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Exercise induced bronchoconstriction in elite athletes

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Exercise induced bronchoconstriction in elite athletes: measuring the fall

K Holzer, J A Douglass

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Decreased FEV_1 in response to bronchial provocation challenge remains the method of choice for diagnosing EIB in elite athletes, but the exact level of fall which represents an abnormal response still needs to be determined

The problem of exercise induced asthma (EIA) in elite athletes was first recognised because of the disproportionately high numbers of athletes at the elite level using β_2 agonists for asthma treatment during competition. In response to this problem, the International Olympic Committee's Medical Commission (IOC-MC) and other major sporting bodies have instituted guidelines requiring objective evidence of asthma to permit medication use by elite athletes in competition.[1] These guidelines have highlighted the need for bronchial provocation challenge tests in the diagnosis of asthma in the elite athlete group.

Exercise induced bronchoconstriction (EIB)

EIA describes the transitory increase in airway resistance that occurs following vigorous exercise.[2] However, because exercise may be the only provoking factor in some patients, especially in elite athletes where there are no other symptoms or signs of asthma, the term "exercise induced bronchoconstriction" (EIB) may be more appropriate. This allows the separation of a physiological response from a disease.[3]

Problems with diagnosing EIB

Emerging data suggest that the clinical diagnosis of EIB is relatively inaccurate. Rundell and co-workers found that only 61% of athletes positive to a field exercise challenge test reported symptoms while 45% of those negative to the challenge also reported symptoms.[4] Similar findings were reported in a study of 50 elite Australian summer sport athletes by Holzer and co-workers[5] in which seven of the 26 athletes (27%) with a positive challenge test for EIB reported no exercise related respiratory symptoms, and only 24 of the 34 athletes (71%) who reported symptoms had a positive bronchial provocation challenge test. These findings indicate that some athletes who are clearly symptomatic after exercise and who may exhibit performance decrements may have normal spirometric values after exercise. The presence or absence of symptoms is therefore not a reliable indicator for diagnosing EIB.

Available bronchial provocation challenge tests

The diagnosis of EIB demands confirmation by demonstration of a decrement in lung function associated with exercise or a surrogate, usually achieved by bronchial provocation testing. There are a range of bronchial provocation challenge tests available to screen for or confirm the diagnosis of EIB, each with differing efficacy in the diagnosis as a consequence of the different methods and agonists used. Importantly, the efficacy of each of these challenge tests in the diagnosis of asthma in an individual with chronic asthma may be different from that in the diagnosis of EIB in athletes.

The eucapnic voluntary hyperventilation (EVH) test is the current challenge test recommended by the IOC as the optimal laboratory based challenge test for the identification of EIB.[1] Phillips et al[6] showed that the airway response in asthmatics—as measured by changes in forced expiratory volume in 1 second (FEV_1) and specific conductance (sGaw)—to hyperpnoea with 5% CO_2 was similar to that provoked in the same asthmatic subjects by exercise at the same ventilation. The protocol used required the subject to perform hyperpnoea by inhaling dry air containing 5% CO_2 at room temperature for 6 minutes at a ventilation equivalent to 30 times baseline FEV_1. EVH has been reported to have a high specificity for active asthma, diagnosing 90% of asthma cases when a fall in FEV_1 of 10% is taken as abnormal and 100% when a 15% fall is considered abnormal.[7] The symptoms provoked by EVH are very similar to those that occur following exercise (cough, chest tightness, dyspnoea, and wheeze). The major advantage of using EVH over exercise to provoke bronchoconstriction is the ability of the subject to reliably achieve and sustain a minute ventilation that is higher than that which could be obtained on exercise.

Pharmacological challenge tests, which rely on the administration of agents such as histamine and methacholine to act

directly on the airway smooth muscle receptors to induce bronchoconstriction, have frequently been used as challenge tests to diagnose EIB in both the clinical and research settings. These challenge tests assess non-specific bronchial hyper-responsiveness (BHR), so a positive challenge test does not necessarily indicate a diagnosis of EIB. Similarly, a negative pharmacological challenge test does not exclude a diagnosis of EIB, particularly when investigating a random population with non-specific respiratory symptoms. In a population of elite Australian summer sport athletes, the methacholine challenge test was found to have a high positive predictive value (100%) for hyperpnoea induced bronchoconstriction.[5] However, the negative predictive value was only moderate (61%). In this study the methacholine challenge test only detected nine of the 25 athletes with a positive EVH challenge test, although all the athletes with a positive methacholine challenge test also had a positive EVH challenge test. This suggests that most summer athletes with non-specific BHR suggestive of underlying asthma are likely to develop EIA when competing and training at high levels. This study also highlighted the presence of EIB in elite athletes, as distinct from EIA. EIB was shown as a prevalent but separate condition in which the athletes are negative to a methacholine challenge test but positive to an EVH challenge test, suggesting that BHR occurring in a number of elite athletes may not reflect asthma per se but possibly injury to the airways as a consequence of the high ventilation rates achieved during exercise. The pharmacological challenge tests thus have a low sensitivity to detect EIB in elite athletes and are therefore not recommended as a bronchial provocation challenge test in the diagnosis of EIB in athletes.

Exercise challenge tests performed both in the laboratory or on the field have been shown to have a high specificity but only moderate sensitivity for EIB. The laboratory challenge test performed on a treadmill or cycle ergometer is limited by an inability to achieve the desired workload, and thus ventilation rate to induce EIB, in elite or conditioned athletes. Furthermore, athletes are often asked to perform an exercise to which they are not accustomed. In a study comparing the EVH, laboratory exercise, and methacholine challenge tests in known asthmatics, the laboratory exercise challenge was found to be clearly inferior to the other two challenge tests in the diagnosis of EIB.[8] The field challenge test, in which athletes perform a challenge using their primary exercise, is limited by an inability to standardise both the cardiovascular workload and environmental conditions of temperature and humidity—important

factors in the development of EIB. Both Mannix et al[9] and Rundell et al[10] have found that field exercise challenge tests have a lower sensitivity for EIB than the EVH challenge test. In a study of 38 winter athletes, 11 were found to have a positive field challenge and 17 a positive EVH challenge.[10] Similarly, Mannix et al[9] found that nine of 29 competitive figure skaters had a positive exercise challenge and 12 had a positive EVH challenge.

Osmotic challenge tests, comprising the inhaled hypertonic saline challenge test and the inhaled dry powder mannitol challenge tests, are indirect challenge tests often used in the diagnosis of asthma and EIB. In clinically recognised asthmatics, the airway response to an osmotic challenge with either a wet aerosol of 4.5% saline or a dry powder aerosol of mannitol compares well with the response to exercise and EVH, and either test can be used as a surrogate for exercise to identify those with EIB. Riedler et al,[11] in a study performed in 350 children, found good agreement between exercise and inhaled hypertonic saline, except in the case of mild asthma. Brannan et al[12] assessed the use of inhaled mannitol in the diagnosis of EIB and found that 22 of the 23 subjects (96%) with a positive exercise challenge also had a positive inhaled mannitol challenge. Furthermore, in the elite athlete population the sensitivity and specificity of inhaled mannitol for the detection of EIB, as defined by a positive EVH test, was 96% and 92% respectively.[13] An advantage of osmotic challenge tests is that the osmotic agents are given in progressively increasing doses with the airway response measured after each dose. This contrasts with the protocols for testing with exercise and EVH in which a single episode of exercise or hyperventilation of 6–8 minutes is used to obtain an airway response. A progressive protocol increases the relative safety of the challenge and this, in conjunction with the portability of the equipment used, suggests that mannitol challenges could be used at the point of need in an office based practice. The hypertonic saline challenge is currently the only osmotic challenge test recognised by the major sporting bodies for EIB; the inhaled dry powder mannitol challenge is currently undergoing further assessment.

The determination of the presence or absence of asthma or EIB in each of these challenge tests relies on a reduction in the lung function of the athlete following the administration of the challenge. Universally, a fall in the FEV_1 from baseline is the accepted measure. Depending on the type of challenge test, the accepted fall in the FEV_1 for a positive challenge varies from 10% to 20% and must occur within a

specified period following the administration of the challenge dose, or within a specific cumulative dose of administered agent. The IOC-MC accepts a fall in FEV_1 from baseline of 10% for the EVH and exercise tests, both in the field and laboratory, 15% for the hypertonic saline challenge test, and 20% for the methacholine challenge test. These figures have been determined by comparative studies between the challenge tests in known asthmatics, but the quantitation of the percentage fall in lung function in populations of elite athletes has not been performed to enable determination of a population based cut off value.

Study by Dickinson et al

The paper published in this edition of *Thorax* by Dickinson and colleagues[14] finally resolves the question of whether the sensitivity of challenge testing for EIB in athletes could be increased by using forced expiratory flow at 50% of vital capacity (FEF_{50}) as the measure of expiratory flow in preference to FEV_1. This intriguing possibility has been suggested on many occasions because of the relatively poor concordance of symptoms with challenge findings in the diagnosis of EIB, supported by epidemiological studies (predominantly in children) showing that airflow at low lung volumes such as FEF_{50} increases the sensitivity of exercise challenge tests.[15] Dickinson and colleagues have clearly shown in elite athletes that, while as might be expected FEV_1 and FEF_{50} were correlated, the sensitivity of the test was not improved by the use of FEF_{50} as the criterion for judging challenge responsiveness.

Does this suggest that the small airways are not involved in EIB? On the contrary, bronchial lavage findings reported by Sue-Chu and co-workers[16] suggest that lymphocytic inflammation is found in elite winter athletes with EIB, indicating that small airways are involved in bronchoconstriction in elite athletes. Rather, the discrepancy in the findings is likely to be due to the difficulties of maintaining a constant FVC in patients with airflow limitation, thus affecting FEF_{50}.

The diagnosis of EIB in athletes therefore revolves around the type of bronchial provocation challenge test used rather than the type of lung function measurement. The IOC recommends the EVH challenge test as the optimal challenge test for the diagnosis of EIB in athletes. Reliance solely on a history of exercise related respiratory symptoms or the use of an inappropriate bronchial provocation challenge test may result in misdiagnosis of EIB. Furthermore, the use of lung function measures such as FEF_{50} may lead to further misdiagnosis. A change in FEV_1 in response to bronchial provocation

challenge is the universally recognised and accepted method of diagnosis for EIB in elite athletes. What still needs to be more clearly determined is the exact level of fall of FEV_1 in response to challenge in elite athletes which represents an abnormal response.

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Smoking cessation and airway inflammation in COPD
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Why does airway inflammation persist after the smoking stops?

J C Hogg

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Important new observations on the behaviour of T lymphocytes and plasma cells following prolonged smoking cessation in patients with COPD

The toxic gases and particles generated in tobacco smoke come into contact with lung tissues each time a puff of smoke is inhaled, and this tissue injury recurs in a cyclic fashion as each cigarette is smoked. A 20 pack year smoking history indicates that the subject's lungs have received 20 of these short cyclic exposures per day for a cumulative total of 7300 exposures per year and 146 000 exposures over the lifetime of their smoking habit. This complex pattern of acute upon chronic inhalation injury reduces the innate defences of the lung by interfering with mucociliary clearance,[1] diminishing the inflammatory cytokine response to other stimuli,[2] and disrupting the epithelial barrier.[3 4] The tissue damaged by the smoke becomes infiltrated with innate and adaptive inflammatory immune cells and, even though tobacco smoke exposure may suppress the immune response,[5] the lymphoid cells collect to form the follicles with germinal centres that document the presence of the adaptive immune response.[6] The antigens that drive this immune response have not been clearly identified, but both microbial antigens that accumulate as a result of colonisation and infection of the lower respiratory tract, and possibly autoantigens created within injured lung tissue, have been implicated.[6–8]

The classic longitudinal study of chronic bronchitis and emphysema conducted by Fletcher and associates in the late 1950s and 1960s established that only 20–25% of smokers develop airflow limitation.[9] These investigators also observed beneficial effects from stopping smoking that have been confirmed in early stage (GOLD 1 and 2) disease by a randomised controlled trial.[10] The fact that COPD is limited to a susceptible minority of smokers,[9] and those that successfully stop smoking both slow their rate of decline in forced expiratory volume in 1 second (FEV_1) and delay their death,[9 10] is not easy to reconcile with cross sectional observations on lung tissue pathology where the chronic inflammatory response that is thought to drive the process is observed in everyone that smokes and seems to persist long after the smoking has stopped.[6 11 12] Although this discrepancy has been partially reconciled by observations indicating that the response to tobacco smoke is amplified in the minority of smokers that develop COPD,[13 14] the precise mechanisms for either the amplification step found in association with the group that develop COPD or the persistence of the inflammatory immune response following the removal of the smoking stimulus remain to be clarified.

Lapperre and colleagues[15] address this problem in this issue of Thorax in a study of 114 patients in GOLD stages 2 and 3 COPD who were not receiving either inhaled or oral steroids at the time of the study. There were 99 men, and 42 had quit smoking for a median time of 3.5 years. They found that, as a group, the ex-smokers had higher numbers of CD4+ lymphocytes and plasma cells than current smokers while there was no difference in the numbers of neutrophils, macrophages, or CD8+ cells

inhibitors. A meta-analysis of the data obtained from the BR12 and ISEL studies may indicate whether EGFR expression confers a survival advantage in patients treated with EGFR inhibitors. The findings described above refer to relapsed NSCLC patients. However, we do not have any data on the role of EGFR monotherapy when used as first line treatment, particularly in poor performance patients or as maintenance treatment following chemotherapy. Prospective large scale clinical studies with translational component need to be performed to identify the most optimal paradigm for selection of patients for treatment with EGFR inhibitors. Defining the mechanisms of resistance to EGFR inhibitors, coupled with identifying the molecular and clinical profile of responding versus non-responding patients in ongoing trials, remains a very important priority. A randomised phase III study examining the role of EGFR inhibition as first line treatment for patients with advanced NSCLC is currently in progress in the UK, attempting to answer some of these questions.

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