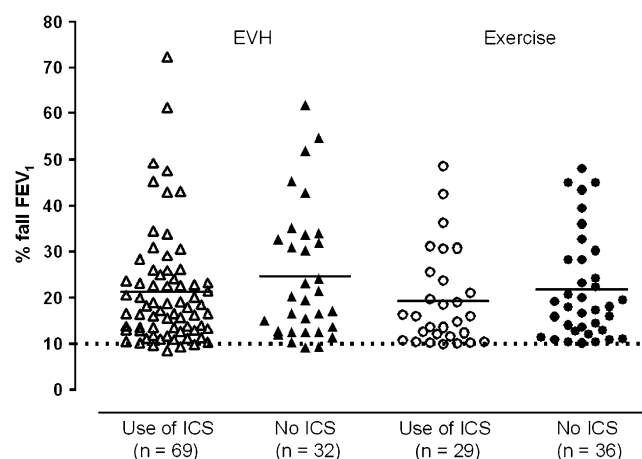


FIG 2. Individual values for the decrease in FEV_1 after exercise and EVH in athletes using ICSs and those not using ICSs. The majority of responses documented were severe enough to suggest that the athletes would benefit from better treatment of their asthma.

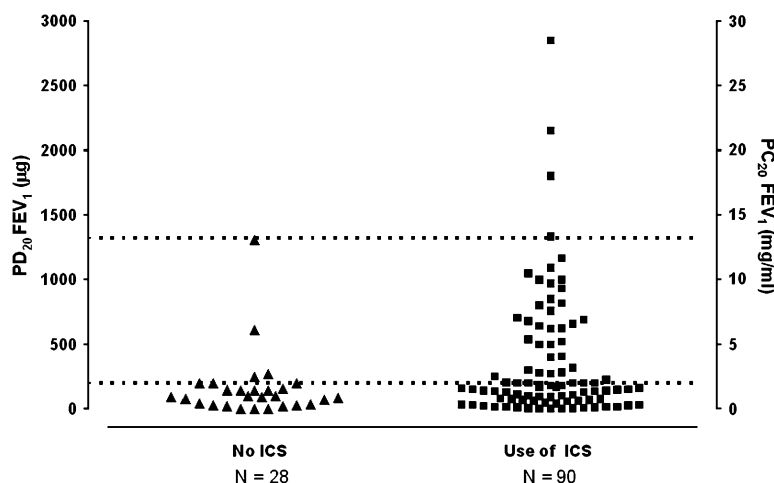


FIG 3. Individual values for the dose (PD_{20}) or concentration (PC_{20}) of methacholine required to provoke a 20% decrease in FEV_1 . Note that the majority of subjects being treated with ICSs had values within the same range as those not being treated with ICSs.

Comparison with the Sydney Games

The number of applications for permission and approvals to use IBAs in the Athens Games is summarized together with the International Study of Asthma and Allergies in Childhood rating¹³ for the 8 countries with the highest percentage of applications and the 4 countries with the lowest percentage of applications for Sydney and Athens. Compared with the Sydney Games, there was a reduction in the total number of applications (607/10,672 [5.7%] vs 490/10,653 [4.6%], $P = .0004$) and approvals (607/10,672 [5.7%] vs 445/10,653 [4.2%], $P < .0001$) for use of IBAs. Applications and approvals were unchanged for Great Britain and significantly decreased for Australia, New Zealand, Canada, and the United States (Table III). With regard to sport disciplines, more than 76% of submissions were from athletes participating in athletics that provided only 43% of the participating athletes (canoeing,

rowing, swimming, modern pentathlon, cycling, and triathlon). The submission rate for approval was significantly decreased only for the triathlon (from 24% to 12.1%, $P = .04$). Compared with approval by notification in Sydney, the approval rate in Athens was significantly lower for the triathlon (24% vs 10.1%, $P = .01$) and swimming (11.2% vs 8.5%, $P = .017$) and was unchanged for the other sport disciplines.

DISCUSSION

Overall, 4.2% of the 10,653 athletes who competed in Athens were approved for use of IBAs. Compared with the previous Summer Games in Sydney, with a notification rate for β_2 -agonist use of 5.7% of 10,672 athletes, there was a 19% reduction in applications and a 26% reduction in approvals to use an IBA in Athens. Interestingly, for the

TABLE III. Total number of athletes notifying use of an inhaled β_2 -agonist in Sydney compared with the number of applications and approvals for Athens for the 8 NOCs with the highest percentage of applications and for the 4 NOCs with the lowest percentage of applications

NOC (IR)	Sydney		Athens				
	Total	Notifications	Total	Applications	P value	Approvals	P value
Great Britain (1)	311	62 (19.9%)	264	64 (24.2%)	NS	62 (23.4%)	NS
New Zealand (2)	147	31 (21.1%)	147	10 (6.8%)	.0006	10 (6.8%)	.0006
Australia (3)	620	128 (20.7%)	469	67 (14.3%)	.006	66 (14.1%)	.005
Canada (5)	296	55 (18.6%)	262	15 (5.7%)	<.0001	11 (4.2%)	<.0001
Ireland (4)	64	9 (14.1%)	49	6 (12.2%)	NS	6 (12.2%)	NS
United States (8)	594	112 (18.9%)	534	55 (10.3%)	<.0001	50 (9.4%)	<.0001
Finland (16)	70	10 (14.3%)	53	9 (17.0%)	NS	4 (7.5%)	NS
Switzerland (NA)*	102	14 (13.7%)	98	16 (16.3%)	NS	16 (16.3%)	NS
Ukraine (NA)	231	0	245	2 (0.8%)	NS	2 (0.8%)	NS
China (51)	280	0	387	0	NS	0	NS
Korea (44)	285	0	267	0	NS	0	NS
Russia (50)	434	0	444	0	NS	0	NS

NOC, National Olympic Committee; IR, International Study of Asthma and Allergies in Childhood ranking for asthma prevalence; NS, nonsignificant; NA, not available.

*Classed as moderate on the European Community Respiratory Health Survey.

countries with a high prevalence of reported asthma symptoms,¹³ all but Great Britain and Ireland had a reduction in the percentage of athletes approved for Athens.

Applications from countries with a high prevalence of reported asthma symptoms varied, from a marked reduction for New Zealand, Australia, Canada, and the United States to unchanged results for Great Britain and Ireland and an increase for France. The reasons for these changes in the application rates are unclear. It might be a consequence of the IOC policy of objective documentation of EIB because we do not know the number of tests that were prepared for submission to the IOC. Another reason might be that the athlete could be treated with ICSs only. In Athens, but not in Sydney, athletes were required to notify the IOC if they were inhaling an ICS. Thirty-seven athletes did so, including the 14 whose applications to inhale a β_2 -agonist were rejected.

Inclusion of athletes using ICSs only, with the approval to use IBAs, results in an overall prevalence of 4.3% for asthma and EIB in the Athens Games. This is about half the prevalence of asthma reported some years ago on the basis of questionnaires and use of medications.¹⁴ The lower percentage suggests the possibility of either an overprescribing of IBAs for athletes in the past or a genuine reduction in asthma prevalence. Alternatively, the requirement for objective testing during the Athens Games might have served as a deterrent for making an application for use of β -agonists. In the absence of a requirement for objective documentation of EIB, it is likely that the prescription of IBA treatment might have been on the basis of exercise-related respiratory symptoms. We now know from recent studies that symptoms such as dyspnea, cough, wheeze, and mucus in elite athletes are not synonymous with a diagnosis of asthma or EIB.^{1,2}

The data presented in response to objective tests suggest that there is underrecognition of the severity of asthma and undertreatment in some elite athletes. This has recently

been substantiated by the report on the British Olympic teams of 2004.¹⁵ The use of such tests to investigate athletes with exercise-related symptoms will permit an evidence-based opportunity to prescribe better treatment and might improve compliance with treatment. Moreover, in those with airway inflammation consistent with asthma, the benefit of treatment with ICSs on reducing the severity of exercise-induced asthma is well established.¹⁶

Regular use of IBAs without a medical indication can become a health issue in itself. Airway responsiveness to a hyperosmolar stimulus is increased after daily use of an IBA in subjects with rhinitis but without concomitant asthma.³ The prevalence of rhinitis is high in athletes, such that the regular use of IBAs could increase the risk of development of AHR and contribute to the development of EIB.¹⁷ Possible mechanisms include desensitization of β_2 -receptors on mast cells,¹⁸ the effect of strenuous exercise on the release of mast cell mediators (eg, leukotrienes and prostaglandins) in healthy subjects,¹⁹ and alteration of the contractile properties of airway smooth muscle by repeated exposure to plasma products.^{17,20}

Compared with the 2002 Winter Games, there was a much higher percentage of athletes in the Athens Games who submitted results of an EVH test, especially from Great Britain and Denmark, with 57% and 71%, respectively. This test requires a high ventilation of dry air at a room temperature of 20°C to be sustained for 6 minutes and leads to the required rate of water loss to cause EIB.²¹ The sensitivity of this test to detect EIB is greater than tests with exercise in the field at 2°C.²²

The selected cutoff values for a positive test response to methacholine were made for several reasons. In athletes responding to a pharmacologic agent, there is a need to distinguish athletes without symptoms from those with symptoms. In the study by Langdeau et al,²³ the airway responses of sedentary control subjects to methacholine were only separated from those of athletes with respiratory

symptoms at the 2 mg/mL value. Another reason relates to the need to be specific for the condition. A PC₂₀ value of 1 mg/mL is highly specific of asthma diagnosis²⁴ in young college students. The current, although arbitrary, definitions for the 2 methacholine challenges commonly used define values between 4 and 16 mg/mL as borderline.¹¹ The cutoff value of 13.2 mg/mL or 1320 μ g for those taking ICSs is higher than the value of 1000 μ g (10 mg/mL) used in the European Respiratory Health Survey to identify AHR.²⁵

It is of interest that there was no significant difference between the PD₂₀ values for athletes with and without ICS treatment. This might be related to the duration of ICS treatment. Alternatively, this observation could imply that the higher cutoff point of a PD₂₀ of 1320 μ g for those taking ICSs is probably unwarranted. With a 95% CI of 205 μ g, our data suggest that 400 μ g (4 mg/mL) might be acceptable as the cutoff point in the future, even for those taking ICSs. This is in accordance with other studies, in which PC₂₀ values usually remain at less than 4 mg/mL in ICS-treated subjects.^{26,27} A lower cutoff point for methacholine for those taking ICSs would provide an acceptable balance between sensitivity and specificity to identify currently active asthma and potentially avoid health-related problems arising from the use of ICSs.²⁸ ICSs are not very effective in modifying AHR to methacholine in elite athletes.²⁹ Furthermore, they inhibit apoptosis of neutrophils,³⁰ the dominant cell in the airways of athletes.³¹

What are the implications for the future? If it is generally accepted by team doctors that objective measurement to identify asthma and EIB is useful and contributes to improved health in the athlete, then the policy will have served its purpose. The report on the responses of British athletes with a past history of EIB or symptoms of EIB or asthma tested for the 2004 Summer Games supports this suggestion.¹⁵ Few athletes would have an interest in taking medication regularly that was not having a beneficial effect on their "asthma" symptoms. Even fewer are likely to want a misdiagnosis of asthma on the public record. Asthma is still an impediment for entry into some occupations, and an unsubstantiated diagnosis could become an unexpected problem in the future for the athlete.

The new joint American Thoracic Society–European Respiratory Society guidelines for response to bronchodilator recommends a significant response to bronchodilator as a 12% increase above baseline value, and this value will be adopted for use in the future.³² As with the 1991 American Thoracic Society statement,³³ the new guidelines³² for bronchodilators continue to acknowledge that "when using percent change from baseline as the criterion, most authorities require 12-15% increase in FEV₁ and or FVC as necessary to define a meaningful response," and we chose the less ambiguous value of 15% of baseline value.³⁴ There were 5 persons who were not approved who had a value between 12% and 14.9%, but for some of these, there were other reasons as well for nonapproval. Two of these 5 athletes won medals.

Although some investigators suggest that a cutoff point of a 7% or greater decrease in FEV₁ in response to exercise is appropriate for elite athletes,^{1,35} this lower value was

considered unacceptable because of the inherent variability in repeated measures of FEV₁.³⁶ Only 6 applicants were rejected on the basis of their response to physical challenge, and if the cutoff value had changed to greater than 8%, only one more athlete would have been approved.

Finally, the hyperosmolar aerosol test (4.5% saline) was included because this type of challenge provides an inexpensive surrogate for hyperpnea to identify EIB.^{37,38}

In conclusion, there was a significant reduction in the use of IBAs in the percentage of athletes competing in Athens relative to Sydney. The reduction was most obvious in the applications from countries with a high reported prevalence of asthma symptoms. This reduction is encouraging because there are health-related issues to using asthma drugs, some that are well known, such as the unwanted side effects of steroids,²⁸ and others that are only now being appreciated through the study of genetic polymorphisms.³⁹ With few exceptions, the applications were of high standard, and the data presented probably reflect the prevalence of asthma in elite athletes performing summer sports. This prevalence is significantly lower when compared with the values reported on the basis of symptoms and use of medication alone. The respiratory symptoms on exercise of elite athletes are similar to those of patients with classical asthma. For this reason, many might be prescribed medication on the basis of symptoms alone when objective measurement would allow a more specific diagnosis to be made and a healthier outcome to be achieved.

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Correction

With regard to the June 2004 article entitled "Response to inhaled albuterol during nocturnal asthma" (2004;113:1058-62): Figure 1 has incorrect labeling on the y-axis. Instead of 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 100, the numbers should be 40, 50, 60, 70, 80, 90, 100, respectively. A corrected version of the figure appears below.

