Review article

Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA² LEN

Aims: To analyze the changes in the prevalence of asthma, bronchial hyperresponsiveness (BHR) and allergies in elite athletes over the past years, to review the specific pathogenetic features of these conditions and to make recommendations for their diagnosis.

Methods: The Task Force reviewed present literature by searching Medline up to November 2006 for relevant papers by the search words: asthma, bronchial responsiveness, EIB, athletes and sports. Sign criteria were used to assess level of evidence and grades of recommendation.

Results: The problems of sports-related asthma and allergy are outlined. Epidemiological evidence for an increased prevalence of asthma and BHR among competitive athletes, especially in endurance sports, is provided. The mechanisms for development of asthma and bronchial hyperresponsiveness in athletes are outlined. Criteria are given for the diagnosis of asthma and exercise induced asthma in the athlete.

Conclusions: The prevalence of asthma and bronchial hyperresponsiveness is markedly increased in athletes, especially within endurance sports. Environmental factors often contribute. Recommendations for the diagnosis of asthma in athletes are outlined.


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

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Sustained increased ventilation as a result of frequent heavy-duty training and competition together with environmental factors like cold air and chlorine in pool water cause inflammation and BHR and are the probable causes for the increased prevalence of exercise-induced asthma (EIA) and BHR in competitive endurance athletes. Criteria for the diagnosis of EIA and BHR in athletes are given. A combination of symptoms and objective criteria as positive exercise test, positive bronchodilator test or the presence of BHR to direct (e.g. methacholine or histamine) or indirect (e.g. exercise, eucapnic voluntary hyperpnoea or hypertonic aerosols) stimuli is required. The research needs further exploration of the relationship been physical exercise and development of BHR as well as for the assessment of diagnostic methods in relationship to sensitivity, specificity, positive and negative predictive values in the athletic population.

Asthma and allergy represent increasing problems for the actively competing athletes with increasing prevalence of exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB) reported especially among elite endurance athletes (1–3). EIA and EIB are the terms used to describe the transient narrowing of the airways that follows vigorous exercise. The term EIA is used to describe symptoms and signs of asthma provoked by exercise and EIB describes reduction in lung function after an exercise test or a natural exercise.

It was reported for the first time in 1989 in a study on competing swimmers that high-level endurance training increased nonspecific BHR to histamine depending on the intensity of the physical training (4). Nine years later, the finding of inflammatory changes in bronchial biopsies from young skiers was reported (5). The effect of intensive physical activity may be enhanced by untoward environmental conditions during the activity, such as cold ambient temperatures for winter sports and organic chlorine products from indoor swimming pools in swimmers (6).

Furthermore, the heavy training with the extremely high level of physical fitness and maximum oxygen uptake (V'O₂ max) reached nowadays by elite athletes, may make it difficult to discriminate between physiological and pathological limitations to maximum exercise. This underlines the need for developing good diagnostic criteria for EIB and BHR in relationship to sports.

It has become a matter of concern that the use of inhaled asthma drugs, and in particular inhaled β₂-agonists, has become increasingly widespread among elite athletes. In 1993, the Medical Commission of the International Olympic Committee (IOC) restricted the use of inhaled β₂-agonists even in asthmatic athletes, permitting only the short-acting β₂-agonists (SABA) salbutamol and terbutaline by inhalation for use in relation to sports by asthmatic athletes. Salbutamol and terbutaline should be prescribed by physicians and with confirmation of an asthma diagnosis by the treating physician.

Based on studies regarding the effect of inhaled SABA and long-acting β₂-agonists (LABA) upon performance (endurance, strength and speed), the IOC Medical Commission allowed inhaled salmeterol from 1996 and later inhaled formoterol (from 2001) for use in relation to sports. Further regulations were introduced by IOC Medical Commission in November/December 2001 shortly before the winter Olympic Games in Salt Lake City, requiring application and documentation of increased reversibility to bronchodilators, BHR and/or EIB prior to participating in competitions by printed lung function measurements (7). Later on, minor modifications have been made several times by the World Anti-Doping Association (WADA) and IOC Medical Commission. From 2006 all restrictions on topical steroids except for inhaled corticosteroids was removed. Presently applications to use inhaled corticosteroids and inhaled β₂-agonists must be made both to WADA for international sports and to IOC Medical Commission for the Olympic Games.

The regulations were felt too strict and complicated by many respiratory and sports physicians (8). There was a concern that too strict criteria for the diagnosis of asthma, which should be based on clinical conditions, could lead to under-diagnosis and under-treatment of asthma in athletes. Among the objectives of Sports Medicine formulated by IOC, it is stated that all participants shall have equal competitive conditions, and that sports should not cause any long-lasting harm or disease for the participants (9). Asthmatic athletes should therefore receive optimal treatment both symptomatically and prophylactically for their asthma.

Because of these concerns, the European Academy of Allergy and Clinical Immunology (EAACI) and the European Respiratory Society (ERS) established a joint Task Force to outline the problem of asthma and allergy in sports, to establish diagnostic criteria and treatment guidelines for asthma, EIA and other exercise-related respiratory problems in relationship to sports in line with the requirements of evidence-based medicine. The present Task Force report does not represent a systematic review, but when assessing the existing evidence in some areas, we have followed the SIGN criteria (Scottish Intercollegiate Guidelines Network Grading Review Group) as reported by Harbour and Miller (10) and used in several guidelines. The criteria for evidence levels and grades of recommendations are given in Table 1.

Epidemiology

Asthma and BHR among athletes

Studies reporting the prevalence of asthma among athletes are listed in Table 2. Medline was searched for relevant papers up to November 2006. Search words were asthma, bronchial responsiveness, EIB, athletes and
Epidemiology and pathogenetic mechanisms of respiratory and allergic disorders in sports

Table 1. Criteriae for levels of evidence and grades of recommendation employed in the present Task Force report

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 + + High-quality meta--analyses, systematic reviews of RCT or RCT with a very low risk of bias</td>
<td>A At least one meta--analysis, systematic review or RCT rated as 1 + + directly applicable to the target population or a systematic review of RCT or a body of evidence consisting principally of studies rated as 1 + directly applicable to the target population and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>1 + Well-conducted meta--analyses, systematic reviews of RCT or RCT with a low risk of bias</td>
<td>B A body of evidence including studies rated as 2 + + directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1 + + or 1+</td>
</tr>
<tr>
<td>1– Meta--analyses, systematic reviews or RCT, or RCT with a high risk of bias</td>
<td>C A body of evidence including studies rated as 2 + directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2 + +</td>
</tr>
<tr>
<td>2 + + High-quality systematic reviews of case--control or cohort studies or high-quality case--control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
<td>D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+</td>
</tr>
<tr>
<td>2 + Well-conducted case--control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
<td>Nonanalytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>2– Case--control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>3 Nonanalytic studies, e.g. case reports, case series</td>
<td></td>
</tr>
<tr>
<td>4 Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

Grades of recommendations

A At least one meta--analysis, systematic review or RCT rated as 1 + + and directly applicable to the target population or a systematic review of RCT or a body of evidence consisting principally of studies rated as 1 + directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2 + + directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1 + + or 1+

C A body of evidence including studies rated as 2 + directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2 + +

D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+


sports. Relevant papers were included after individual inspection. Voy in 1986 (11) reported from a screening programme organized by the US Olympic Committee that 67 out of 597 American Olympic Athletes for the Los Angeles 1984 summer Olympic Games suffered from EIA or asthma. The asthmatic athletes won 41 medals during the Olympic Games. High prevalence of asthma were also reported from later Olympic Games (12), and in 1996 an asthma prevalence of 45% was reported in cyclist and swimmers (29). Maiolo et al. (30) reported the prevalence of BHR (48%) to histamine was also found among competitive athletes of various sports compared with 36% among controls (28). High prevalence of asthma in 14% compared with 2% among controls, current physician-diagnosed asthma or BHR) was found in 23% of the athletes compared with 4% of the controls, and/or BHR as given by the IOC Medical Commission, Dickinson reported prevalence among the participants in the Olympic Games in 2002 (7) and 4.2% in the summer Olympics in 2004 (16). From data collected over the three recent summer Olympic Games, in Atlanta 1996, Sydney 2000 and Athens 2004 (data received from Ken Fitch, IOC Medical Commission), it appears that the usage of inhaled β₂-agonists is the largest in endurance sports with cycling on top with 15.4% of all competitors, followed by triathlon and swimming (Tables 3a and b) (17).

Winter sports. Larsson et al. (1) reported in 1993 that 23 of 42 elite cross-country skiers had a combination of BHR and asthma symptoms compared with only 1 of the 23 referents. Shortly after Heir and Oseid (2) showed in a questionnaire-based report a prevalence of doctor-diagnosed asthma of 14% in 155 actively competing skiers compared with 5% in twice-matched controls; moreover, the prevalence of asthma diagnosis increased with increasing age in the actively competing skiers. This was followed by reports of high prevalence in Norwegian and Swedish skiers (18), in competitive figure skaters (19, 20), in elite cold-weather athletes (21) and among participants in the 1998 American Olympic National team for winter sports including gold medalists (22).

Summer sports. Feinstein et al. (23) found EIB in 9 out of 48 male football players, whereas BHR to methacholine (PD20-methacholine < 16.3 μmol) was found in 35.5% of the Norwegian national female soccer team (24). Of the Canadian professional football players 56% had positive bronchodilator test (increase in forced expiratory volume in 1 s, FEV1 ≥ 12%) to inhaled salbutamol (25). Among American track and field athletics, 10% of the men and 23% of the women suffered from EIB after a national competitive event with higher incidences after long-distance events (26).

Helenius and Haahela (27) published several studies on Finnish elite track and field athletes. Physician-diagnosed asthma was reported in 17% of long-distance runners, 8% of speed and power athletes and 3% of controls. In another study, total asthma (current asthma, physician-diagnosed asthma or BHR) was found in 23% of the athletes compared with 4% of the controls, current asthma in 14% compared with 2% among controls and positive skin prick test (SPT) in 48% of the athletes compared with 36% among controls (28). High prevalence of BHR (48%) to histamine was also found among swimmers (29). Maiolo et al. (30) reported the prevalence of asthma in 15% and atopy in 18% of 1060 Italian competing summer athletes. Higher prevalence of asthma among endurance athletes as compared with speed and power athletes was reported in a Norwegian study (31). Employing the objective criteria for diagnosing asthma and/or BHR as given by the IOC Medical Commission, Dickinson reported prevalence among the participants in the Olympic Games in 2004 and 2000 to be 21.2% and
Table 2. Prevalence of asthma among athletes – overview of published studies

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Method</th>
<th>Condition</th>
<th>Population (n: prevalence)</th>
<th>Study type</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voy RO (11)</td>
<td>Questionnaire</td>
<td>EIA, asthma</td>
<td>American Olympic summer athletes (597): 11%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Weiler JM et al. (12)</td>
<td>Questionnaire</td>
<td>EIA</td>
<td>Olympic summer athletes: 11%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Heilbling A et al. (14)</td>
<td>Questionnaire</td>
<td>Asthma and rhinitis</td>
<td>Swiss athletes (2080): Asthma: 7.1%; Rhinitis: 16.8%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Larsson K et al. (1)</td>
<td>Methacholine BHR + symptoms</td>
<td>BHR, asthma symptoms</td>
<td>Skiers (42): 95.5%; Referents (29): 4%</td>
<td>Case-control</td>
<td>2–</td>
</tr>
<tr>
<td>Heir T and Oseid S (2)</td>
<td>Questionnaire</td>
<td>Doctor-diagnosed asthma</td>
<td>Skiers (153): 14%; Controls (306): 5%</td>
<td>Case-control</td>
<td>2+</td>
</tr>
<tr>
<td>Weiler JM et al. (13)</td>
<td>Questionnaire</td>
<td>EIA</td>
<td>Olympic summer athletes (699): &gt;20%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Provost-Craig MA et al. (19)</td>
<td>Exercise test in the rink</td>
<td>EIB</td>
<td>Competitive figure skaters (100): EIB: 30%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Mannix ET al. (20)</td>
<td>Exercise test in the rink</td>
<td>EIB</td>
<td>Competitive figure skaters (124): EIB: 35%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Mannix ET al. (106)</td>
<td>Exercise test in the rink + eucapnic hyperventilation</td>
<td>EIB, bronchoconstriction after eucapnic hyperventilation</td>
<td>Competitive figure skaters (29): EIB: 55%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Feinstein RA et al. (23)</td>
<td>Exercise test</td>
<td>EIB (&gt;15% reduction in FEV₁)</td>
<td>Male football players (48): 19%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Sandal A (24)</td>
<td>Methacholine BHR</td>
<td>BHR, asthma</td>
<td>Female national soccer players (17): 35.5%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Ross RG et al. (25)</td>
<td>Reversibility to salbutamol</td>
<td>Bronchodilator reversibility</td>
<td>Canadian professional football players (34): Positive in 50%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Schoene RB et al. (26)</td>
<td>Exercise test competition</td>
<td>EIB</td>
<td>Track and field athletes, Male (50): 10%; Female (23): 26%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Helenius UJ et al. (27)</td>
<td>Questionnaire, interview</td>
<td>Physician-diagnosed asthma</td>
<td>Long-distance runners (107): 17%; Speed and power (106): 8%; Controls (124): 3%</td>
<td>Case-control</td>
<td>2+</td>
</tr>
<tr>
<td>Helenius UJ et al. (28)</td>
<td>Questionnaire, BHR (histamine)</td>
<td>Physician-diagnosed asthma/current asthma</td>
<td>Long-distance runners (71): Speed and power (49): Swimmers (42): Controls (45): 4%/2%</td>
<td>Case-control</td>
<td>2+</td>
</tr>
<tr>
<td>Helenius UJ et al. (29)</td>
<td>Questionnaire, BHR (histamine)</td>
<td>BHR (histamine)</td>
<td>Swimmers (29): 48%; Controls (19): 16%</td>
<td>Case-control</td>
<td>2–</td>
</tr>
<tr>
<td>Langdeau JB et al. (147)</td>
<td>BHR (metacholine)</td>
<td>BHR (metacholine)</td>
<td>Competitive athletes in various sports (49%): compared with sedentary controls (28%)</td>
<td>Case-control</td>
<td>2–</td>
</tr>
<tr>
<td>Lumme A et al. (66)</td>
<td>BHR to histamine, induced sputum</td>
<td>Ice hockey players and healthy controls</td>
<td>Ice hockey players (88) and healthy controls (44): Asthma is common in elite ice hockey players, showing a mixed type of neutrophilic and eosinophilic airway inflammation</td>
<td>Case-control</td>
<td>2</td>
</tr>
<tr>
<td>Rundell KW et al. (21)</td>
<td>Questionnaire, sports-specific exercise test</td>
<td>Asthma symptoms, EIB</td>
<td>Elite cold/weather athletes (158): EIB: 26%; ≥2 asthma symptoms: 29%</td>
<td>Patient series</td>
<td>3</td>
</tr>
<tr>
<td>Wilber RL et al. (22)</td>
<td>Sport-specific field EIB test and laboratory EIB test</td>
<td>EIB</td>
<td>The American Olympic National team in winter sports (170): EIB: General: 23% Cross-country skiers: 50%; Cross-sectional</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Maiolo C et al. (30)</td>
<td>Questionnaire</td>
<td>Asthma, atopy</td>
<td>Italian summer athletes (1060): Asthma: 15%; Atopy: 18%</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
<tr>
<td>Nystad W et al. (31)</td>
<td>Questionnaire</td>
<td>Asthma</td>
<td>Norwegian elite athletes (n = 1620) and normal population (n = 1680)</td>
<td>Cross-sectional</td>
<td>3</td>
</tr>
</tbody>
</table>

EIA, exercise-induced asthma; EIB, exercise-induced bronchoconstriction; BHR, bronchial hyper-responsiveness; EVH, eucapnic hyperventilation; FEV, forced expiratory volume.
Rhinitis and conjunctivitis occur commonly in athletes as exemplified by the term: the athlete’s nose (33). Helbling et al. (14) reported in 1990 that 16.8% of 2060 Swiss athletes suffered from allergic rhinitis. Katelaris et al. (34) reported that of 214 Australian athletes from 12 Olympic sports disciplines, 56% suffered from allergic rhinoconjunctivitis and 41% had both symptoms and positive SPT. In addition, in competitive swimmers as compared with controls more frequent aeroallergen sensitization was reported (35). Bonnadonna et al. (36) reported that 48.6% of 144 skiers suffered from cold-induced rhinitis, a problem which may be independent of allergen exposure. Rhinitis has an added importance in the frequent report of combined nasal and asthmatic symptoms in patients with allergic rhinitis (37), and the presence of rhinitis should make the physician aware of the possibility of concomitant asthma in the athlete. Compared with the prevalence of allergic rhinitis in the normal population, the prevalence rates cited are clearly higher compared with the corresponding countries in the last phase three report from the recent report of ISAAC phase three study (38).

Another condition with specific relevance to exercise and physical activity is exercise-induced anaphylaxis, first described by Sheffer and Kaplan (39). This condition occurs together with food allergy (40, 41). A 10-year follow-up showed that the symptoms tended to decrease with modifications of the individual’s exercise habits and avoidance of foods (42). Exercise-induced anaphylaxis can occur related to many types of food, but has in particular been related to wheat allergy (43). Exercise-induced anaphylaxis occurs when the exercise takes place within 1–2 h after intake of the relevant food allergen. Treatment is as for anaphylaxis in general and avoidance of the particular food allergen.

### Exercise and airway physiology in healthy and asthmatic athletes

Changes in airway calibre during exercise

The usual ventilatory response to exercise for minute ventilation ($V'_E$) is to be dominated by an increase in tidal ventilation.

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**Table 3a. Percentage of all competitors applying to inhale a β2-agonist at the summer Olympic Games in Atlanta 1996, Sydney 2000 and Athens 2004; the mean percentage use in some sports with high and low usage over the three games and the rank in each game**

<table>
<thead>
<tr>
<th>Sport</th>
<th>Percentage</th>
<th>Ranking in each game</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance sports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycling</td>
<td>15.3</td>
<td>1</td>
</tr>
<tr>
<td>Triathlon</td>
<td>†</td>
<td>2</td>
</tr>
<tr>
<td>Swimming (including synchro)</td>
<td>11.3</td>
<td>4</td>
</tr>
<tr>
<td>Modern pentathlon</td>
<td>10.1</td>
<td>3</td>
</tr>
<tr>
<td>Swim, diving, polo, synchro</td>
<td>7.6</td>
<td>6</td>
</tr>
<tr>
<td>Rowing</td>
<td>7.5</td>
<td>7</td>
</tr>
<tr>
<td>Canoeing</td>
<td>6.1</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Softball</td>
<td>5.3</td>
<td>7</td>
</tr>
<tr>
<td>Short ‘bursts’ of effort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Track and field</td>
<td>4.0</td>
<td>9</td>
</tr>
<tr>
<td>Taekwondo</td>
<td>†</td>
<td>17</td>
</tr>
<tr>
<td>Badminton</td>
<td>3.9</td>
<td>10</td>
</tr>
<tr>
<td>Tennis</td>
<td>2.2</td>
<td>22</td>
</tr>
<tr>
<td>Handball</td>
<td>2.2</td>
<td>23</td>
</tr>
<tr>
<td>Football</td>
<td>1.9</td>
<td>18</td>
</tr>
<tr>
<td>Boxing</td>
<td>1.7</td>
<td>15</td>
</tr>
<tr>
<td>Weightlifting</td>
<td>1.6</td>
<td>25</td>
</tr>
<tr>
<td>Shooting</td>
<td>1.5</td>
<td>23</td>
</tr>
<tr>
<td>Wrestling</td>
<td>1.4</td>
<td>25</td>
</tr>
<tr>
<td>Table tennis</td>
<td>1.2</td>
<td>28</td>
</tr>
<tr>
<td>Gymnastics</td>
<td>1.1</td>
<td>22</td>
</tr>
</tbody>
</table>

**Table 3b. Percentage of all athletes applying to inhale a β2-agonist at the winter Olympic Games in Nagano 1998, Salt Lake City 2002 and Torino 2006; the mean percentage use in some sports with high and low usage over the three games and the rank in each game**

<table>
<thead>
<tr>
<th>Sport</th>
<th>Percentage</th>
<th>Ranking in each game</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance sports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-country skiing</td>
<td>17.6</td>
<td>1</td>
</tr>
<tr>
<td>Speed skating</td>
<td>16.2</td>
<td>2</td>
</tr>
<tr>
<td>Nordic combined</td>
<td>13.8</td>
<td>4</td>
</tr>
<tr>
<td>Short-track skating</td>
<td>8.8</td>
<td>4</td>
</tr>
<tr>
<td>Biathlon</td>
<td>8.1</td>
<td>6</td>
</tr>
<tr>
<td>Short ‘bursts’ of effort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snowboard</td>
<td>4.6</td>
<td>7</td>
</tr>
<tr>
<td>Figure skating</td>
<td>4.1</td>
<td>9</td>
</tr>
<tr>
<td>Ski jumping</td>
<td>3.2</td>
<td>14</td>
</tr>
<tr>
<td>Ice hockey</td>
<td>3.0</td>
<td>13</td>
</tr>
<tr>
<td>Luge</td>
<td>2.8</td>
<td>12</td>
</tr>
</tbody>
</table>

*All applications (notifications) approved in 1998; in 2002 and 2006, applications needed to meet International Olympic Committee (IOC)-established criteria to receive permission to use β2-agonist(s).†Not rank as there was no participation in Atlanta where notifications of β2-agonist use were much lower.

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20.7%, respectively, with a positive bronchoprovocation or bronchodilator test (32).
volume ($V_T$) at low-to-moderate work loads, with respiratory frequency increasing at high levels of exercise. This pattern, however, may vary among subjects and types of exercise, but it is also affected by lung size (44), airway calibre or both. In normal subjects, the maximal flow is not achieved during exercise, which is generally terminated because of peripheral muscle fatigue. The effect of exercise on airway calibre has been described to be variable both in healthy and asthmatic subjects. Tissue resistance decreases with breathing frequency for any given tidal volume (45), but it may also be altered during exercise because of an increase in lung elastic recoil, possibly associated with increments of blood flow and surface tension. Epinephrine levels increase during exercise (46) and may influence bronchomotor tone. Crimi et al. (47) showed that exercise has a potent bronchodilator effect in subjects with induced or spontaneous asthma. In the healthy athlete, bronchodilation during exercise has been described during studies of exercise performance with and without inhaled $\beta_2$-agonists. In randomized double-blind placebo-controlled studies, it was shown that bronchodilation occurred during maximum exercise, and that inhaled $\beta_2$-agonists did not increase bronchodilation caused by exercise alone (48, 49).

**Pathogenesis of EIA**

McFadden et al. (50) suggested that airway cooling and vasoconstriction as a result of respiratory heat loss with consequent hyperaemia and rewarming of the bronchial vasculature is the probable cause of EIB. Through thermal mapping they demonstrated decreasing temperature from the upper trachea to sub-segmental bronchi with increasing ventilation (51). Airway cooling may stimulate receptors in the airways, causing bronchial constriction through a reflex pathway. Furthermore, because of vasoconstriction of the bronchial circulation induced by cold air, a secondary reactive hyperaemia may occur, with resulting oedema and airway narrowing. However, there is evidence to suggest that vascular engorgement and mucosal oedema are not the primary effectors of EIB. Bronchovascular hyperpermeability in dogs persisted for at least 24 h after hyperpnoea (52). However, EIB did not develop in canine airways when cooling and rewarming occurred in the absence of hyperpnoea-induced airway drying (53, 54).

Second, there is substantial evidence to indicate that EIA is effected through the release of mediators from mast cells and other inflammatory cells of the airways (55). Increased urinary levels of the mast-cell mediator 9α,11β prostaglandin F2 were found after exercise challenge in patients with EIA compared with patients without EIA (56). Reiss et al also found increased levels of LTE4 after exercise challenge (57). Signs of eosinophil and neutrophil activation [increased serum eosinophilic protein (ECP) and serum myeloperoxidase (MPO)] were found in top athletes after heavy training exercises, but not after moderate training exercises (58). The mediator release provoked by exercise is maintained as the main reason for considering EIA as an indirect measure of bronchial responsiveness.

During breathing, respiratory vapour loss increases rapidly with increasing ventilatory rate (59) and increasingly so when inhaling cold air. Air of $37^\circ$C fully saturated with vapour contains 44 mg of H$_2$O/l. Air of room temperature (22°C) with 50% relative humidity contains approximately 9.7 mg of H$_2$O/l and air of $-10^\circ$C with 50% relative humidity contains only 1.15 mg of H$_2$O/l air. Thus with the high ventilation rates of top athletes during exercise (up to $>280$ l/min), the potential for water to be lost from the lower airway is considerable. The main factor causing the mediator release is now thought to be the change in osmolarity of the periciliary fluid lining the surface of the respiratory mucosal membranes (60). Hallstrand et al. (61) demonstrated release of the mediators histamine, tryptase and cysteinyl leukotrienes into the sputum together with columnar epithelial cells whereas prostaglandin E(2) and thromboxane B(2) significantly decreased. It is thought that biochemical events associated with regulatory volume changes of the cells in response to an osmotic stimulus are associated with the biochemical events that are involved in the release of mediators (62). Under conditions of significant respiratory heat loss both mechanisms may work together to cause EIA. However, airway cooling is not a prerequisite for EIA, and breathing hot dry air can result in severe EIA (59, 60).

**Determinants for the development of BHR, airway inflammation and asthma in the athlete**

**Effects of heavy exercise**

Studies reporting the presence of BHR and airway inflammation are listed in Table 4. Medline was searched for relevant papers up to November 2006. Search words were asthma, bronchial responsiveness, airways inflammation, exercise-induced bronchoconstriction, athletes and sports. Relevant papers were included after individual inspection.

As already mentioned an open case-control study demonstrated an increase in bronchial responsiveness correlating with the exercise intensity in both asthmatic and healthy elite competitive adolescent swimmers after 3000 m swimming in an indoor swimming pool (4). Later an increase in bronchial responsiveness during the competitive season in young competitive skiers during their military services as compared with ordinary military recruits was reported (63). In young competitive skiers as compared with healthy somewhat older medical students, not particularly physically active, the skiers had lymphoid aggregates in their bronchi and signs of
Table 4. Studies on bronchial responsiveness and airways inflammation in relationship to exercise in top athletes, including the effect of the athlete’s environment

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Method</th>
<th>Condition</th>
<th>Population (n)</th>
<th>Study-type effect</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsen KH et al. (4)</td>
<td>BHR (histamine), lactate</td>
<td>Asthma and healthy young swimmers</td>
<td>Swimmers: Healthy (n = 13); Asthmatic (n = 6)</td>
<td>Case-control; PC\textsubscript{20}-Histamine increased after 3000 m heavy swimming, correlating to increase in lactate</td>
<td>2</td>
</tr>
<tr>
<td>Heir T (63)</td>
<td>BHR (methacholine)</td>
<td>Healthy training and nontraining</td>
<td>Military recruits, competitive skiers and nontraining recruits</td>
<td>Case-control; PC\textsubscript{20}-Histamine increased during winter competing season, but not in nontraining controls</td>
<td>2</td>
</tr>
<tr>
<td>Sue-Chu M et al. (5)</td>
<td>Bronchial biopsies; BHR: cold-air inhalation</td>
<td>Healthy</td>
<td>Training ski gymnasists (n = 30) and nontraining medical students</td>
<td>Case-control; lymphoid follicles in bronchial biopsies from skiers, not controls</td>
<td>2</td>
</tr>
<tr>
<td>Heir T et al. (78)</td>
<td>BHR (methacholine)</td>
<td>Healthy training and nontraining</td>
<td>Military recruits and competitive ski</td>
<td>Case-control; PC\textsubscript{20}-Histamine decreased when training with a respiratory virus infection, but not in nontraining</td>
<td>2–</td>
</tr>
<tr>
<td>Helenius U et al. (29)</td>
<td>Induced sputum and BHR to histamine</td>
<td>Swimmers and nonswimmers</td>
<td>29 swimmers and 19 controls</td>
<td>Case-control; elite swimmers had more often decreased PC\textsubscript{20}-Histamine than control subjects; sputum from swimmers contained higher per cent eosinophils and neutrophils and higher concentrations of EPO and HNL than sputum from controls</td>
<td>2</td>
</tr>
<tr>
<td>Helenius U et al. (65)</td>
<td>Induced sputum and BHR to histamine</td>
<td>Swimmers</td>
<td>42 swimmers followed for 5 years</td>
<td>Case-control follow-up; in swimmers who had stopped high-level training, BHR and asthma attenuated or disappeared; mild eosinophilic airway inflammation aggravated in highly trained swimmers who remained active during the 5-year follow-up; our results suggest that it may develop during and subside after an active sports career</td>
<td>2</td>
</tr>
<tr>
<td>Karjalainen EM et al. (64)</td>
<td>Bronchial biopsies</td>
<td>Skiers, asthmatics and healthy subjects</td>
<td>Skiers (n = 40, 16–20 years); Healthy (n = 12); Mild asthmatics (n = 12)</td>
<td>Case-control; tenascin in biopsies did not correlate to BHR</td>
<td>2</td>
</tr>
<tr>
<td>Lumme A et al. (66)</td>
<td>Induced sputum; BHR to histamine</td>
<td>Ice hockey players and healthy controls</td>
<td>Ice hockey players (n = 88) and healthy controls (n = 44)</td>
<td>Case-control; asthma is common in elite ice hockey players, showing a mixed type of neutrophilic and eosinophilic airway inflammation</td>
<td>2</td>
</tr>
<tr>
<td>Bonsignore MR et al. (71)</td>
<td>Induced sputum, neutrophilia, L-selectin</td>
<td>Healthy outdoor swimmers, training effect</td>
<td>Swimmers (n = 7)</td>
<td>Case series; airways neutrophilia (induced sputum) increased during endurance training and outdoor competing</td>
<td>3</td>
</tr>
<tr>
<td>Bonsignore MR et al. (72)</td>
<td>Induced sputum, neutrophilia, L-selectin, exhaled nitric oxide</td>
<td>Marathon running; after run and reconvalescence</td>
<td>Healthy middle-aged amateur marathon runners (n = 9)</td>
<td>Case series; airways neutrophilia increased after marathon run</td>
<td>3</td>
</tr>
<tr>
<td>Morici G et al. (73)</td>
<td>Induced sputum, cell counts</td>
<td>Healthy; all out rowing test</td>
<td>Nonasthmatic competitive rowers (n = 16, mean age: 16 years)</td>
<td>Case series; increased sputum cell counts after maximum rowing test; change from neutrophils to bronchial epithelial cells</td>
<td>3</td>
</tr>
<tr>
<td>Ransonen O et al. (58)</td>
<td>S-ECP, s-MPO</td>
<td>Elite skiers heavy-to-moderate training</td>
<td>National cross-country skiing teams (n = 15)</td>
<td>Case series; S-ECP and S-MPO increased significantly more after hard training compared with moderate training</td>
<td>3</td>
</tr>
<tr>
<td>Lassen K et al. (80)</td>
<td>BAL, cells</td>
<td>Exposure to –23°C vs +22°C, light intermittent work</td>
<td>Healthy individuals (n = 8, 24–43 years)</td>
<td>Case-control; increased BAL number of granulocytes and alveolar macrophages after 2 h of intermittent moderate work in –23°C in healthy individuals</td>
<td>2</td>
</tr>
<tr>
<td>Boulet LP et al. (148)</td>
<td>Induced sputum</td>
<td>Training session</td>
<td>Swimmers and runners, with and without BHR</td>
<td>Cross-sectional; increased neutrophils in hyper-responsive swimmers</td>
<td>3</td>
</tr>
<tr>
<td>Bernard A et al. (81)</td>
<td>Surfactant proteins A and B, EIB</td>
<td>EIB, pool attendance</td>
<td>Healthy children (n = 236), SPA and SPB (n = 1881, EIB)</td>
<td>Cross-sectional; increased serum SPA and SPB in school children related to their cumulative swimming pool attendance</td>
<td>3</td>
</tr>
<tr>
<td>Lagerkvist BJ et al. (82)</td>
<td>Clara cell protein, CC16</td>
<td>Pool attendance</td>
<td>Children (n = 57, 10–11 years)</td>
<td>Cross-sectional; decreased serum CC16 (a sign of lung epithelial injury) in swimming compared with nonswimming children both before and after exercise</td>
<td>3</td>
</tr>
</tbody>
</table>

EIB, exercise-induced bronchoconstriction; BHR, bronchial hyper-responsiveness; CP, eosinophilic cationic protein; MPO, myeloperoxidase; BAL, bronchoalveolar lavage; SPA, surfactant protein A.
bronchial remodelling (tenascin) as demonstrated by bronchial biopsies in addition to increased responsiveness to cold air (5, 64). A mixed type of eosinophilic and neutrophilic inflammation was found in elite swimmers (29, 65), ice-hockey players (66) and cross-country skiers (64, 67, 68). Swimmers with exercise-induced bronchial symptoms had significantly higher sputum eosinophil counts than symptom-free swimmers (29). The inflammation may represent a form of repeated thermal, mechanical or osmotic airway trauma resulting in a healing or remodelling process, and seems to be directly associated with heavy training as discontinuing high-level exercise has proved effective in reducing eosinophilic airway inflammation, as shown by a 5 years follow-up study of competitive swimmers (65). The athlete’s inflammation (neutrophils over-represented) may explain why indices for airway inflammation, BHR and symptoms have responded poorly to inhaled corticosteroids (69) or leukotriene antagonists (70) in the few controlled studies performed.

Bonsignore et al. (71) reported a relationship between airways neutrophilia (in induced sputum) and endurance training in seven swimmers’ training and competing outdoors. They also reported similar findings in nine nonasthmatic middle-aged amateur marathon runners (72). An increased number of cells in sputum was found in nine young competitive rowers before and after an all-out rowing test and a change in cell dominance from neutrophils to bronchial epithelial cells (73). Increasing serum levels of eosinophil cationic protein and myeloperoxidase as signs of eosinophil and neutrophil activation, respectively, were found before and after repeated heavy and moderate training sessions in the Norwegian national cross/country skiing teams and corresponding to the level of training (58). By using induced sputum comparison in asthmatic subjects with and without EIB, Hallstrand et al. (74, 75) reported that injury to the airway epithelium, overexpression of cysteinyi leukotrienes, relative under-production of prostaglandin E(2) and greater airway eosinophilia are distinctive immunopathologic features of asthma with EIB (74, 75). Boulet et al. (76) reported that a 1-h high-intensity training session was associated with an increase in airway neutrophils among hyper-responsive swimming athletes, but not in hyper-responsive runners or athletes without responsiveness, while airway responsiveness remained unchanged in all groups. A recent experimental study in mice showed that compared with sedentary mice, bronchiolar epithelium of trained mice demonstrated progressive loss of ciliated cells and increased apoptosis and proliferation, indicating damage and repair processes of respiratory epithelium in exercising mice (77). Most probably the athletes represent a heterogeneous group in this respect, and the response may differ between different sports, possibly also dependent on the environment in which the sport takes place. Further research is needed in this field to completely understand these processes.

Environmental factors

Certain environmental factors may further aggravate the effect of heavy training on the airways. Heir et al. (78, 79) found that bronchial responsiveness to methacholine increased for up to 6 weeks after an upper respiratory tract infection and after training in a cold environment. Larsson et al. (80) found in healthy individuals increased number of granulocytes and alveolar macrophages in BAL after 2 h of intermittent moderate work in a temperature of –23°C. Drobnic et al. (6) reported increased levels of organic chlorine products in swimming pools, whereas Bernard et al. (81) reported that increased occurrence of EIB and BHR, as well as increased serum levels of surfactant proteins A and B (as sign of increased permeability of the mucosal lining of the alveoli) in school children were related to their cumulative swimming pool attendance. Swimming school children in northern Sweden had decreased levels of serum Clara Cell protein (CC16) as compared with nonswimming children (82). Varraso et al. (83) found that the production of reactive oxygen species in swimmers was not only related to training but also to exposure to chlorinated compounds. In addition, other forms of pollution affect performance in athletes (84). Rundell (85) reported high levels of airborne ultra-fine particulate matter emitted from ice resurfacing machines in indoor ice rinks. Thus, there is much indirect evidence from epidemiological studies in athletes to suggest that both pollen exposure in summer athletes (3), cold air and respiratory infections in skiers (79), chlorine exposure in swimmers (29) and fine particles in ice rinks (85) have an adverse effect on respiratory health in competitive athletes (86, 87).

The diagnosis of asthma and EIA in the athlete

The diagnosis of asthma is clinical and based on history of symptoms, physical examination of signs indicating the presence of bronchial obstruction and variability in lung function spontaneously or due to bronchodilators (88). The main symptoms of asthma are recurring episodes of bronchial obstruction. The term current asthma is used when at least one episode of asthma has occurred during the last year. The competing athlete frequently reports the presence of respiratory symptoms in relationship to exercise, but the diagnosis of asthma or EIA may be difficult because of the variability and nonspecificity of symptoms (21, 89). The peripheral muscles and the cardiovascular system respond to training by increasing their capacity. The lung and the airways do not have a similar response to exercise. The lung’s diffusion capacity and pulmonary capillary blood volume remain unaltered in the highly trained athlete, whereas maximum pulmonary blood flow increases with enhanced maximum oxygen uptake. In the same manner, in response to physical training, ventilatory requirement increases with
Epidemiology and pathogenetic mechanisms of respiratory and allergic disorders in sports

no alteration in the capability of the airways and the lungs produce higher flow rates or higher tidal volumes with little or no change in the pressure-generating capability of inspiratory muscles (90). Furthermore, it has been demonstrated that in healthy highly trained elite endurance athletes, exercise-induced hypoxemia occurs in more than 50% (91, 92). Thus, distinguishing EIB from physiological respiratory limitations to physical exercise becomes important.

Testing for EIB

EIB by exercise testing was reported in 1985 in 70–80% of the asthmatic patients (93). However, presently this has changed dramatically with the widespread use of anti-inflammatory treatment of asthma with inhaled corticosteroids. EIB is rapidly and markedly influenced by inhaled corticosteroids (94–96), and this puts increased demand on the standardization of exercise test with respect to exercise load and environmental factors. Whereas studies performed in the early 1970s, led to recommendation about a sub-maximal exercise load with heart rate at the level of 170/min (97), the latest American Thoracic Society (ATS) guidelines recommend that an exercise load of 80–90% of the calculated maximum is employed in the testing of EIB with inhalation of air with a relative humidity below 50% and an ambient temperature of 20–25°C while running on a treadmill for 6–8 min (98). However, it was later demonstrated that there are significant differences in the magnitude of EIB between an exercise load of 85% and 95% (99). It was demonstrated that EIB is heavily influenced by the humidity and temperature of the inhaled air (100), and that the use of inhaled cold air (–20°C) during exercise testing markedly increased the sensitivity in diagnosing EIB without decreasing specificity in asthmatic children (101). Good reproducibility of testing for EIB has been demonstrated when controlled for environmental conditions (102, 103). Thus, strict environmental standardization with a high enough exercise load is important in the testing for EIB and using EIB as a monitoring device for asthma. Both ERS and ATS recommendations set a 10% reduction in FEV₁ as criterion for EIB (98, 104). In addition, eucapnic voluntary hyperpnoea has been recommended and used successfully in a wide range of summer and winter athletes (105). Eucapnic voluntary hyperpnoea has been found by some to have a higher sensitivity than exercise by itself (106).

Bronchodilator response

Airways response to inhaled bronchodilators is of value to detect airways obstruction, but has limited value as a basis for diagnosis of asthma (107). The bronchodilator response is a continuous variable, and a defined ‘cut-off’ value is therefore arbitrary (108). However, the criterion for a positive bronchodilator response recommended by European Respiratory Society is 12% increase in FEV₁ expressed as per cent predicted after inhaled bronchodilator or a 200 ml increase (109). Because of its simplicity, however, it is more common to record the increase in reversibility in per cent of baseline.

Measurement of BHR by other indirect stimuli

EIB may be seen as a measure of indirect bronchial responsiveness by causing bronchoconstriction indirectly by release of mediators (60, 110). Other indirect stimuli have also been used to assess bronchial responsiveness including inhalation of cold, dry air (111), dry air (112), hyperosmolar aerosols like hypertonic saline (113) and inhaled mannitol (112, 114, 115) and inhalation of adenosine monophosphate (AMP) (116). Generally, it might be stated that indirect tests are more specific for asthma, whereas the direct tests are more sensitive, but not to the same extent as the difference between asthma and other chronic lung disorders (101, 116, 117). When combining two indirect stimuli as cold air inhalation and exercise, the sensitivity may increase while maintaining a high level of specificity (101). The method of inhalation of AMP has also demonstrated a higher degree of sensitivity while maintaining specificity (116). It has been suggested by an independent panel of the Medical Commission of the IOC to use eucapnic hyperventilation with dry air (with the addition of 5% CO₂) as a screening test for EIA in athletes (112). Eucapnic hyperventilation of dry air of temperature 20–25°C has been demonstrated to correlate well with EIB and has been used in summer and winter athletes. However, when performed for 4 min with dry cold air it has been shown to have a low sensitivity in adults to detect asthma and bronchial responsiveness (118). Mannitol and eucapnic hyperventilation have been shown to have a comparable sensitivity (115); in contrast one report shows higher sensitivity of eucapnic hyperventilation in young athletes to detect BHR than methacholine (89). In order to have a high sensitivity, a reduction of 10% in FEV₁ has been considered as the appropriate limit for indirect tests compared with 15%, which have traditionally been used for some of these tests (for mannitol 15%). It has been demonstrated in several studies that the sensitivity of inhaling cold dry air is greater than the response to dry air only (119–122) including one recent study in preschool children (123), whereas only one study has reported the opposite (124). The potency of the eucapnic voluntary hyperpnoea protocol recommended by the IOC Medical Commission independent panel probably relates to the use of 6 min at a target ventilation of 85% maximum voluntary ventilation (112).

It was found in the early 1970s that a free-range running test was a stronger stimulus for provoking EIB in children than either running on a treadmill or performing a cycling test (125). For athletes it has been maintained that performing field tests with the specific exercise type employed in their type of sport is optimal for diagnosing
EIB and asthma. Rundell et al. (126) demonstrated 71% of athletes who had EIB after a specific field test had a negative response to a laboratory treadmill test. However, the environmental conditions in their laboratory included a relative humidity of 60% which in itself may protect against EIB. The same group reported a higher sensitivity to eucapnic hyperventilation than the exercise field test (127), as also was reported by Dickinson et al. (105). Stensrud et al. (128) recently reported metacholine bronchial provocation to be more sensitive to identify top athletes with direct/indirect BHR, satisfying the requirements of the IOC Medical Commission than a competitive exercise field test (cross-country skiing competitive event) (128).

Measurement of direct bronchial responsiveness using a pharmacological agent

Different stimuli may cause different responses in the same persons. It has been found that thermal stimuli to the airways involve narrowing of bronchi at a segmental level, whereas inhaled methacholine has its effect more distally in the bronchi (129). Hargreave (130) and Cockcroft (131) reported in the late 1970s the use of inhaled histamine or methacholine as a tool to measure bronchial responsiveness quantitatively. They demonstrated that the test differed between asthmatic patients and healthy individuals and Cockcroft reported that a histamine PC$_{20}$ $\leq$ 8 mg/ml had a sensitivity of 100% to diagnose asthma in a random sample of 500 college students, whereas the specificity was low. With a cut-off of 1 mg/ml the positive predictive value was 100, but the sensitivity was low. Cockcroft (131) concluded that a PC$_{20}$-Histamine $> 8$ or 16 mg/ml ruled out current asthma in most instances in the absence of treatment with inhaled corticosteroids (132). Later Yan et al. (133) simplified the test measuring the cumulative inhaled dose instead of using concentrations at tidal breathing. They used a hand-held Devilbiss nebulizer and deep inspiration to total lung capacity. Later other nebulizers, triggered electronically by inspiration, were used giving accurate deliveries of aerosol (134). Inspiration-triggered nebulizers have been combined with computer programmes to calculate PD$_{20}$ of the provocative agent (APS Jäger). When the ATS gave recommendations about measurements of BHR, they chose the tidal breathing method, calculating PC$_{20}$ or alternatively the five-step dosimeter method using slow deep inhalations to total lung capacity (98). Wubbel et al. (135) compared the two methods and found comparable results, whereas Cockcroft et al. (136) found that the PC$_{20}$ of the tidal breathing method was half of that obtained by the five-step dosimeter method, i.e. a PC$_{20}$ of 1.3 mg/ml of the tidal breathing method compared with 2.4 mg/ml of the five-step dosimeter method (136). They also reported that the bronchoprotective effect of inhaling methacholine by total lung capacity inspiration may influence the interpretation of the test result.

The use of different methods may mean that results from different laboratories are not always comparable (137). Certain laboratories have developed their own methods with their own reference values. Nevertheless these methods of measuring bronchial responsiveness have been quite stable with acceptable intraclass correlation coefficients.

When assessing the diagnostic value of this method for asthma, the patient groups used for assessment are important. Cockcroft et al. (132) found that a PC$_{20}$-Histamine of above 8 or 16 mg/ml ruled out current asthma in most instances based on a random sample of college students. In epidemiological studies of general populations a defined level of PC$_{20}$ or PD$_{20}$ to either histamine or methacholine does not always compare well with the diagnosis of asthma obtained by questionnaires (138). When exercise challenge was compared with direct bronchial challenges, some children reacted to exercise and some to methacholine or histamine, probably demonstrating that the two methods describe different properties of the airways. In one study, only 18 of 44 children with a 15% fall in FEV$_1$ after exercise responded to histamine (139). A similar low sensitivity using methacholine to identify responses to eucapnic voluntary hyperpnoea was found in elite summer athletes (115). Only 36% of the athletes having a fall of 10% or more after eucapnic voluntary hyperpnoea had response to 7.8 µmol of methacholine. Some of these discrepancies may be accounted for by the deep-breath technique used in the Yan method (89). When children with asthma and other chronic lung diseases were compared, it was found that exercise test had a very high specificity for asthma, but a low sensitivity, whereas methacholine challenge had a higher sensitivity but a low specificity (101, 117).

Several studies report on the findings of bronchial responsiveness or EIB in athletes, but few studies report on the efficacy of these methods as diagnostic tools. Turcotte et al. (140) in 100 high-level athletes and 50 sedentary controls found that a questionnaire made for chest tightness, wheezing, cough, postnasal drip, detected 37 out of 44 (84%) subjects with a PC$_{20}$-Histamine less than 8 mg/ml both in athletes and controls. The questions regarding chest tightness and wheeze had the highest specificity. Anderson et al. (7) chose cut-off points on the basis of specificity rather than sensitivity for methacholine challenges to identify people with asthma, using cut-off levels of methacholine challenges (PC$_{20}$ $\leq$ 2 mg/ml) in athletes not treated by inhaled corticosteroids and PC$_{20}$ of 13.2 mg/ml for those treated with inhaled corticosteroids for more than 3 months, in order to obtain approval to use inhaled $\beta_2$-agonists. These points were used for the applications received at the Olympic Games in 2002. Others felt that these cut-off point rules were too low (8).

The diagnosis of asthma in athletes sets the ground for permission to use inhaled $\beta_2$-agonists as reliever agents and inhaled corticosteroids as controller therapy in relation to sports. As reviewed later in this document,
there exists overwhelming evidence that inhaled β2-agonists and inhaled corticosteroids do not improve performance in healthy athletes. A possible beneficial effect is thus limited to the asthmatic athlete through treatment of the disease. This favours an approach which should give priority to sensitivity over specificity in the use of laboratory methods as a tool in documenting the diagnosis of asthma in order to allow asthmatic athletes to be treated according to the present guidelines, also when participating in sports.

It is the opinion of this Task Force that the following recommendations should be employed for the diagnosis of asthma in relation to sports.

Recommendations for the diagnosis of asthma, EIB and BHR in athletes

The report of recurrent symptoms of bronchial obstruction as chest tightness, wheeze and cough provoked by different stimuli and in particular by exercise is a prerequisite for the diagnosis of asthma or EIA in athletes. Sometimes respiratory symptoms not typical for EIA may occur not related to exercise, but as cough and phlegm at other times of the day. Laboratory tests alone are not sufficient for the diagnosis. The report of symptoms should be verified by the demonstration of reversibility of airflow obstruction, EIB or other methods of diagnosing either indirect or direct BHR. At times, even asymptomatic BHR may be present. Possible differential diagnoses should be investigated by a combination of patient history, clinical examination and judgement and adequate laboratory and field tests and examinations. A recommended procedure is shown in Table 5.

Table 5. Procedure for the diagnosis and the application to obtain approval for using inhaled steroids and/or inhaled β2-agonists in sports. As change of existing rules may be issued, the responsible physician should keep informed through the websites of WADA (World Anti-Doping Association) and IOC (International Olympic Committee) for the Olympic Games. As medical regulations for assessment of bronchial hyper-responsiveness (BHR) through pharmacological provocation may vary somewhat between different countries and the country-specific regulations should be observed. A combination of positive response to step 1 and either step 2, 3 or 4 is required.

<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>1.</td>
<td>Obtain history of respiratory symptoms and perform clinical examination with focus on signs of bronchial obstruction</td>
</tr>
<tr>
<td>2.</td>
<td>Lung function measurement (preferred method: spirometry or maximum expiratory flow volume loops) with demonstration of significant reversibility to inhaled bronchodilator (inhaled β2-agonist or other)</td>
</tr>
<tr>
<td>3.</td>
<td>Assessment of exercise-induced bronchoconstriction by standardized exercise test with sufficient exercise load</td>
</tr>
<tr>
<td>4.</td>
<td>Assessment of one of the other measures of bronchial responsiveness according to rules given by sports authorities and medical regulations: a) BHR to metacholine (alternatively histamine) b) Other measures of indirect BHR: eucapnic hyperventilation test; inhalation of cold dry air; adenosine monophosphate inhalation test; mannitol inhalation test and exercise field test</td>
</tr>
</tbody>
</table>

1. When demonstrable symptoms and objective and signs of bronchial obstruction like wheeze, cough, heavy breathing, occur either spontaneously or because of physical exercise in athletes, treatment may be necessary or advisable even if objective measurements have not been performed. However, the presence of such symptoms should lead to the necessary follow-up with adequate objective measures.

2. When prescribing treatment for asthma or symptoms suggesting asthma to an athlete, the athlete should be followed to assess the effect of treatment. With lack of treatment effect, the treatment should be modified or stopped if considered inadequate or the diagnosis reconsidered. The athlete should always be treated at the lowest medication level necessary to control symptoms.

3. When an athlete participates in international sports, a combination of medical history and laboratory tests should be documented as basis for the diagnosis of asthma and the possibility to use asthma medication. The laboratory test may either be the demonstration of EIB, reversibility to inhaled β2-agonists or the demonstration of BHR to direct or indirect stimuli.

a. EIB: A standardized exercise test at a high enough and standardized exercise load, breathing air of stable temperature and humidity (20–25°C and 40–50% relative humidity) should be employed, either in a laboratory or as a field test, demonstrating at least 10% reduction in FEV₁ from baseline after exercise. The type of exercise may be varied in accordance with the type of sport practiced, although running is most often the best suited for provoking EIB.

b. Responsiveness to inhaled bronchodilators: An increase in FEV₁ of 12% (in per cent of baseline or of predicted value) before and after inhalation of a bronchodilator, preferably an inhaled β2-agonist, administered by a pressurized metered dose inhaler, dry powder inhaler or a nebulizer.

c. Direct bronchial responsiveness: In athletes who have received inhaled corticosteroids for a period of 3 months or longer, a PC_{20} to either histamine or methacholine less than 16 mg/ml or a PD_{20} less than 3.2 mg (16 μmol) should be documented. In athletes who have not received such medication, the levels should be: PC_{20} ≤ 4 mg/ml or PD_{20} ≤ 0.8 mg (4 μmol). In laboratories with their own developed reference values for bronchial responsiveness, these could be employed after the references levels of the laboratory have been scientifically documented.

d. Other measures of indirect bronchial responsiveness: A reduction in FEV₁ of 10% before and after the provocative agent is considered adequate and comparable with the stimulus of the standardized exercise test. The test can be inhalation of cold, dry air or dry air as in the eucapnic hyperventilation test. Other test agents such as inhalation of hyperosmolar aerosols as hypertonic saline or mannitol...
may also be used. For mannitol, the dose inhaled to cause a decrease in FEV\(_1\) of 15% is determined (PD\(_{15}\)).

**Differential diagnosis of EIB**

There are several important differential diagnoses to EIA and EIB in an athlete. Studies have demonstrated that most of the elite athletes referred for respiratory problems do not suffer from asthma or EIA (141). A listing of several differential diagnoses is presented in Table 6.

One frequent differential diagnosis is exercise-induced inspiratory stridor or vocal cord dysfunction (142). The symptoms are inspiratory stridor occurring during maximum exercise, and stopping when the exercise is terminated unless hyperventilation is maintained. There are audible inspiratory sounds from the laryngeal area, and bronchodilators or other asthma medication are not of help. The condition most often occurs in young well-trained athletic girls from approximately 15 years of age. Symptoms only occur during maximum exercise. The symptoms are thought to be because of the relatively small cross-sectional area of the laryngeal orifice, which may be even further reduced by the negative pressure created on inspiration during heavy exercise. One possible differential diagnosis often called vocal cord dysfunction (VCD) to this syndrome is paradoxical movement of the vocal cords with adduction during inspiration which may also occur without exercise. The diagnosis of VCD/exercise-induced inspiratory stridor can be made clinically and confirmed and differentiated by direct fibre-optic laryngoscopy during exercise.

Swimming-induced pulmonary oedema (SIPE) is another possible differential diagnosis to EIA. SIPE occurs in well-trained swimmers after a heavy swimming session. This condition was recently reported in 70 previously healthy swimmers, who developed typical symptoms of pulmonary oedema together with a restrictive pattern in pulmonary function, which remained for up to 1 week after the swimming incident (143).

In addition, other chronic disorders including heart diseases and other respiratory disorders may have an effect on physical performance and thus be a possible differential diagnosis related to EIA. Over- and underweight might also influence the diagnosis, but this is rarely a concern in athletes.

Poor physical fitness or overtraining may represent possible differential diagnoses to EIA. This is especially so when the physical fitness and exercise performance are not up to the expectations of the athletes or possible parents or trainers. Lack of success in sports may be explained by often minor respiratory complaints which may be mistaken for asthma.

Finally, reports have been made concerning exercise-induced arterial hypoxemia (144). This occurs especially in highly trained athletes and is thought to be primarily because of diffusion limitations and ventilation-perfusion inequality. It is postulated that incomplete diffusion in the healthy lung may be because of a rapid red blood cell transit time through the pulmonary capillary. Physical training improves muscle strength and endurance, with increased ionotrophic and chronotrophic capacities of the cardiovascular system. No such effects occur in the respiratory tract. Ventilatory requirement rises with no alteration in the capability of the airways and the lungs produce higher flow rates or higher tidal volumes with little or no change in the pressure-generating capability of inspiratory muscles (90). The result is exercise-induced arterial hypoxemia which may occur in up to 50% of highly trained athletes (92, 145, 146). This reduction in arterial oxygen saturation may be confused with EIA.

Thus, several differential diagnoses to EIA exist (Table 6). Whatever the cause for the respiratory difficulties, it is important to make a thorough examination and rule out possible differential diagnoses.

### Table 6. Differential diagnosis of exercise-induced asthma in sports

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise-induced asthma (EIA)</td>
<td>Symptoms occurring shortly after (sometimes during) physical exercise. If observed: expiratory dyspnoea, expiratory rhonchi and other signs of bronchial obstruction. Gradual improvement either spontaneously or after inhaled bronchodilator. Reduction in forced expiratory volume in 1 s by at least 10% after exercise.</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Symptoms occur during maximum exertion. Symptoms disappear after stopping exercise (unless hyperventilating). If observed: inspiratory stridor, audible inspiratory sounds from laryngeal area. No signs of bronchial obstruction. No effect of pretreatment with inhaled bronchodilator. Flattened part of inspiratory flow volume loop during stridor.</td>
</tr>
<tr>
<td>Swimming-induced pulmonary oedema (SIPE)</td>
<td>Shortness of breath and cough during or immediately after swimming associated with evidence of pulmonary oedema. Symptoms and signs: shortness of breath, cough, sputum production, haemoptysis, reduced oxygen saturation (SpO(_2)). After swimming, restrictive spirometric pattern persisting for up to 1 week.</td>
</tr>
<tr>
<td>Other chronic lung disorders</td>
<td>When accompanied by reduced lung function: limitations to exercise occurring during exercise with often reduction in SpO(_2). Related to underlying disorder.</td>
</tr>
<tr>
<td>Other general diseases – heart disorders</td>
<td>Related to expectations and training level; high heart rate after low-grade exercise load; muscular stiffness.</td>
</tr>
<tr>
<td>Poor physical fitness</td>
<td>Occurs in well-trained athletes with high VO(_2) max; primarily because of diffusion limitations and ventilation–perfusion inequality. Incomplete diffusion in the healthy lung may be the result of rapid red blood cell transit time through the pulmonary capillary.</td>
</tr>
<tr>
<td>Exercise-induced arterial hypoxemia</td>
<td></td>
</tr>
</tbody>
</table>
Epidemiology and pathogenetic mechanisms of respiratory and allergic disorders in sports

Procedure of diagnosing EIA/EIB or other asthma-related symptoms in athletes

A procedure following the order that is explained next is recommended in the examination of athletes with respiratory symptoms (Table 5). The diagnostic criteria are common to the criteria for the common asthmatic patient. However, certain modifications must be made because of the regulations set by IOC and WADA for the use of asthma drugs in sports. An overview of the recommended procedure is shown in Table 5.

1. Careful case history with focus on exercise-related symptoms or other symptoms of asthma and possible allergic disease.
2. Clinical examination with focus on possible signs of bronchial obstruction.
3. Lung function, in particular maximum expiratory flow volume loops with assessment of reversibility to an inhaled β2-agonist like salbutamol.
4. Assessment of bronchial responsiveness, either by a direct or indirect method:
   a) bronchial provocation with metacholine (or histamine);
   b) exercise test standardized for assessing EIB;
   c) other tests of indirect bronchial responsiveness like eucapnic hyperventilation test, inhalation of cold dry air, AMP inhalation, mannitol inhalation and exercise field test.
5. Exercise test with maximum intensity to diagnose possible exercise-induced VCD.

Other specific examinations may become necessary depending on the findings and symptoms. The choice of the test may depend on facilities in the laboratory, case history and the medical regulations in the different countries. More than one test may be necessary. To satisfy the criteria of the IOC Medical Commission and obtain permission to use inhaled β2-agonists in relationship to Olympics and other forms of competitive sports, a positive test related to item 3 or 4 shown before is necessary.

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References


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