

News and commentaries

Diagnosis of asthma and permitted use of inhaled β_2 -agonists in athletes

The prevalence of asthma and bronchial hyperreactivity has been reported to be higher in athletes than in the general population. This has also been related to reported asthma in order to obtain permitted use of β_2 -agonists, whose assumption in athletes is ruled by anti-doping regulations. The paper addresses the issue whether the recently established and evaluated rules of the International Olympic Committee on tests and procedures for diagnosis of asthma in athletes and permitted use of β_2 -agonists are consistent with an adequate diagnosis and management of asthma according to international guidelines.

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The high prevalence of asthma in athletes

Asthma has a very high prevalence in athletes, ranging from 3.7 up to 22.8% in the systematic review of Helenius and Haahtela (1). Prevalence rates reported in different studies largely vary, depending on the type of sports and criteria used for diagnosis. However, the risk for asthma in athletes seems to be significantly higher than in the normal population, particularly when risk factors such as atopy and exercising are combined: in fact, the risk for asthma in atopic swimmers is 97-fold the risk of non-atopic normal subjects (2). Certainly, a mixed type of eosinophilic and neutrophilic inflammation correlating with clinical asthma and bronchial hyperreactivity has been reported in swimmers (3), ice-hockey players (4) cross-country skiers (5), and endurance athletes (6). Interestingly, eosinophilic airway inflammation, clinical asthma and bronchial hyperresponsiveness attenuate or disappear in many of the swimmers who stop active training, while they usually

persist or aggravate after a follow-up period of 5 years of persisting active training (7).

Moreover, studies performed on comparable population samples indicate that asthma in athletes is on the increase, as its prevalence was 9.7% in US Olympic athletes in 1976 and 16.7% in 1996 (8).

Tests and procedures required by the International Olympic Committee for diagnosis of asthma

Anderson and co-workers (9) evaluated the application of tests and procedures required by the International Olympic Committee (IOC) to diagnose asthma in athletes and 'to identify those athletes who are justified, on medical grounds, in taking inhaled β_2 -agonists (IBAs) before a sporting event'.

In the accompanying editorial to the paper (10), John M. Weiler raises the question why Olympic athletes should

provide 'objective evidence' of their asthma to be permitted to take IBAs, in view of the fact that permitted IBAs have not been proved to enhance athletic performances. We, on behalf of the Interest Group on Allergy, Asthma and Sports of the European Academy of Allergology and Clinical Immunology, addressed the same question in an unpublished letter to the IOC at the time the new anti-doping rules were published in the World Anti-Doping Agency web-site (<http://www.wada-ama.org>). This was essentially dictated by the concern – as we wrote – that 'the need of documentation should not come in conflict with optimal treatment guidelines of asthmatic patients'. Certainly, the requirement of 'objective evidence' of asthma did not result in a significant difference in the percentage of athletes taking IBAs, as the 5.2% relative to the 2002 Winter Olympics of Salt Lake City (when the new rules were firstly applied) well compares with the 5.6% of the 1998 Winter Olympics of Nagano and the 5.5% of the 2000 Summer Olympics of Sydney (when just notification of asthma from a physician and no 'objective evidence' was required) (11, 12).

But the major question to be addressed is whether tests required by the IOC are suitable to identify asthmatic athletes.

The new IOC regulations for Salt Lake City Olympic Games required athletes to provide evidence of one of the following to be allowed to take IBAs:

1. A 12% or greater increase of the predicted value of FEV₁ after administration of a permitted IBAs.
2. A 10% or greater decrease in FEV₁ after challenge with physical stimuli such as exercise in the field or laboratory or eucapnic voluntary hyperpnea (EVH).
3. A methacholine PD₂₀ less than 1 µmol (200 µg) or a PC₂₀ less than 2 mg/ml; for those on topical steroids the methacholine PD₂₀ has to be less than 6.6 µmol (1320 µg) or the PC₂₀ less than 13.2 mg/ml (listed as 4 mg/ml by mistake in the IOC web-site).

The available data do not allow to determine how specific and sensitive the above-mentioned tests and thresholds are for diagnosis of asthma in athletes. In fact, only the percentages of applicants who could provide test results (89%) and of positive responses (65%) are given in the paper of Anderson et al. (9). On the contrary, no data are available regarding the prevalence of asthma in the athletes participating in the Salt Lake City Olympics or about the bronchial response of nonasthmatic athletes as well as of athletes with asthma who – for different reasons (possibly including the failure to prove a positive response to tests) – did not apply to IOC.

Further studies are therefore recommended to document whether the IOC tests and thresholds are sensitive enough for the diagnosis of asthma in athletes. The following considerations raise some doubts about this:

1. In more recent studies of Olympic athletes, the prevalence of asthma is well above the 5.2% found by applying the criteria for IBAs use in Salt Lake City, being 21.9%

at the 1998 Nagano Winter Olympics according to Weiler and Ryan (11) and 21.9% or 10.9% at the 2000 Sydney Olympics according to Katelaris et al. (12) and Lapucci et al. (13), respectively.

2. Of the 165 applicants, only 147 (89%) provided the data required by the IOC, and among these only 91 (65%) had a positive response to either a bronchodilator, a physical challenge, or a pharmacological challenge with methacholine or histamine.
3. Bronchodilator response was positive in 13 of 28 athletes, as defined by a change in FEV₁ larger than 12% of predicted. Although Anderson and co-workers support the IOC requirement as being the most suitable threshold to define 'an unequivocal response to bronchodilator', it may lead to gross underestimation. For example, a subject with predicted FEV₁ of 5.00 l would be required to respond to bronchodilator with a 0.60 l increase. If this subject has a measured FEV₁ of 4.5 l and an increase by 12% of this value, i.e. 0.54 l, the response would be defined as negative by the IOC, but positive according to the American Thoracic Society (ATS) criteria (14). So, criteria for airway reversibility in athletes should be different and more restrictive than in the general population?
4. The sensitivity of bronchial responses to physical stimuli has been shown to be low in asthmatics, especially on inhaled steroids (9).
5. The values of PD₂₀ required for methacholine challenge to be defined as positive are very restrictive. In epidemiological studies, a PD₂₀ of 16 µmol methacholine is often used as threshold for bronchial hyperresponsiveness. In asthmatic subjects, bronchial hyperresponsiveness is often considered as severe with values of PD₂₀ below 1 µmol, moderate between 1 and 4 µmol and mild between 4 and 16 µmol. The thresholds of 1 µmol and of 6.6 µmol for athletes using topical steroids can well identify moderate and severe asthmatics but might fail to identify mild asthmatics or asthmatics under control with treatment. In these subjects IBAs are just considered among the drugs of choice by asthma guidelines (15). In addition, if the scope of the challenge is to identify nonasthmatic subjects among those with a pretest probability to have asthma greater than in the general population, a high threshold should be used. In other words, for this purpose one should look for sensitivity and not specificity of the test.

The role of metacholine challenge and other provocation tests for the diagnosis of asthma in athletes

Anderson and co-workers state that challenges with pharmacological agents are not considered as the challenges of choice to demonstrate the need for IBAs and their acceptability as evidence of asthma in the elite

athletes in future Olympiads is questionable. The statement is based on the quotation (16) that a positive response to a pharmacological agent does not necessarily identify a person with exercise-induced asthma (EIA)/exercise-induced bronchoconstriction (EIB) and on the claim that there is no common operating procedure for administration and calculation of the delivered dose with a pharmacological agent.

We fully agree that the results of methacholine challenge do not necessarily overlap with those of exercise challenge, but a reason for discrepancy may be merely due to the definitions of positive response used. Generally, a 10% decrease in FEV₁ is assumed to be a sure sign of EIB while a 20% is required for methacholine. It is quite unclear why a given change in FEV₁ is significant for one stimulus and insignificant for another. Apart from this, it is unquestionable that there are subjects with clear asthma who do not show EIB, but instead dilate during exercise. So the factor limiting their exercise performance is not EIB but rather the airway caliber at the start of exercise. These subjects would not be recognized as positive by either exercise or hyperventilation tests, yet they would benefit from IBAs. So, if the goal is the diagnosis of asthma and not of EIA/EIB, there is no doubt that methacholine challenge, performed with the available standard procedure (14) and with adequate thresholds, is the test of choice, largely applied by the scientific community to prove airway hyperreactivity. *De facto*, this was the test most frequently reported in the applications to IOC: 57 cases vs 28 for bronchodilator response, 40 for exercise test, and 17 for EVH. In fact, the EVH test is not easily performed in all laboratories and is well accepted by all athletes.

Therefore, in view of the relevant positioning the methacholine challenge has in the diagnoses of bronchial hyperreactivity and asthma, we strongly recommend that this shall also be considered by the IOC in establishing criteria for the diagnosis of asthma in athletes participating in future Olympics.

The need for a correct diagnosis and management of asthma in athletes

Finally, we would like to express two major concerns in relation to the current regulations for the diagnosis of asthma in Olympic athletes:

1. The risk of underdiagnosis of asthma. Apart from considerations already expressed about thresholds for methacholine challenge for the diagnosis of mild asthma, it should also be emphasized that the WHO ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines (17) provide evidence that a large proportion of rhinitis subjects have subclinical bronchial obstruction and recommend that all rhinitic patients should be studied for asthma. The prevalence of allergic rhinitis among Olympic athletes is high (18.8% according to Lapucci et al. (13), 29.0% according to Katelaris et al. (12). Apparently, tests recommended by IOC regulations are not sensitive enough to document subclinical bronchial obstruction in rhinitic athletes.
2. The risk of an inadequate management of asthma. In fact, as topical steroids often inhibit responses to bronchial challenges, there is the risk that athletes discontinue ongoing treatments with these drugs to prove their asthma and justify the use of IBAs.

Moreover, the use of IBAs by itself should not be viewed as an 'illegal' or 'wrong' attitude. Anderson and co-workers in their study note that after Sweden commenced a program of education of their athletes on asthma and its correct management, the percentage of Swedish Olympic athletes asking for permission to use IBAs decreased significantly. We agree that educational programs for athletes and team physicians, like those of the Swedish, are highly recommended, just because they help understand the role of controller drugs in keeping asthma under remission (even without using IBAs or other reliever drugs on demand), but certainly not because the use of IBAs should be discouraged.

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