Running out of breath

Dr Danica BONELLO SPITERI

ABSTRACT

There is emerging evidence that the prevalence of exercise-induced bronchospasm (EIB) is significantly under-reported in many sports. Little is known about the potential performance improvement that may exist when sports players are detected and treated for EIB, but optimal airway health is crucial for anyone undertaking regular exercise at any level. Athletes may not be aware of an underlying diagnosis of EIB, as they may be asymptomatic, whilst other athletes may present with asthma-like symptoms but, upon testing, there is a negative test for EIB. The pathophysiology of bronchoconstriction that occurs in EIB differs from that which occurs in normal asthma, due to the large volumes of air that pass through the respiratory airways resulting in drying out of the aveolar fluid with resultant chemical release. A eucapnic voluntary hyperpnoea (EVH) challenge is the gold standard to detect underlying EIB when it results in a 10% drop from the baseline forced expiratory volume in one second (FEV_1) in comparison to the baseline spirometric FEV_1. When a negative EVH challenge results, alternative respiratory diagnoses must be sought and treated. Hence not all exercise related breathing disorders encountered in family practice should be labelled as exercise induced asthma and treated as such.

Key words / Phrases

Exercise induced asthma; eucapnic voluntary hyperpnoea; athlete; bronchoconstriction; exercise.

INTRODUCTION

Exercise induced asthma (EIA) is a condition that is overdiagnosed and underdiagnosed throughout the physically active population. Overdiagnosis occurs since most patients initially present to their family physician with various respiratory associated symptoms in relation to undertaking exercise. Through lack of understanding of what EIA constitutes and possible alternative diagnoses, most patients are labelled as 'exercise induced asthma' and started on the routine inhalers without any proper investigation or follow up. A better understanding of EIA would enable the family physician to better manage this condition as it has been noted that most patients still resort to their family physician rather that respiratory specialists in order to control their symptoms. Alternative diagnoses for exercise related breathing disorders may not be considered by family doctors, making the overdiagnosis problem larger. Underdiagnosis occurs since EIA can affect both the recreational and elite athlete, yet it is totally asymptomatic; hence it not easily picked up, either by the family doctor or by the patient, unless it is considered.

PREVALENCE

The sporting population is known to have a higher incidence of asthma than the general population. Athletes participating in summer sports have a lower prevalence of exercise-induced bronchospasm (EIB) than those practising winter sports, where in the latter the prevalence of EIB can range between 21-62% in different sports (Dickinson, McConnell and Whyte, 2011).

PATHOPHYSIOLOGY OF EIA

EIA occurs when a person undertakes exercise, resulting in a large amount of air exchange occurring throughout the bronchial and alveolar airways. Usually air is humidified through the nasal passages when inhaling, but at high levels of exercise these are bypassed, so the lower airways are responsible for humidifying the inhaled air. This increases the chance of the alveoli becoming dehydrated and the surface fluid will increase in osmolality. The bronchial epithelial cells respond by shrinking and releasing inflammatory mediators which results in bronchial constriction that limits airway flow, mainly in expiration (Anderson, et al., 1982). EIA is always reversible, either spontaneously upon cessation of

exercise or else following inhaled-agonists. This process is termed bronchoconstriction of the alveolar airways resulting in exercise induced asthma, or better termed, exercise induced bronchoconstriction.

SCREENING FOR EIB

As already outlined, there is often a potential for over or underdiagnosis of EIB, but the main worry concerns the risk of underdiagnosis. Overdiagnosis can occur when athletes are diagnosed with EIB on the basis of reporting symptoms (e.g. cough, wheeze, chest tightness, shortness of breath, sputum), where in reality, upon testing they would be negative for EIB (Ansley, et al., 2012). Underdiagnosis can occur when athletes who do not report any symptoms will test positive when tested for EIB.

Rundell, et al., (2001) found that when EIB is gauged in athletes depending on their symptoms, only 61% of athletes with EIB were detected. On the other hand, 45% of athletes with two or more symptoms related to asthma were not found to have EIB on testing. Thus, positive symptoms are insensitive to identifying EIB and a negative symptom is not specific. The main reason for screening for EIB is to prevent any detrimental effects on the athlete and the athlete's performance both during training and also during competition. The International Olympic Committee Medical Commission (IOC-MC) states that all safety measures should be taken to ensure that sports does not affect the health or welfare of athletes (Samaranch, 1998); thus athletes should be screened for EIB to ensure that there is optimum airway health. Asthma-related deaths in elite athletes often occur in conjunction with a sporting event (Becker, et al., 2004), and uncontrolled asthma itself plays a significant role in unexplained death.

There is increasing evidence that elite athletes fail to recognize and/or report symptoms that are related to EIB, as was described by Dickinson, McConnell and Whyte (2011) when 228 athletes from different sporting backgrounds underwent the eucapnic voluntary hyperpnoea (EVH) challenge to assess for EIB. In the UK, any athlete that competed at the 2008 and 2012 Olympics was screened for EIB; however non-Olympic athletes do not have any guidance as to who should and who should not be screened.

Athletes participating in sports where there is the presence of certain environmental pollutants are also at increased risk for EIB. Chlorine compounds in swimming pools and certain chemicals through car pollution pose an additional risk to athletes. These act as allergic triggers and may potentially exacerbate bronchospasm in athletes who already have increased susceptibility to EIB. Hence it makes it more essential to screen athletes for EIB. EIB varies in its manifestations from mild performance impairment to, rarely, severe bronchospasm with respiratory failure. Symptoms are often subtle, such as fatigue, or else may occur only in specific environments. Despite the fact that not all athletes are aware of ongoing EIB following exertion, they will recover spontaneously and airflow returns to baseline within 60 minutes, even in the absence of bronchodilator intervention.

The research by Dickinson, McConnell and Whyte (2011) verified that the presence of symptoms related to asthma was found both in athletes with and without EIB. Elite athletes may fail to associate any dyspnoea or other respiratory symptoms to EIB, but rather attribute this to physical exertion as part of their normal intense training or competition regime. Some athletes may also avoid reporting symptoms of EIB as they may be under the impression that it would signify a weakness on their behalf, or that they would risk not being chosen for the elite squad. Hence, routine screening for EIB implemented for all athletes would assist in reassuring both the coaches and athletes that EIB can be detected and treated accordingly with adequate medication. This would ensure that EIB athletes are not at a disadvantage in comparison to their non-EIB fellow athletes (Dickinson, et al., 2006).

EUCAPNIC VOLUNTARY HYPERPNOEA CHALLENGE

The EVH challenge is the most sensitive test to detect EIB as it detects a greater number of athletes that exhibit airway hyper-responsiveness than a sport specific or laboratory based exercise challenge (Dickinson, et al., 2006). This is because an athlete may undergo a laboratory or field test and not encounter the same conditions that initiate EIB. If there are high humidity levels, these may not trigger EIB, hence giving a false negative result. The EVH challenge is superior to other non pharmacological methods of testing since it has a tighter control over the main causes of airway hyper-responsiveness, mainly the inspired water content and the minute ventilation. EVH is also paradoxically more sensitive and specific for EIB than an exercise challenge performed either in the laboratory or in the field (Mannix, Manfredi and Farber, 1999).

The EVH challenge is a measure of prevalence of bronchial hyper-responsiveness in a group, such as that analysed by Holzer, Anderson and Douglass (2002),

where a prevalence of 50% was identified and 60% of these had reported asthma symptoms. This is in contrast to the methacholine challenge test, undertaken in the same study, which revealed a prevalence of only 18% with methacholine. In the latter group, all the subjects had reported asthma symptoms. This lends further to the evidence that EVH challenge is a more sensitive test for the diagnosis of bronchial hyper-responsiveness, than either asthma symptoms or methacholine challenge testing.

Initially a baseline spirometry is carried out to determine the forced expiratory volume in one second (FEV_1) and to calculate the target hyperventilation rate (30 x FEV_1). An EVH challenge is conducted in the laboratory which involves the athlete hyperventilating, whilst sitting down at rest, for 6 minutes (30 x baseline FEV_1) breathing in a gas mixture containing 5% carbon dioxide, 21% oxygen and 74% nitrogen. The inspired air temperature is 19.1ºC and the relative humidity is 2%. (Anderson, et al., 2001). After, the 6 minute test spirometry is carried out at 3, 5, 7, 10 and 15 minutes post test to monitor any change, especially any drop in the FEV_1.

A fall of ≥10% in FEV_1 following exercise or a stimulus is considered to be diagnostic of EIB according the European Respiratory Society (ERS) and American Thoracic Society (ATS) (Roca, et al., 1997). This was further widened to state that the fall should occur over two consecutive time points, based on the possibility that respiratory muscle fatigue can decrease the maximum effort needed to perform FEV_1 after exercise. This is to avoid a poor respiratory effort being misdiagnosed as EIB. The 10% value was chosen as this represents a basis for limiting exercise performance, and correlates with a 26% reduction in airway flow rates in flow volume loops (Custovic, et al., 1994).

Throughout pharmacological (methacholine or histamine) testing of EIB, a requirement of 20% drop in FEV_1 is commonly applied. However, if this drop is applied to an EVH challenge, it will be missing clear cases of asthma, yet such a threshold would be highly specific for EIB. A threshold of 10% drop in FEV_1 has a sensitivity of 63% and specificity of 90% (Hurwitz, et al., 1995), and this is the recommended level for general use, including athletes. In circumstances where avoidance of a false positive diagnosis is of utmost important, a threshold of 15% drop in FEV_1 can be employed, as this is highly specific for asthma.

FEV_1 was the spirometric parameter that is mostly altered following an EVH challenge. It is slightly more accurate overall than the forced expiratory flow at the 25% point to the 75% point of the forced vital capacity ($FEF_{25-75\%}$) in distinguishing asthmatics from non-asthmatics. If an individual is well motivated, peak expiratory flow rate can also be used instead of FEV_1, but this is more related to effort than the other parameters that can be obtained through spirometry. Hence it is less useful.

TREATMENT OF EIB

Once EIB has been diagnosed, through obtaining a positive test on the EVH challenge, proper management of EIB needs to be addressed. Athletes with a diagnosis of EIB should be treated according to the same British Thoracic Society (BTS) guidelines for asthma. The BTS guideline on the management of asthma (British Thoracic Society, 2016) advises a step-wise management plan according to severity of the disease, and moving up or down the ladder as needed, if control is good for more than 3 months.

Step 1:

Occasional short acting inhaled β_2-agonist (SABA) when required for symptomatic relief. If used more than once daily or having night time symptoms, go to step 2.

Step 2:

Add inhaled steroid (beclomethasone, budesonide or fluticasone) on a regular basis. Short acting β_2- agonists must not be used as maintenance.

Step 3:

Increase the dose of the inhaled steroid (beclomethasone, budesonide, fluticasone). Alternatively a long acting β_2-agonist (LABA), salmeterol, can be added onto the inhaled steroid regime. If there are problems with the high dose inhaled steroid, go to step 2, and add on either a long acting β_2-agonist or modified release oral theophylline.

Step 4:

Add on ≥1 of the following: inhaled long-acting β_2-agonist, modified release oral theophylline, inhaled ipratropium, modified release oral β_2-agonist, high dose inhaled bronchodilators, cromoglycate or nedocromil.

Step 5:

Add regular oral prednisolone as a one daily dose, preferably in the mornings.

It must not be forgotten that athletes are bound to the rules and regulations of the World Antidoping Association (WADA); hence they may require the use of a therapeutic use exemption (TUE) if the athlete requires any medication that is in the WADA prohibited substances list.

Most athletes with EIB are unable to control their symptoms with solely a SABA, thus a LABA is also taken in conjunction with a SABA. However, over time athletes with EIB are requiring additional doses of SABAs in order to control their EIB, or else the majority are also resorting to the use of inhaled corticosteroids.

A number of findings support this:

- a minority of athletes do not have adequate EIB prevention with β_2-agonists when inhaling the recommended dose.
- daily use of β_2-agonists increases the severity of EIB as well as decreasing the duration of protection against EIB.
- once an athlete is suffering from EIB, the recovery period after inhalation of a β_2-agonist is extended, the more a β_2-agonist is used on a daily basis, as well as requiring additional doses of LABA/SABA to achieve the same effect over time.
- bronchial hyper-responsiveness can be induced or increased by regular use of β_2-agonists.

The underlying concept is that there is desensitization or tolerance of the β_2-receptor as a result of daily drug usage (Bisgaard, 2000), Desensitisation is implicated to occur on the bronchial smooth muscle and/or the mast cell due to uncoupling of the receptors and internalization or sequestration of uncoupled receptors is followed by degradation, resulting in a net downregulation of receptors, since receptor resynthesis is not as fast.

There are also negative findings in relation to the regular, daily use of β_2-agonists as described by Anderson, Caillaud and Brannan (2006):

- There exists a minority of asthmatic athletes whose EIB does not respond to the clinically recommended dose of β_2-agonists. Anderson, Caillaud and Brannan (2006) detected unexpectedly high failure rates to control EIB after 4 weeks of regular treatment with a LABA (salmeterol), thus indicating that not all subjects have their asthma under control with a regular LABA, and thus may require the use of inhaled corticosteroids for improved control.
- Daily treatment of EIB with β_2-agonists can increase the severity of EIB (Anderson, Caillaud and Brannan, 2006). This is thought to be due to the enhanced release of a preformed mediator such as histamine.
- Daily inhalation of LABA decreases the length of time of protective effect against EIB. With SABA, protection against EIB was not evident 6.5 hours after the dose was administered. This was seen in 72% of subjects with EIB who were prescribed a SABA (Anderson, et al., 1991). In subjects who were given LABA, there is still a reduction in the duration of protection against EIB over time. This tolerance effect was not affected by changing to a once daily dose or by addition of a corticosteroid inhaler. The total time in hours of protection against EIB was significantly decreased after 4 weeks and after 8 weeks of treatment, in comparison to just 3 days of a LABA, namely salmeterol.
- The recovery of EIB from a standard dose of β_2-agonist is slower, when β_2-agonists are used on a daily basis (Storms, et al., 2004), thus requiring additional doses from a LABA or SABA.
- Bronchial hyper-responsiveness can be increased by the daily use of β_2-agonists.

MANAGEMENT OF A NEGATIVE EVH CHALLENGE

Some athletes may present with exercise related breathing difficulties, yet when an EVH challenge is performed, there is no drop in the FEV_1; hence this is a negative test result, and refutes the diagnosis of EIB. In such cases, disordered breathing patterns should be looked at and addressed, such as vocal cord dysfunction and exercise related laryngeal obstruction. In such cases, a good history is also indicative of the problem, where the athlete will, upon close questioning, admit to an inspiratory, rather than expiratory, difficulty with breathing. They will also report a 'wheeze', however this is often actually stridor, as it is often during the inspiratory aspect of respiration. It is often female endurance athletes, who have a tendency to anxiety and perfectionism as part of their personality, who have a higher tendency to present with this clinical picture, but it is not exclusive. In this scenario, various breathing rehabilitation techniques need to be implemented for the athlete to control the dysfunction and/or obstruction. This would involve learning how to perform diaphragmatic breathing in preference to apical lung breathing, which is often noted whilst performing the EVH challenge, or when asking the patient to inhale and exhale deeply a few times in clinic.

Repiratory muscle training, such as through the use of a 'powerbreathe' aid can help to strengthen respiratory

muscles, including the diaphragm, and allow the athlete to learn to 'relax' the vocal cords.

A psychologist's input may be considered for those who have a perfectionist or anxious personality or in the case of athletes feeling the 'pressure to perform', as this can be found even at young age groups.

Nevertheless, it is still worthwhile screening for EIB, as both conditions can co-exist and may need to be tackled synchronously.

CONCLUSION

Athletes have a higher prevalence of EIB than the general population, yet the main concern is that a number of these athletes do not realize they have EIB.

The family doctor is usually the first port of call for both elite as well as recreational athletes, hence the importance of a detailed history, which can possibly elicit the difference between underlying EIB or other respiratory issues.

A family doctor may initially opt to treat the athlete as EIB, and treat with appropriate inhalers, according to the BTS guidelines. However, follow up is important, as this is the main area where distinction can be made whether or not the athlete is well controlled with inhalers. If upon follow up, the athlete still reports a lack of control of his/her EIB symptoms, it may be worthwhile referring for EVH testing to determine whether or not EIB is present, or whether it is due to alternative breathing patterns that may be impairing normal respiration. In this case, inhalers are not recommended.

A history of inspiratory stridor, especially towards the end of competition or training helps the family doctor to suspect vocal cord dysfunction, rather than EIB, hence respiratory muscle training is more suitable in these cases, rather than inhaler based treatment.

The gold standard test to refute or accept whether EIB is present or not, still remains an EVH challenge, should there be any doubt about the exact diagnosis.

The International Olympic Committee medical commission aims to ensure that there is no long lasting harm or disease to sports participants. Therefore, athletes who demonstrate EIB through an EVH challenge should receive optimal treatment, both for prophylaxis and for symptomatic EIB.

Both winter and summer sports are likely to have a high prevalence of EIB. Hence this means that there are a large number of athletes who fail to recognise and report symptoms that may be related to EIB. This makes screening of athletes a valuable exercise to ensure optimal athlete health.

Dr Danica BONELLO SPITERI
MD MRCP MSc (SEM) FFSEM MSc (Sports Biomechanics)
Area of Expertise: Sports & Exercise Medicine
Email: danica_spiteri@hotmail.com

REFERENCES

Anderson, S., Agyros, G., Magnussen, H. et al., 2001. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. *Br J Sports Med,* 35, pp. 344-7.

Anderson, S., Caillaud, C. and Brannan, J., 2006. β-agonists and exercise-induced asthma. *Clin Rev Allergy Immunol*, 31, pp. 163-180.

Anderson, S., Rodwell, L., Du Toit, J. and Young, I., 1991. Duration of protection by inhaled salmeterol in exercise induced asthma. *Chest*, 100, pp. 1254-1260.

Anderson, S., Schoeffel, R., Follet, R., Perry, C., Daviskas, E. and Kendall, M., 1982. Sensitivity to heat and water loss at rest and ruing exercise in asthmatic patients. *Eur J Resp Dis*, 63, pp. 459-471.

Ansley, L., Kippelen, P., Dickinson, J. and Hull, J., 2012. Misdiagnosis of exercise-induced bronchoconstriction in professional soccer players *Allergy*, 67(3), pp. 390-395.

Becker, J., Rogers, G., Rossini, H.. Mirchandani, G. and D'Alonzo, E., 2004. Asthma deaths during sports: report of a 7-year experience. *J Allergy Clin Immunol*, 113, pp. 264-267.

Bisgaard, H., 2000. Long-acting beta$_2$-agonists in management of childhood asthma: A critical review of the literatures. *Peadiatr Pulmonol*, 29, pp. 221-234.

British Thoracic Society, 2016. British guideline on the management of asthma. [online]. Available at: <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/> [Accessed 15 July 2017].

Custovic, A., Arifhodzic, N., Robinson, A. and Woodcock, A., 1994. Exercise testing revisited. The Response to exercise in normal and atopic children. *Chest*, 105, pp. 1127-1132.

Dickinson, J., McConnell, A. and Whyte, G., 2011 Diagnosis of exercise induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise induced bronchoconstriction. *Br J Sport Med*, 45, pp. 1126-31.

Dickinson, J., Whyte, G., McConnell, A. and Harries, M., 2006. Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. *Br J Sports Med*, 40, pp. 179-183.

Holzer, K., Anderson, S. and Douglass, J., 2002. Exercise in elite summer athletes: challenges for diagnosis. *J Allergy Clin Immunol*, 10(3). pp. 374-380.

Hurwitz, K., Argyros, G., Roach, J. et al., 1995. Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. *Chest*, 108, pp. 1240-1245.

Mannix, E., Manfredi, F. and Farber, M., 1999. A comparison of two challenge tests for identifying exercise induced bronchospasm in figure skaters. *Chest*, 115, pp. 649-653.

Roca, J., Whipp, B., Agusti, A. et al., 1997. Clinical exercise testing with reference to lung diseases: Indications, standardization and interpretation strategies. Position document of the European Respiratory Society. *Eur Resp J.,* 10, pp. 2662-2689.

Rundell, K., Im, J., Mayers, L., Szmedra, L. and Schmitz, H., 2001. Self reported symptoms and exercise induced asthma in the elite athlete. *Med Sci Sports Exerc*, 33, pp. 208-213.

Samaranch, J., 1998. *The Olympic Book of Sports Medicine*. London, UK: Blackwell Scientific Publications, pp. vi-vii.

Storms, W., Chervinsky, P., Ghannam, A., Bird, S., Hustad, C. and Edelman, J., 2004. A comparison of the effects of oral montelukast and inhaled salmeterol on response to the rescue bronchodilatation after challenge. *Respir Med*, 98, pp. 1051-1062.