Review article

Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA\textsuperscript{2}LEN*

Aim: The aims of part II is to review the current recommended treatment of exercise-induced asthma (EIA), respiratory and allergic disorders in sports, to review the evidence on possible improvement of performance in sports by asthma drugs and to make recommendations for their treatment.

Methods: The literature cited with respect to the treatment of exercise induced asthma in athletes (and in asthma patients) is mainly based upon the systematic review given by Larsson et al. (Larsson K, Carlsten KH, Bonini S. Anti-asthmatic drugs: treatment of athletes and exercise-induced bronchoconstriction. In: Carlsten KH, Delgado L, Del Giacco S, editors. Diagnosis, prevention and treatment of exercise-related asthma, respiratory and allergic disorders in sports. Sheffield, UK: European Respiratory Journals Ltd, 2005:73–88) during the work of the Task Force. To assess the evidence of the literature regarding use of \( \beta_2 \)-agonists related to athletic performance, the Task Force searched Medline for relevant papers up to November 2006 using the present search words: asthma, bronchial responsiveness, exercise-induced bronchoconstriction, athletes, sports, performance and \( \beta_2 \)-agonists. Evidence level and grades of recommendation were assessed according to SIGN criteria.

Results: Treatment recommendations for EIA and bronchial hyper-responsiveness in athletes are set forth with special reference to controller and reliever medications. Evidence for lack of improvement of exercise performance by inhaled \( \beta_2 \)-agonists in healthy athletes serves as a basis for permitting their use. There is a lack of evidence of treatment effects of asthma drugs on EIA and bronchial hyper-responsiveness in athletes whereas extensive documentation exists in treatment of EIA in patients with asthma. The documentation on lack of improvement on performance by common asthma drugs as inhaled \( \beta_2 \)-agonists with relationship to sports in healthy individuals is of high evidence, level (1+).

Conclusions: Exercise induced asthma should be treated in athletes along same principles as in ordinary asthma patients with relevance to controller and reliever treatment after careful diagnosis. There is very high level of evidence for the lack of improvement in athletic performance by inhaled \( \beta_2 \)-agonists.

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Key words: asthma; allergy; bronchial responsiveness; doping; exercise-induced asthma, sports.

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Treatment of asthma has been extensively covered in international guidelines over the last 15 years (1–3). The guidelines consider many aspects of asthma, but not the specific situation in the athlete, particularly regarding the use of reliever and controller treatment (1). When choosing treatment for athletes compared with the ordinary asthma patient, some additional factors should be considered. For the top athlete it is important not only to control symptoms of asthma and prevent progression, but it becomes equally important to stop disease processes to reduce their impact upon sports performance, often performed under extraordinary circumstances. Therefore, the prescribed treatment should have an optimal effect upon asthma, but also the possibility of potential side effects of treatment should be carefully considered.

Based upon work from the present Task Force, Larsson et al. (4) recently presented a systematic review on the treatment of athletes and exercise-induced bronchoconstriction (EIB), which included only randomized double-blind placebo-controlled or drug-comparison studies with eight subjects or more. Treatment of EIB has been extensively studied in asthmatic subjects over the last 30 years, but not so in athletes with EIB. Thus, it is not known whether athletes with EIB or ‘sports asthma’ respond similarly to subjects with classical allergic or nonallergic asthma. However, there is no evidence supporting different treatment for EIB in asthmatic athletes and nonathletes (4). The same principles as for asthma management in general may be applicable to exercise-induced asthma (EIA): controller (anti-inflammatory) and reliever (premedication before exercise and treatment of symptoms) therapy.

### International regulations for use of asthma drugs in sports

In order to be allowed to use the most common asthma drugs in relationship to international competitive sports, it is necessary to obtain permission to do so from World Anti-Doping Association (WADA) or International Olympic Commission (IOC) medical committee. IOC Medical Commission gives the necessary permission in relationship to Olympic Games; WADA is responsible for other international competitive sports. IOC set up restrictions for the use of inhaled β2-agonists already in 1993. These have later been modified repeatedly. It is necessary to apply before the competitions. During the previous Olympic Games in Torino 2006, the following rules were applied by the IOC:

One of the following objective tests must be satisfied:

a) Positive bronchodilator test: ≥12% increase in forced expiratory volume (FEV) 1% predicted after inhalation of permitted β2-agonist.

b) Exercise challenge or eucapnic voluntary hyperpnoea with ≥10% fall in FEV1.

c) Metacholine: PC20 < 4 mg/ml or PD20 ≤ 2 μmol in steroid naive subjects. If inhaled steroids ≥3 months: PC20 FEV1 ≤ 6.6 mg/ml or PD20 ≤ 13.6 μmol. It is mandatory to submit laboratory worksheets to have metacholine bronchial provocation tests accepted.

d) WADA has used the following rules.

Topical steroids: There are presently no restrictions for topical use on skin, nose and eye. However, for the use of inhaled corticosteroids there are restrictions. Application (therapeutic use exemption, TUE) is needed both for inhaled corticosteroids and inhaled β2-agonists. Inhaled β2-agonists are also not permitted out-of-competition. For the use of inhaled β2-agonists WADA has now declared the following: ‘It is preferred to leave to the professional judgement of the physician the medical conditions under which these drugs are to be prescribed’ (explanatory notes 2006). The team manager and team doctor are also responsible when an athlete is caught in doping. A concentration of urinary salbutamol ≥1000 ng/l is considered an adverse analytical finding regardless of the grant of any form of TUE.

For the physician-treating athletes it is necessary to know the regulations given by WADA and IOC, Medical Commission. The regulation is often changed to some extent, and the physician should keep himself up to date by referring to the website of WADA and IOC.

Table 1 shows the present permitted and prohibited anti-allergic and anti-asthma drugs in relationship to the TUE regulations.

### Controller treatment of EIA

A thorough assessment of the treatment of EIA in the athlete is discussed by Larsson et al. (4). A brief summary is given here. It should be emphasized that in general the ordinary international guidelines for asthma should be followed. However, specific concerns for the athlete have been mentioned.

**Inhaled corticosteroids**

Optimal treatment of asthma aiming at reducing bronchial hyper-responsiveness (BHR) and maintaining control of disease activity is important for mastering EIA and enabling the athlete to participate freely in physical training, sports activity and competitions. Anti-inflammatory treatment by inhaled corticosteroids is presently the most important and effective management for asthma and for mastering EIA. Already after 1 week of regular treatment with inhaled budesonide in children EIA improved significantly, but to obtain a significant reduction also in the fall of maximum
A notification for the use of inhaled corticosteroids and an application for the use of any of the following inhaled bromide, topically ipratropium bromide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WADA rules</th>
<th>IOC rules</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-histamines</td>
<td>Permitted</td>
<td>Permitted</td>
<td></td>
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<tr>
<td>Anti-leukotrienes</td>
<td>Permitted</td>
<td>Permitted</td>
<td></td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Prohibited in competition, require TUE approval</td>
<td>Prohibited in competition, require TUE approval</td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>Require an abbreviated TUE approval</td>
<td>Needs notification</td>
<td></td>
</tr>
<tr>
<td>Oral β-agonists</td>
<td>Prohibited</td>
<td>Prohibited</td>
<td>Documentation of bronchial hyper-responsiveness, reversibility to inhaled bronchodilators, positive exercise test, eucapnic hyperventilation test or cold air challenge must be documented*</td>
</tr>
<tr>
<td>Inhaled salbutamol, terbutaline, formoterol, salmeterol</td>
<td>Require an abbreviated TUE approval</td>
<td></td>
<td>A concentration of salbutamol &gt;1 μg/ml in urine is considered an adverse analytical finding unless proven due to therapeutic use of inhaled salbutamol</td>
</tr>
<tr>
<td>Ephedrine, methylephedrine, pseudoephedrine</td>
<td>Prohibited in competition, pseudoephedrine permitted</td>
<td>Prohibited in competition, pseudoephedrine permitted</td>
<td>Ephedrine and methylephedrine concentration in urine &gt;10 μg/ml represents an adverse analytical finding</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Permitted</td>
<td>Permitted</td>
<td>Immunotherapy should not be performed before or after physical exercise</td>
</tr>
<tr>
<td>Inhaled or nasal ipratropium bromide</td>
<td>Permitted</td>
<td>Permitted</td>
<td></td>
</tr>
<tr>
<td>Olsidum cromoglycate</td>
<td>Permitted</td>
<td>Permitted</td>
<td></td>
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</tbody>
</table>

* A notification for the use of inhaled corticosteroids and an application for the use of any of the following inhaled β2-agonists must be made to the medical committee of the International Olympic Commission (IOC) at the latest 2 weeks before the Olympic Games. For the last Olympic Games in Torino a website was created where an on-line application could be made (http://www.olympic.org/uk/games/torino/atue/index_uk.asp). To be permitted to use inhaled salbutamol, terbutaline, salmeterol or formoterol at least one of the following requirements had to be met: (i) either a positive bronchodilator test with an increase in forced expiratory volume in 1 s (FEV1) of ≥10%; (ii) or a positive methacholine bronchial challenge test with a PC20 ≤ 4 mg/ml or a PD20 ≤ 2 μmol in steroid naïve athletes (without inhaled steroids for the last three months) or in athletes using inhaled steroids with a PC20 ≤ 6.6 mg/ml or a PD20 ≤ 13.6 μmol. The WADA-prohibited list of drugs in sports is usually updated and changed every year, and also the IOC regulation may be changed before the next Olympic Games. The physician treating athletes should keep orientated about these regulations.

### Expiratory Flow25–75 (MEF25–75)

Further treatment for 3–4 weeks was necessary (5) (evidence level, EL: 1 +). Inhaled corticosteroids increased the protective effect of the inhaled β2-agonist, terbutaline, given before physical activity (5) (EL: 1 +). Attenuation in exercise-induced decrease was also seen only after 1 week of therapy with inhaled ciclesonide at doses greater than 40 μg. However, maximal attenuation in exercise response continues to increase at doses greater than or equal to 200 μg, even after 3 weeks of therapy (6). Inhaled corticosteroids improve EIA more rapidly than BHR measured by methacholine bronchial provocation. After 2–3 months of treatment with inhaled corticosteroids in children, the anticipated improvement of EIA was reached (7) (EL: 1 +), whereas ongoing improvement of methacholine-induced bronchial responsiveness, was observed for up to 22 months (8). In children with mild asthma, a low dose of inhaled corticosteroids significantly improved EIA over a 3 months’ treatment period (9) (EL: 1 +).

### Few Studies on the Effect of Inhaled Corticosteroids

Few studies on the effect of inhaled corticosteroids on asthma and BHR have been performed in athletes, and no studies in top-athletes. Sue-Chu et al. (10) performed a randomized placebo-controlled study in 25 young competitive skiers with asthma-like symptoms or bronchial hyper-responsiveness from a specialized high-school for skiers giving budesonide 400 μg twice daily or placebo over a period of 10–32 weeks over the competitive season. They could not find any effect on cellular inflammation in the bronchial mucosa or tenascin expression from bronchial biopsies, nor any cellular differences in broncho-alveolar lavage (BAL) fluid between active and placebo treatment. No effect was found on bronchial hyper-responsiveness. However, with few subjects in each group, and with only five subjects with reported bronchial hyper-responsiveness, the study may have been underpowered (EL: 2 –).

Inhaled corticosteroids have both systemic and local side-effects that should be taken into account particularly in relationship to sports and EIB. Of particular concern are adrenal suppression, growth retardation in children and adolescence and reduction in bone density especially with some inhaled corticosteroids (11). Adrenal suppression is rare, but known to occur by use of high doses of inhaled corticosteroids. Priftis et al. (12) found this in 15 out of 72 children on low-to-moderate doses of inhaled budesonide (EL: 2 –). As a result of adrenal suppression hypoglycaemic convulsions were
reported in several case reports, especially in patients using fluticasone dipropionate (13–16) (EL: 3).

Priftis et al. (12) also reported a reduced height velocity SD score. Reduction in growth was not reported in the same children who demonstrated adrenal suppression (EL: 2+). A low reduction in growth, often occurring in the initial stage of using inhaled steroid has been noted by several authors (17–19) whereas others have not been able to confirm this finding (20, 21).

Reduction in bone mineral density has been noted as another possible systemic side effect of inhaled corticosteroids (22, 23). Although rare, this possibility should be considered, especially when treating asthmatic women practicing endurance sports, as female marathon runners have been noted to be at particular risk for osteoporosis.

Leukotriene antagonists

Leukotriene antagonists (LA) of both the main categories (leukotriene synthesis inhibitors and leukotriene receptor antagonists) reduce EIA. One single dose of LA protects significantly better against EIA than placebo in adults (24) (EL: 1+), and 2 days treatment with a leukotriene synthesis inhibitor (zileuton) caused a protection of 40% against EIA (25). Two-days use of montelukast, a leukotriene receptor antagonist, significantly reduced EIA both in children and adults (26, 27) (EL: 1), as was also found after 1 week of treatment in children (28) (EL: 1). Comparison studies with the long-acting inhaled β2-agonist, salmeterol, demonstrated that the protection against EIA obtained by montelukast after 3 days, remained unchanged after 8 weeks of treatment in adults, whereas tolerance to salmeterol had developed after this time (29) (EL: 1+). The lack of development of tolerance to montelukast for EIB was recently confirmed also in children by de Benedictis et al. (30) for a 4-week period, but in their study several patients did not respond to montelukast (EL: 1). Also for inhaled steroids lack of response has been reported in some although fewer patients (31).

In athletes only few studies have been performed for the effect of montelukast on EIB. Helenius et al. (32) could not find any effect upon asthma-like symptoms, BHR, exhaled nitric oxide and sputum cell parameters in a randomized placebo-controlled cross-over study in 16 ice-hockey players with EIB (EL: 1). On the other hand, Rundell et al. (33) in their randomized double-blind placebo-controlled cross-over study reported that montelukast gave protection against EIB and lung function reduction after eucapnic hyperventilation in most, but not all of the 11 physically active subjects with EIB (EL: 1+). A Norwegian double-blind randomized cross-over study in 16 adults with EIB demonstrated that montelukast improved their physical performance (running time and Borg score for exhaustion), but without altering gas exchange parameters (34). It may be concluded that montelukast has a protective effect on most athletes with EIB, but not in all (EL: 1).

Disodium cromoglycate and nedocromil sodium

The other anti-inflammatory asthma drugs, which have been used for many years, are disodium cromoglycate (DSCG), and the related nedocromil sodium (35). The most commonly reported beneficial effect of DSCG and nedocromil sodium on EIA is the protection when taking the drugs immediately before exercise (36) (EL: 1+). Recent data demonstrate that 40 mg of DSCG inhibits the increase in prostaglandins in response to an osmotic stimulus, and this may be the mode by which it protects against EIB (37).

Reliever treatment of EIA

Treatment before exercise

Several different pharmacological agents administered before exercise protect against EIA. The most common group of therapeutic drugs taken before physical exercise is inhaled β2-agonists, but DSCG or nedocromil sodium and more rarely inhaled ipratropium bromide are also used.

β2-agonists

The class of drugs most studied in this respect, and demonstrated to be effective against EIB, are the inhaled β2-agonists. Larsson et al. (4) cited 39 trials and for a detailed discussion this report can be referred to. By the 1970s it was established that orally administered β2-agonists offered poor protection against EIB compared with the same inhaled drug (38, 39) (EL: 2). Furthermore, it was shown that the short-acting inhaled β2-agonists have an almost immediate effect on EIB, with a maximum effect 20 min after inhalation. The recommended dose of inhaled salbutamol is 0.2–0.4 mg which corresponds to an inhaled dose of 0.5–1 mg of terbutaline. The effect may still be observed 3 h after inhalation, but disappears after 4 h (40). Anderson et al. (41) compared the short-acting inhaled β2-agonist salbutamol with the long-acting salmeterol and found salmeterol to be active against EIB from 30 min to 6.5 h after inhalation whereas salbutamol was as effective as salmeterol 30 min after, but not so from 2.5 to 6.5 h after inhalation (41). Another study demonstrated an effect of inhaled salmeterol in children with EIB lasting up to 10–12 h after inhalation (42). Formoterol, another long-acting inhaled β2-agonist has a similar long-lasting protective effect on EIB and the added benefit of having an onset of protective effect as rapid as salbutamol or terbutaline (43).
Even if the inhaled β₂-agonists have an important protective effect on EIB, EIB is frequently not completely abolished, as exemplified by one study with a maximum reduction in FEV₁ after exercise of 18–19% after inhaling salmeterol compared with 30% after placebo (42).

It has been observed that after regular use of long-acting inhaled β₂-agonists, the protective effect on EIB is somewhat reduced, and this is referred to as tolerance. This tolerance development has been shown after 4 and 8 weeks of regular treatment of salmeterol (29, 44, 45). Whether the tolerance development has any clinical significance, is uncertain, but cannot be ruled out in athletes. However, use of the drugs three or less a week did not result in development of tolerance (46). The problem of tolerance and down-regulation of β2 receptors on mast cells and its relevance to EIB has recently been reviewed (47).

It may be of interest that recently another concept has been developed for treating asthma, namely to use a combination of inhaled corticosteroid with the long-acting β₂-agonist formoterol both for exacerbation and for the regular therapy. However, the regular use of long-acting inhaled β₂-agonist for EIB alone should presently be considered with some concern. For treatment of asthmatic athletes the use as needed of such a combination may be of interest, and studies in this field should be performed. First, the aforementioned problem with development of tolerance should be considered. The development of tolerance to most of the effects of inhaled β₂-agonists has been described (48); it has also been discovered for the protection against EIB (44), but it is not as well recognized that this tolerance is not prevented by inhaled corticosteroids (44). Second, a systematic review suggested an increased risk of severe cardiovascular side effects in patients who uptake long-acting inhaled β₂-agonists on a regular basis (49).

Third, Food and Drug Administration (FDA) issued an alert in November 2005 against the regular use of inhaled long-acting β₂-agonists, referring to the results from, at that time, an unpublished randomized case-control study on the effects of inhaled β₂-agonists (50). This led to a search for evidence and Salpeter and Salpeter (51) published a systematic review on severe side effects and deaths in patients who uptake inhaled β₂-agonists regularly. This systematic review has later been criticized (52). Although the question about the long-term safety of inhaled β₂-agonists is still unresolved, these different studies should be taken into consideration when treating athletes and other patients with inhaled β₂-agonists. It is recommended not to provide long-acting β₂-agonists without simultaneously giving inhaled steroids.

**Ipratropium bromide**

Ipratropium bromide may be effective against EIA in some but not usually the majority of patients (53, 54) (EL: 1). An additional protective bronchodilator effect may be obtained when ipratropium bromide is added to an inhaled β₂-agonist (55). Freeman et al. (56) reported that ipratropium bromide improved lung function both before and after exercise in asthmatic men as compared with nonasthmatic men, but had no effect on cardiorespiratory or cardiovascular parameters of performance after a step-wise cycle exercise test.

**Recommendations for the treatment of EIA in athletes**

Treatment of EIA should follow the general guidelines for treating asthma. Reports of symptoms of EIA and other chronic respiratory symptoms in athletes should be verified by objective diagnosis by standardized exercise test or other measures of direct or indirect BHR, as there are several important differential diagnoses for EIA.

1. EIA without other clinical manifestations of asthma may be best controlled by the use of short-acting inhaled β₂-agonists taken 10–15 min before exercise (grade of recommendation, GR: A).
2. EIA combined with other asthma symptoms may best be controlled by anti-inflammatory treatment either alone or in combination with reliever treatment. Inhaled corticosteroids in low-to-moderate doses are the preferred treatment (GR: A).
3. In certain circumstances (i.e. in asthmatic athletes with obvious EIA, but not satisfying the requirements set up by WADA and/or IOC Medical Commission for using inhaled corticosteroids) LA alone may be tried, but should be clearly followed up for assessment of treatment effect (GR: B).
4. Without complete control with inhaled corticosteroids either adding
   a) short-acting inhaled β₂-agonists (GR: A) before exercise or
   b) long-acting inhaled β₂-agonists may be tried (GR: A)
   c) An LA can be tried in addition to inhaled corticosteroids (GR: A).

Be aware of the possibility of developing tolerance to inhaled β₂-agonists used on a regular basis (GR: B), and the reports of nonresponse in some to patients to LA (22) (GR: B).

5. In some patients, the combination of inhaled corticosteroids, long-acting inhaled β₂-agonists and LA may be needed to control exercise-related symptoms.
6. In addition, sodium cromoglycate or nedocromil sodium (GR: A) or ipratropium bromide (GR: B) may be tried for EIA after individual assessment, either alone or in addition with other treatments.

It is to be noted that a lack of response to treatment may be because of misdiagnosis which requires reassessment of the diagnosis of EIA. Another cause of lack of response is the possible lack of compliance with
treatment. This should be taken into consideration as well as inhaler technique.

Effect of asthma drugs upon performance in healthy athletes and the relationship to doping

Asthmatic athletes are dependent on an optimal and successful management of their asthma to be able to perform successfully in sports. On the other hand, asthmatic athletes should not be given better conditions than their healthy peers because of the possibility that drugs used in the treatment of asthma might improve physical performance. In this respect focus has been centred especially on the use of $\beta_2$-agonists and steroids. No systemic administration of these drugs is permitted in relationship to sports, whereas administration by inhalation has been permitted for by the use of asthmatic, but not healthy athletes. These drugs are mentioned in the doping list with specific restrictions, whereas the asthma drugs theophylline, ipratropium bromide, LA, DSCG and nedocromil sodium and also anti-allergic drugs like anti-histamines are not subject to restrictions. Local steroids such as for dermatological use, nasal and conjunctival applications have been subject to certain restrictions, but are presently permitted without inhibition. Inhaled corticosteroids and inhaled $\beta_2$-agonists are presently the commonly used asthma drugs with some restrictions. The history of these restrictions is mentioned in the introductory para. However, assessment of a possible enhancing effect on performance of these drugs is especially relevant for recommendations given for athletes with asthma, and is therefore carefully discussed next. An overview of the existing studies related to

Table 2. Animal studies related to effect on muscle performance by $\beta_2$-agonists

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criswell DS et al. (66)</td>
<td>Rats injected with clenbuterol ($n = 7$) and saline ($n = 7$)</td>
<td>Clenbuterol induced shift and hypertrophy towards type II myosin heavy chain (MCH) muscle fibres</td>
</tr>
<tr>
<td>Dodd SL et al. (67)</td>
<td>Study as above, further results; clenbuterol</td>
<td>Muscle fatigue increased with clenbuterol treatment; clenbuterol-induced increase in muscle mass and maximal force generation due to hypertrophy of both fast and slow fibres</td>
</tr>
<tr>
<td>Suzuki J et al. (68)</td>
<td>10 days clenbuterol treatment on 10- and 37-weeks-old rats</td>
<td>Increase in fibre cross-sectional area in skeletal and left ventricular heart muscle; decrease in total capillary density in skeletal muscle and increased diffusion distance for oxygen</td>
</tr>
<tr>
<td>Hayes A and Williams DA (69)</td>
<td>Dystrophic mice; clenbuterol and swimming programme; open study</td>
<td>Increases in the force-generating capacity of the soleus (30–40%), resulting from clenbuterol treatment were maintained after a swimming programme in mice</td>
</tr>
<tr>
<td>Lynch GS et al. (70)</td>
<td>Controlled randomized mice study (male C57 BL/10 mice); oral clenbuterol in drinking water and low-intensity swimming treatment vs sedentary untreated untrained mice</td>
<td>Oral clenbuterol treatment with and without training; long-term clenbuterol treatment did not affect the normalized maximal tension of fast or slow fibres, but increased the proportion of fast fibres in the soleus muscle</td>
</tr>
<tr>
<td>Duncan ND et al. (71)</td>
<td>The effect of clenbuterol treatment on exercise performance evaluated in three studies. Groups of male rats assigned to an endurance swimming group, a treadmill sprint running group or a voluntary wheel running group; rats were allocated into a group that received clenbuterol in their drinking water or an untreated control group</td>
<td>Treated rats exhibited a reduction in exercise performance compared with untreated rats; treated rats showed cardiac hypertrophy, with absolute heart mass increase by 19% and heart mass relative to body mass increase by 20%; the hearts of sedentary rats treated with clenbuterol showed extensive collagen infiltration surrounding blood vessels and in the wall of the left ventricle; the results indicate strongly that chronic clenbuterol administration deleteriously affects exercise performance in rats, potentially due to alterations in cardiac muscle structure and function</td>
</tr>
<tr>
<td>Van Der Heijden HF et al. (72)</td>
<td>Salbutamol; in vitro study of rat diaphragm; salbutamol was given intracardially before excision of diaphragm</td>
<td>Maximum shortening velocity increased 15% after salbutamol treatment, and maximum power output increased 25%. During repeated isotonic activation, the rate of fatigue was faster in the salbutamol-treated diaphragm, but both salbutamol-treated and control diaphragm fatigued to the same maximum power output; Endurance time during repetitive isotonic contractions was 10% shorter in the salbutamol-treated diaphragm.</td>
</tr>
<tr>
<td>Buchanan R et al. (73)</td>
<td>In vitro isolated rat soleus muscle; effect of electrical stimulation and salbutamol</td>
<td>Excitation- and $\beta_2$-agonist-induced activation of the Na$^+$-K$^+$ pump in rat soleus muscle improves restoration of the Na$^+$-K$^+$ homeostasis during work and optimizes excitability and contractile performance</td>
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</table>
β₂-agonists has been given in Tables 2–6. In addition to papers known to the members of the Task Force, Medline was searched for relevant papers up to November 2006. Search words were asthma, bronchial responsiveness, exercise-induced bronchoconstriction, athletes, sports, performance and β₂-agonists. Relevant papers were included after individual inspection.

Inhaled corticosteroids can be used by athletes with asthma after application for TUE to the responsible sports organization (WADA, IOC Medical Commission or to some of the international sports associations). Very few studies exist related to the possible enhancing effect on performance by inhaled corticosteroids in healthy athletes. Papalia (57) performed a study in well-trained healthy athletes and found no improvement in performance.

Inhaled β₂-agonists are subject to specific requirements as regards the presence of BHR or reversibility to bronchodilators to be permitted the use during the period covering the IOC regulations (usually the period when the Olympic village is open). WADA does not have the same requirements but some athletic organizations like the International Association of Athletic Federations (IAAF)

### Table 3. Effect of systemic β₂-agonists on performance

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study description</th>
<th>Result</th>
<th>Evidence level</th>
</tr>
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<tbody>
<tr>
<td>Violante B et al. (74)</td>
<td>Infusion; open study; seven healthy persons; infusion of aminophylline, followed by salbutamol and then saline (placebo); the strength of respiratory muscles, as measured by maximal inspiratory pressure (MIP), and the ventilatory endurance, as measured by sustainable inspiratory pressure (SIP), were measured</td>
<td>No statistically significant difference in muscle strength after aminophylline or salbutamol compared with placebo; no significant changes in 12-min walking distance, perceived exertion rate, anaerobic threshold, maximal work output, maximal oxygen uptake neither after aminophylline nor after salbutamol</td>
<td>3</td>
</tr>
<tr>
<td>Javaheri S et al. (75)</td>
<td>Oral: in five normal subjects, fatigue was induced by breathing through an inspiratory resistance; studies were performed at two levels of diaphragmatic tension-time index (TTdi) of 0.25 and 0.30; at each TTdi, either placebo or albuterol (4 mg thrice daily) was taken for 3 days</td>
<td>All subjects experienced side effects of sympathetic stimulation; albuterol did not significantly increase the strength of the fresh diaphragm; few subjects; open study</td>
<td>3</td>
</tr>
<tr>
<td>Rolett EL et al. (76)</td>
<td>Oral: dynamic quadriceps muscle exercise was performed by 12 healthy male volunteers for 50 or 80 min at an average workload of 38 W with and without terbutaline; open study</td>
<td>Addition of terbutaline during exercise caused leg blood flow to increase 13% from 5.10 ± 0.16 to 5.75 ± 0.13 l/min and arterial K⁺ concentration to fall monoelexponentially by 0.90 ± 0.05 mM with a rate constant of 0.26/min; terbutaline increased, rather than decreased, the wash-out of K⁺ from working quadriceps by 40% to an average value of 0.23 ± 0.02 mmol/min kg per muscle</td>
<td>3</td>
</tr>
<tr>
<td>Lanigan C et al. (77)</td>
<td>Oral: experimental; terbutaline, tuloberterol, caffeine and maximum tolerated doses; effect on resp. and limb muscle strength and endurance in healthy subjects</td>
<td>No effect of β₂-agonists; slight effect on strength by caffeine</td>
<td>3</td>
</tr>
<tr>
<td>Caruso JF et al. (78)</td>
<td>Oral: RCT; the effects of albuterol and isokinetic exercise on the quadriceps muscle group; 9 weeks of isokinetic knee extensions twice weekly; albuterol (n = 13) or placebo (n = 9) was administered for 6 weeks; groups received 16 mg/day of either treatment; training consisted of three sets of 10 repetitions at 45°/s; data were collected at weeks 0, 6 and 9</td>
<td>Albuterol yielded superior values for concentric peak torque, total work, average power, concentric peak torque to body weight ratio, time to eccentric peak torque; results indicate that therapeutic doses of albuterol administered with resistance exercise may augment strength gains</td>
<td>1</td>
</tr>
<tr>
<td>van Baak MA et al. (79)</td>
<td>Oral: RCT. 16 non-/asthmatic men; salbutamol, 4 mg per placebo</td>
<td>Increased PEF, peak torque (knee extensors and flexors), endurance time; no effect on VO₂, respiratory exchange ratio, heart rate, plasma free fatty acid and glycerol concentrations have no clinically relevant beneficial effects on ventilatory muscle function and exercise tolerance in healthy subjects</td>
<td>1</td>
</tr>
<tr>
<td>Collomp K et al. (80)</td>
<td>Oral: RCT; eight healthy volunteers; double-blind; salbutamol 6 mg, caffeine 200 mg; placebo; cycling for 2 min ×2</td>
<td>Mean power not significantly different</td>
<td>1</td>
</tr>
<tr>
<td>Suzuki J et al. (81)</td>
<td>Oral: RCT double-blind placebo-controlled; healthy subjects, fenoterol 5 mg orally and placebo</td>
<td>In normal subjects fenoterol reduced diaphragmatic fatigue and decreases the motor command to the diaphragm, resulting in a decrease in IES during inspiratory threshold loading and a prolongation of endurance</td>
<td>1+</td>
</tr>
</tbody>
</table>

RCT, randomized-controlled trial; PEF, peak expiratory flow; IES, inspiratory effort sensation.
Treatment and possible doping in respiratory and allergic disorders in sports

Table 4. Effect of inhaled β₂-agonist on power output and speed

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study description</th>
<th>Result</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signorile JF et al. (59)</td>
<td>Short-acting: RCT, blinded; 15 healthy nonasthmatic subjects (eight males, seven females, 18–33 years); four supramaximal 15-s rides on a bicycle ergometer; salbutamol, 0.36 mg per placebo for 10 min before cycling</td>
<td>Significant difference between the A and P treatments for peak power (A = 886.6 W, P = 850.3 W) and fatigue (A = 27.2%, P = 24.4%). No effect on heart rate</td>
<td>1</td>
</tr>
<tr>
<td>Meuwisse WH et al. (82)</td>
<td>Short-acting: RCT, cross-over double-blind, salbutamol vs placebo; seven nonasthmatic cyclists; cycle ergometry</td>
<td>Nonsignificant decrease in VO₂ max after salbutamol; no difference was found in peak power, maximum heart rate, endurance sprint time, Wingate peak power or total work; few subjects</td>
<td>1</td>
</tr>
<tr>
<td>Morton AR et al. (83)</td>
<td>Short-acting: RCT, double-blind salbutamol and placebo-controlled, cross-over, 17 male athletes in power events, 17–31 years; 10 s all out sprint on bicycle ergometer, peak torque during leg extension and leg flexion</td>
<td>No sign difference between salbutamol and placebo for any parameter</td>
<td>1</td>
</tr>
<tr>
<td>Lemmer JT et al. (84)</td>
<td>Short-acting: RCT, four male cyclists; salbutamol (albuterol) and placebo; very few subjects; low power; evidence level: 1–</td>
<td>Multi-variate ANOVA revealed no significant difference between the albuterol and placebo treatment for the anaerobic power measures: peak power (1136.7 ± 40.9 vs 1124.8 ± 39.8 W), mean ± SE, total work (27,213.6 ± 653.1 vs 27,093.3 ± 677.4 J), time to peak power (4.5 ± 0.2 vs 4.8 ± 0.5 s) and fatigue index (16.5 ± 1.8 vs 16.6 ± 1.8 W/s); peak heart rate (181.6 ± 3.7 vs 181.4 ± 3.8 bpm) or blood lactate (14.0 ± 0.9 vs 13.8 ± 0.8 mmol/l) 3 min after the exercise but were not significantly different between treatments</td>
<td>1</td>
</tr>
<tr>
<td>Morton AR et al. (85)</td>
<td>Long-acting: RCT, double-blind, cross-over; 16 nonasthmatic male cyclists and triathletes, mean age of 23.2 (SD = 3.5) years; salmeterol 50 μmol vs placebo</td>
<td>Lung function variables, reaction time, movement time, alactic anaerobic power, lactic acid anaerobic power and leg-flexion and leg-extension muscular strength were similar among the three treatment groups</td>
<td>1</td>
</tr>
<tr>
<td>McDowell SL et al. (86)</td>
<td>Long-acting: RCT placebo-controlled cross-over; 11 elite nonasthmatic track cyclists performed a 30-s all-out cycle ergometer test 3 h after receiving either 42 μg of salmeterol xinafoate or placebo</td>
<td>No significant differences (P &gt; 0.05) between the placebo and salmeterol for peak power output, total work performed during the 30-s test, per cent fatigue and time to peak power, nor for pulmonary function at any of the time points; blood lactate concentrations before and after administration of drug or placebo were not significantly different and salmeterol did not affect the maximal heart rate</td>
<td>1</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial.

do. Inhaled β₂-agonists as formoterol and salmeterol that have certain systemic effects on heart rate, diastolic blood pressure, and plasma glucose and potassium concentrations (58), and for this group of drugs the possibility of enhanced performance in healthy athletes is especially important and has been extensively studied (Tables 2–6).

Animal experiments (Table 2) mostly performed in rats and mice suggest that infusion and systemic use of β₂-agonists may have an effect on striated skeletal and heart muscle fibres. This can result in increase in cross-sectional areas of muscle fibres and maximal force generation of muscle fibres. This has been shown both for clenbuterol and salbutamol (Table 2).

Systemic use of β₂-agonists, by infusion or oral administration of the short-acting β₂-agonists salbutamol, terbutaline and fenoterol, gives conflicting results concerning the possibility of enhancing athletic performance (Table 3). Most studies do not demonstrate an effect on performance parameters, whereas some indicate an increase in muscular power. However, most of these studies are characterized by rather few included subjects and a varying design, resulting in varying evidence levels. An overview of these studies is given in Table 3.

However, more relevant for the treatment of asthma and asthmatic athletes are results from studies related to performance of inhaled β₂-agonists on healthy athletes (Table 4–6). Studies have been performed on both short- and long-acting inhaled β₂-agonists, concerning the possible effect on power output and speed (Table 4) and endurance performance (Tables 5 and 6). The studies are mostly randomized controlled trials of double-blind placebo-controlled, often cross-over design, and have thus a high evidence level. Some studies are weakened by a low number of subjects. Most studies have been performed in the laboratory employing cycling on ergometer cycles or running on treadmills. Six studies concerning power output are reviewed in Table 4, five studies concerning short-acting and one study concerning long-acting inhaled β₂-agonists. The studies reviewed included from 4 to 17 subjects. One early study (59)
suggested a significant difference in peak power and fatigue between inhaled salbutamol and placebo, whereas the other five studies, including one study on the long-acting inhaled β₂-agonist, salmeterol, reported no significant differences in power output or speed (Table 4).

More studies have concentrated on endurance performance. Twelve studies are cited in Table 5, concerning the short-acting inhaled β₂-agonists salbutamol and terbutalin. Half of the studies report on cycling, the remainder on treadmill running exercise and the studies include from 7 to 20 subjects. Most studies reported improved lung function after inhalation, but in several studies not so immediately after exercise. Only one study reported significant improvement in performance parameters (60). However, this study employed only one-tailed statistical analysis (60). The remaining 11 studies did not report any improvement in endurance performance, two of the studies even reported reduced endurance time after inhaling salbutamol or salmeterol (61, 62). All these studies have a randomized controlled design.

Table 5. The effect of short-acting inhaled β₂-agonists on endurance performance

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study description</th>
<th>Result</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedi JF et al. (87)</td>
<td>Enhancement of exercise performance with inhaled albuterol; RCT, double-blind, placebo-controlled cross-over; 15 nonasthmatic cyclists, simulated race, i.e. 1-h heavy continuous exercise (minute ventilation (VE) 81 l/min BTPS) followed by maximal effort workload to exhaustion, with/without prior inhalation of albuterol inhaler; [La-]b, blood lactate.</td>
<td>Significant increase in forced expiratory flow parameters following albuterol; although not significant, oxygen uptake (VO₂E) and VE were smaller during the 1-h submaximal test following albuterol and VO₂max and V'Emax were higher; there was an increased ride time (186 vs 159 s; P &lt; 0.05); no sample size determination; few subjects</td>
<td>1−</td>
</tr>
<tr>
<td>Morton AR et al. (88)</td>
<td>RCT, double-blind placebo-controlled; 17 healthy athletes; 17–29 years; VO₂max and time to volatile exhaustion</td>
<td>No ergogenic effect of salbutamol</td>
<td>1+</td>
</tr>
<tr>
<td>Meuwisse WH et al. (82)</td>
<td>RCT, cross-over double-blind; seven nonasthmatic cyclists; cycle ergometry</td>
<td>Nonsignificant decrease in VO₂max after salbutamol; no difference was found in peak power, maximum heart rate, endurance sprint time, Wingate peak power or total work; few subjects</td>
<td>1</td>
</tr>
<tr>
<td>Fleck SJ et al. (89)</td>
<td>RCT; double-blind; salbutamol 0.36 mg per placebo; 21 competitive non-asthmatic road cyclists</td>
<td>No significant difference for perceived exertion and VO₂ determined at the submaximal workloads of 150, 200, 225, 250, 275, 300 W and at max.; increased after salbutamol for heart rate, whole blood lactate</td>
<td>1+</td>
</tr>
<tr>
<td>Unnithan VB et al. (90)</td>
<td>RCT, cross-over single-blind; 10 nonasthmatic boys; treadmill run; terbutalin, 0.5 mg; placebo</td>
<td>No sign of effect for running economy, heart rate during submaximal exercise tests or between peak oxygen consumption (V'O₂), peak respiratory exchange ratio, peak heart rate (HR) or total running time during the peak V'O₂ test</td>
<td>1−</td>
</tr>
<tr>
<td>Heir T and Stemshaug H (61)</td>
<td>RCT double-blind cross-over; 17 highly trained male athletes; nebulized salbutamol 0.05 mg/kg per placebo before treadmill run of 110% of VO₂max, run to exhaustion</td>
<td>Shorter endurance time with salbutamol (P = 0.06); lower VO₂max and higher heart rate during the first 4 min; no difference in peak VO₂ and peak heart rate; higher FEV₁ after salbutamol before run, but not after</td>
<td>1+</td>
</tr>
<tr>
<td>Norris SR et al. (91)</td>
<td>RCT; the effect of salbutamol on performance in 15 male endurance cyclists</td>
<td>Inhaled salbutamol 0.4 mg did not differ from placebo in VO₂max, 60 s modified Wingate tests and simulated 20 km trial</td>
<td>1+</td>
</tr>
<tr>
<td>Larsson K et al. (92)</td>
<td>RCT; single-blind; terbutaline 3 mg MDI per placebo; cold chamber –10°C; treadmill run; 20 athletes</td>
<td>Sign; bronchodilation by terbutaline; no significant differences for exercise time, 25.1 (24.3–25.8) min vs 24.9 (24.1–25.6) min, VO₂ and ventilation during exercise or heart rate at maximal workload</td>
<td>1+</td>
</tr>
<tr>
<td>Carlsen KH et al. (62)</td>
<td>RCT double-blind; 18 athletes, salbutamol (0.4 mg), salmeterol (50 μg); placebo; treadmill run</td>
<td>No effect on VO₂max, V'Peak; reduced running time to exhaustion after inhaled salbutamol and salmeterol compared with placebo</td>
<td>1+</td>
</tr>
<tr>
<td>Sandsund M et al. (93)</td>
<td>RCT double-blind; salbutamol 1.2 mg per placebo; running at –15 and +23°C; 8 healthy well-trained athletes</td>
<td>No effect on submaximal and maximal VO₂, heart rate, [La-]b or time to exhaustion; increased FEV₁ before run</td>
<td>1+</td>
</tr>
<tr>
<td>Goubault C et al. (94)</td>
<td>12 triathletes, RCT double-blind, salbutamol 200 μg, 800 μg; placebo; cycle ergometer</td>
<td>No effect on endurance time and postexercise bronchodilatation</td>
<td>1+</td>
</tr>
<tr>
<td>van Baak MA et al. (60)</td>
<td>RCT double-blind cross-over study; 16 cyclists were given 0.8 mg of salbutamol (powder inhaler) or placebo; a certain amount of work to be performed on cycle ergometer over a measured time</td>
<td>Authors report shorter time (mean 1.9 ± 1.8%) after salbutamol to be significant; however, statistical analysis based on one-tailed tests; not significant with two-tailed analysis</td>
<td>1−</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial; FEV₁, forced expiratory volume in 1 s; VE, minute ventilation; VO₂max, maximum oxygen uptake; V'Peak, peak ventilation; MDI, metered dose inhaler; [La-]b, blood lactate.
long-acting $\beta_2$-agonists. Three of the trials were performed in extreme environmental conditions, two with a cold environmental temperature of $-15$ to $-20^\circ$C (63, 64), the other in hypobaric conditions corresponding to an altitude level of 2000 m above sea level (65). None of these studies reported significant differences between the long-acting $\beta_2$-agonists and placebo on endurance performance, also in the extreme environmental conditions studied (Table 6).

Thus, the evidence is convincing that inhaled $\beta_2$-agonists do not improve athletic performance in healthy athletes. The EL is high, and recommendations given based on these studies will be of grade A.

### Conclusions

An increased prevalence of EIA and bronchial responsiveness exist among elite athletes, especially among those involved in endurance sports. The environment in which the sport is performed influences the prevalence; examples are cold environmental temperatures for skiers and athletes active in other winter sports and chlorine products in indoor pools for swimmers. This should have an impact on the rules and regulations issued by the organizations of sports regarding the environment in which sports and competitions can be performed. The Task Force has established recommendations for diagnosis of asthma and BHR which are meant to permit and guide the use of asthma drugs by asthmatic athletes. This was done as it is recognized that athletes may often be misdiagnosed of having EIA without proper objective documentation demonstrating the presence of EIA or BHR. There is no evidence to suggest that asthma drugs can enhance athletic performance. The Task Force has given recommendations for the treatment of asthma and EIA related to sports in agreement with the common international guidelines of asthma management.

### Acknowledgment

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References


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76. ERS: Anderson SD (Australia), Bjermer L (Sweden), Brusasco V (Italy), Carlsen KH (Norway), Drobnic F (Spain), Larsson K (Sweden), Palange P (Italy).

Appendix

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All members of the Task Force participated in the discussions related to the topics handled in the document. All participants participated in writing specific chapters concerning the different parts of the present report. These chapters were published in European Respiratory monograph: Diagnosis, Prevention and Treatment of Exercise-Related Asthma, Respiratory and Allergic Disorders in Sports; European Respiratory Monograph no. 33, Vol. 10, November 2005; European Respiratory Journals Ltd., Sheffield, UK; ISBN: 1-904097-55-3.

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