

## Screening of Athletes for Exercise-Induced Bronchoconstriction

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**Abstract:** Exercise-induced bronchoconstriction (EIB) has a high prevalence in elite athletes, particularly endurance athletes, winter athletes and swimmers. Recent studies have shown that a clinical diagnosis of EIB has only a moderate sensitivity and specificity for EIB. This finding in conjunction with a recent ruling by the IOC-medical commission that all athletes competing in initially the 2003 Winter Olympic Games in Salt Lake City, and now the 2004 Summer Olympic Games in Athens require objective evidence of EIB, support the need for bronchial provocation challenge tests in the diagnosis of EIB.

The recommended bronchial provocation challenge test is the eucapnic voluntary hyperpnea (EVH) challenge; this challenge test has been shown to have both a high sensitivity and specificity for EIB. Pharmacological challenge tests, such as the methacholine challenge test, have been shown to have only a low sensitivity but high specificity for EIB in elite athletes, and are thus not recommended in the athlete with pure EIB. Exercise challenge tests performed both in the laboratory and field have a high specificity for EIB; however those in the laboratory have only a moderate sensitivity for EIB in elite athletes, whilst those in the field are limited by problems with standardization. The osmotic challenge tests, such as the hypertonic saline and newer inhaled dry powder mannitol challenge have both a high sensitivity and specificity for EIB, and may be used as an alternative to the EVH challenge.

**Key Words:** asthma, exercise-induced asthma, exercise-induced bronchoconstriction, screening

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**E**xercise-induced bronchoconstriction (EIB) is defined as a transitory increase in airway resistance that occurs following vigorous exercise.<sup>1</sup> *Exercise-induced asthma* refers to such a narrowing in those people with known asthma. It has been shown to occur commonly in otherwise healthy people, including school children,<sup>2</sup> defense force recruits,<sup>3</sup> and athletes,<sup>4–6</sup> with the highest prevalence occurring in endurance athletes, such as cyclists, distance runners, swimmers, and winter ath-

letes, including cross country skiers and figure skaters. The prevalence of EIB within both the Summer and Winter Olympic teams has been progressively increasing over recent years, which has raised concerns within the International Olympic Committee (IOC) over the diagnosis of EIB and prescription of bronchodilator medications in athletes. In the 2000 Australian Summer Olympic team, the prevalence of EIB was found to be in the order of 21%,<sup>7</sup> in contrast to that within the general community, where the prevalence is within the order of 6% to 12%.<sup>8–10</sup>

The higher prevalence of EIB in athletes is thought to be due to the high training loads in athletes combined with the training environment of the athletes. Exercise may increase the ventilation to up to 200 L/min for short periods in speed and power athletes and for longer periods in endurance athletes.<sup>11</sup> Such increases in ventilation may not only result in mechanical trauma to the airways but also substantially increase the exposure of the airways to air, cold air, allergens, pollutants, and dust, all of which may result in inflammation of the airways and thus bronchial hyperreactivity (BHR). In summer athletes, it is thought that increased exposure of the airways to inhaled allergens may induce an IgE-dependent inflammatory response, which may be a major contributing factor to the development of BHR and, thus, EIB.<sup>12</sup> In swimmers, it is believed that chlorine and its metabolites form a gaseous layer on the surface of the water and surrounding air, which may irritate the airways to result in the development of BHR and EIB.<sup>13,14</sup> Finally, in winter athletes, exposure of the airways to the cold air is thought to be a major factor in the development of BHR and EIB, but it is unclear whether the narrowing is in response to the low temperature of the inhaled air, the low water content of the inhaled air, or a combination of both.<sup>15,16</sup>

A number of studies have shown that EIB is often misdiagnosed, both overdiagnosed and under-diagnosed. Until recently, the diagnosis of EIB revolved around a history of exercise-related breathing symptoms, only very occasionally confirmed by a bronchial provocation challenge test. Recent rulings of the IOC Medical Commission require that all athletes, to be permitted to use inhaled  $\beta_2$ -agonists—medications commonly used in the prevention and/or treatment of asthma or EIB—require objective evidence of airway narrowing.<sup>17</sup> This requirement, in conjunction with the high rate of misdiagnosis, suggests the need for screening for EIB in athletes,

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particularly those involved in endurance sports and swimming. A number of screening methods are available.

## SCREENING METHODS FOR EXERCISE-INDUCED BRONCHOCONSTRICTION

### Clinical/Questionnaires

The symptoms suggestive of EIB consist of exercise-related chest tightness, shortness of breath, cough, and wheeze, classically occurring within the first 10 minutes after moderate to intense exercise. Symptoms occurring during exercise are less likely to be asthma. However, a number of studies have shown that symptom-related diagnoses, either clinical or through questionnaires, have only a moderate sensitivity and specificity for EIB, leading to both an overdiagnosis and an underdiagnosis. It has been shown that airway narrowing may occur in the absence of symptoms; thus, an isolated symptom-based diagnosis is considered by some researchers to be unreliable.<sup>18</sup> In a study performed on intercollegiate athletes referred for pulmonary function tests based on a medical history consistent with EIB, only 46% had a positive laboratory exercise challenge test,<sup>19</sup> while only 76% of male college football players with symptoms suggestive of asthma had a positive methacholine challenge test.<sup>20</sup> In a separate study performed in elite athletes, 45% of those subjects reporting symptoms had a negative exercise challenge test.<sup>18</sup> Holzer et al<sup>21</sup> found that 28% of elite summer sport athletes reported 1 or more respiratory symptom but did not have a positive bronchial provocation challenge. Furthermore, Rundell et al<sup>18</sup> found that only 61% of athletes positive to a field exercise challenge reported symptoms. Similarly, Holzer et al,<sup>21</sup> in a study investigating the relationship between a respiratory-based questionnaire and eucapnic voluntary hyperpnea (EVH) challenge test, observed that only 60% of elite athletes with a positive EVH challenge test reported symptoms. Moreover, some athletes who are clearly symptomatic postexercise and/or exhibit performance decrements in cold conditions demonstrate normal postexercise spirometry.

### Bronchial Provocation Challenge Tests

There are 2 main types of bronchial provocation challenge tests: the direct and indirect challenge tests. The direct challenge tests consist mainly of the pharmacological challenge tests, in which the administered agent acts directly on the airway smooth muscle receptors to cause contraction. The indirect challenge tests, which include exercise challenge tests, the EVH challenge test, and the osmotic challenge tests, result in the production of mediators such as histamine, the leukotrienes, and prostaglandins, which act on the airway smooth muscle receptors to produce contraction and airway narrowing. Evaluating the response to each of these challenge tests revolves around measuring airway parameters, in particular the forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced

expiratory flow from 25% to 75% of the forced expiratory volume, before and after the challenge. The result of the challenge is calculated by determining the maximum percent change in these values as a consequence of the challenge. In both the pharmacological and osmotic challenge tests, the result is expressed as the dose of the administered agent that produces a defined fall in the FEV<sub>1</sub>, while in the EVH and exercise challenge tests, the result of the challenge is expressed as the maximum fall in FEV<sub>1</sub>. Controversy exists as to what percent fall in the FEV<sub>1</sub> defines a positive challenge test, and the value varies for the different challenge tests.<sup>22</sup> Population studies in both normal subjects and asthmatics recommend a fall in the FEV<sub>1</sub> of between 10% and 20%, depending on the type of challenge, as the minimum accepted fall for a positive challenge.<sup>22</sup> The values below are the values that we use in our laboratory.

### Pharmaceutical Challenge Tests:

#### Methacholine/Histamine Challenge Tests

Pharmaceutical challenge tests rely on the administration of agents such as histamine or methacholine, which act directly on the airway smooth muscle receptors to cause contraction in susceptible individuals. This challenge test is performed in a laboratory and requires the administration of increasing doses of the agent. Spirometry is measured after the administration of each dose, prior to the next dose. A fall in the FEV<sub>1</sub> of greater than 20% from baseline values is considered a positive challenge test, but this must occur at a dose of less than or equal to 3.6  $\mu\text{mol}$  (8 mg/mL) to be considered to be indicative of BHR to methacholine and histamine. The result is reported as a PD20 or PC20, depending on the protocol and method used. Although a recommended screening challenge test for chronic asthma, this challenge test has been shown to have a low sensitivity for EIB in athletes.<sup>21</sup> The pharmaceutical challenge tests have the advantages of being relatively safe, as they are performed in a stepwise manner, with spirometry performed prior to the administration of the next dose. They are also readily available. However, they are laboratory-dependent and expensive, and the patients are not exposed to the outside triggers to which they are exposed when exercising.

### Exercise Challenge Tests

Exercise challenge tests may be performed in the laboratory or on the field.

#### Laboratory Exercise Challenge Tests

An exercise challenge test performed in the laboratory may be performed on a cycle ergometer or treadmill. On the cycle ergometer, 1 of 2 protocols may be used: either a single-load protocol, in which the subject exercises at an intensity of 45% to 60% of predicted maximum voluntary ventilation (MVV) for 6 to 8 minutes, or an increasing protocol, with the intensity starting at 60% of the final load in the first minute, then 75% in the second minute, 90% in the third minute, and

100% in the fourth minute.<sup>23</sup> Once the target level is reached, the workload is held for 4 minutes.<sup>24</sup> The standardized treadmill protocol recommends a speed and grade to produce 4 to 6 minutes at near maximum heart rate, with a total of exercise duration of 6 to 8 minutes.<sup>24</sup> During the first 2 to 3 minutes of exercise, both the treadmill speed and grade are rapidly increased until the subject's heart rate is 80% to 90% of the maximum predicted. Spirometry is then measured at regular intervals for up to 30 minutes following completion of either challenge. A positive challenge test is defined as a fall in FEV<sub>1</sub> of greater than 15% from baseline values, while a fall greater than 10% is considered abnormal. Although this type of challenge test has a high specificity for EIB, it often fails to reach a high enough ventilation rate in trained athletes to induce the EIB. Furthermore, it has the following disadvantages: it is not sports-specific, it is not performed in the environment in which the exercise is usually performed, and the equipment is expensive.

#### **Field Exercise Challenge Tests**

A field exercise challenge test involves athletes completing a challenge test while performing the sport in which they are normally involved. Although a number of different protocols may be employed, the aim is to have the athlete exercising at 85% maximum heart rate for a minimum of 4 to 6 minutes. Spirometry is then measured at regular intervals for up to 30 minutes following completion of the challenge. A positive challenge test is defined as a fall in FEV<sub>1</sub> of greater than 15% from baseline, while a fall greater than 10% from baseline is considered abnormal, suggestive of bronchial hyperreactivity, but not definite EIB. Again, this type of challenge is highly specific for the diagnosis of EIB, but it has the disadvantages of no standardization of the cardiovascular workload or environmental conditions of temperature and humidity. Reliance on suitable weather conditions and on the patient's motivation is a further disadvantage.

#### **Eucapnic Voluntary Hyperpnea Challenge Test**

An EVH challenge test is the current challenge test recommended by the IOC for the diagnosis of EIB in elite athletes.<sup>17</sup> It involves the ventilation of a dry gas containing 5% carbon dioxide, 21% oxygen, and the balance nitrogen for a set duration, depending on the protocol used. This concentration of gas is safe, stimulates ventilation, and has been shown to maintain normal end-tidal CO<sub>2</sub> levels throughout the challenge (unlike exercise). There are 2 main challenge protocols, each requiring different levels of MVV, calculated as the baseline FEV<sub>1</sub> multiplied by 35.

##### **Stepped**

The stepped protocol is used in those with severe or unstable airway disease. It involves increasing the patient's ventilation rate over 3 stages<sup>25,26</sup>:

##### *Stage 1*

Three minutes at 30% MVV

Spirometry at 1, 3, 5, and 7 minutes or until stable

##### *Stage 2*

Three minutes at 60% MVV

Spirometry at 1, 3, 5, and 7 minutes or until stable

##### *Stage 3*

Three minutes at 90% MVV

Spirometry at 1, 3, 5, and 7 minutes or until stable

If a fall of in FEV<sub>1</sub> of greater than 20% from baseline occurs, the challenge is ceased.

#### **Single-Stepped**

The single-stepped protocol is used in those with mild asthma or EIB. It follows the protocol of Argyros et al<sup>27</sup> and involves a single level of ventilation at 85% MVV for 6 minutes. The lung function is then measured for up to 15 minutes following the challenge.

A positive challenge test is calculated as a fall in FEV<sub>1</sub> of greater than 10% from baseline. This challenge test has been shown to have a high specificity for EIB.<sup>28</sup> It has the advantage over exercise of being able to achieve and sustain the higher ventilation rates required to induce bronchoconstriction in extremely fit or well-conditioned athletes. In addition, it is inexpensive and easily standardized between laboratories.<sup>27</sup> However, it is laboratory-dependent, and thus, the athlete is not exposed to the outside triggers that may be encountered during exercise. Also, it is currently available only in specialized centers.

#### **Osmotic Challenge Tests**

The osmotic challenge tests induce hyperosmolarity and hypertonicity of the airways without the need to exercise. The hyperosmolarity and hypertonicity have been shown to be the same as those occurring with exercise and EVH, and the result in mast cell degranulation and the release of inflammatory mediators that induce bronchoconstriction. There are 2 main osmotic challenge tests.

##### **Hypertonic Saline Challenge Test**

The hypertonic saline challenge test is the current bronchial provocation challenge test recommended for screening of asthma/EIB in scuba diving medical assessments.<sup>29</sup> It involves the administration of increasing doses of hypertonic saline, achieved by increasing either the duration or the concentration of saline administered. Spirometry is measured after each dose, prior to administration of the next dose. A fall in FEV<sub>1</sub> of greater than or equal to 15% is considered a positive challenge test. This challenge has been shown to be both sensitive and specific in the diagnosis of EIB,<sup>30,31</sup> and furthermore, it may be used to induce sputum for further analysis. It is unfortunately laboratory-dependent, and patients are not exposed to the environmental triggers that they may encounter while ex-

exercising; however, it is a relatively safe and inexpensive challenge test.

### Inhaled Dry Powder Mannitol Challenge Test

The inhaled dry powder mannitol challenge test is a newer challenge test, and its role in the diagnosis of asthma/EIB is still being assessed. It involves the administration of increasing doses of encapsulated dry powder mannitol via a spinhaler.<sup>32</sup> After the administration of each dose, prior to the next dose, spirometry is measured. Currently, a fall in FEV<sub>1</sub> of greater than or equal to 15% is considered a positive challenge test; however, this level may soon be reduced to 10%, as population studies have shown that most nonasthmatics fall less than 10% and most asthmatics fall greater than 10%.<sup>33</sup> This challenge test has been shown to be both a sensitive and a specific challenge test in the diagnosis of asthma/EIB.<sup>25,33</sup> It has the advantages of being cheap and safe, given the monitoring of lung function throughout the stepped challenge, and it offers hope as a future office-based challenge test. The main disadvantages are that patients are not exposed to the environmental triggers that they may encounter while exercising, and in some athletes, a cough may occur.

### Allergy Testing

A strong association has been shown between atopy and EIB, particularly in elite summer athletes. It is recommended that skin sensitivity tests be performed for all common airborne allergens to assess for atopy.

### CONCLUSIONS

It is recommended that all elite athletes involved in endurance sports such as swimming, cycling, and rowing; swimming sports; and winter sports such as cross-country skiing and figure skating should undergo a bronchial provocation challenge test to exclude EIB. Clinical symptoms and questionnaires may be used to guide the diagnosis, but symptoms have been shown to be only a mediocre guide to EIB, both overdiagnosing and underdiagnosing. A trial of inhaled mast cell stabilizers or  $\beta_2$ -agonists prior to exercise may suffice in the recreational athlete, but in the elite or regular athlete, a diagnosis is required. The challenge test currently recommended by the IOC is the EVH challenge test; however, this challenge test may not be readily available due to its current availability in only specialized centers. Exercise challenge tests are highly specific for EIB; however, in the laboratory, they may not achieve a high enough level of ventilation to induce the bronchoconstriction, while in the field, problems with standardization of both the environmental conditions and the workload may occur. The osmotic challenge tests have been shown to be both sensitive and specific challenge tests for the diagnosis of EIB; the hypertonic saline challenge test is the challenge test recommended for medical assessments in scuba diving screenings, while the inhaled dry powder mannitol challenge test, a

challenge test still undergoing assessment, has potential as a future office-based challenge test. Skin sensitivity tests are recommended in all summer athletes to assess the role of atopy in the development and severity of the EIB.

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