ISMJ
International SportMed Journal

Original research article

Impact of exercise-induced bronchoconstriction on athletic performance and airway health in rugby union players

[1*]Dr Danica Bonello Spiteri, MD, [2]Dr John Dickinson, PhD, [3]Dr Jon Greenwell, MBBS, [4]Dr Lee Ingle, PhD

1. Leeds General Infirmary, Leeds, UK.
2. Endurance Research Group, School of Sport and Exercise Science, University of Kent, Chatham Maritime, UK
3. Leeds Carnegie Rugby Football Union Club, Leeds, UK
4. Department of Sport, Health & Exercise Science, University of Hull, Hull, UK

***Corresponding author. Address at the end of text.**

Abstract

Background: There is emerging evidence that the prevalence of exercise-induced bronchospasm (EIB) is significantly under-reported in many sports. There is little known about the potential performance improvement that may exist when sports players are detected and treated for EIB. **Methods:** Professional rugby union players with no previous history of asthma volunteered to participate in the study. Each player performed the rugby football union (RFU) fitness test and completed a eucapnic voluntary hyperpnoea (EVH) challenge at baseline and 12 weeks later. A player with a positive EVH result was prescribed beclomethasone inhaler (200 µg; two puffs per day) for 12 weeks. Players with a negative EVH test were randomly allocated to either a placebo inhaler group or acted as controls. **Results:** Twenty-nine rugby union players (mean ± SD; age 22.1± 4.2 years; body mass 100.1± 6.9 kg; height 1.84± 0.07 m) were recruited. Seven players (24% of total) had a positive EVH challenge with a mean decrease in FEV_1 of -13.6 ±3.5 % from baseline. There was no significant group difference (P=0.359) in performance improvement of the RFU fitness test between the EVH positive group (mean Δ: -22.3 seconds; 8.0 ± 2.8% improvement), placebo group (mean Δ: -16.5 seconds; 6.7 ± 1.6% improvement), and controls (mean Δ: -12.2 seconds; 5.7 ± 3.5% improvement). **Conclusion:** Prevalence of EIB in professional rugby union players was 24%. A 12-week prescription of beclomethasone (200 µg) showed similar improvements in RFU fitness test performance in players diagnosed with EIB compared to players with healthy airway responsiveness.

Keywords: screening; asthma, exercise-induced bronchoconstriction; athletic performance

***Dr Danica Bonello Spiteri, MD**

Dr. Bonello Spiteri graduated in 2004 from the University of Malta, and obtained her MRCP in 2009. She is a specialist registrar in Sports & Exercise Medicine in Leeds and finalised her MSc in SEM in 2011 and her MFSEM in 2013. She also lectures at the Institute of Physical Education and Sport, in the University of Malta.

Dr John Dickinson, PhD

John's current research focus is on dysfunctional breathing in elite athletes and the impact of asthma medication on performance in non-asthmatics. John is currently involved with research projects, funded by WADA, that are investigating the impact of asthma medication on performance in non-asthmatic athletes. John is currently a Lecturer in Sport and Exercise Sciences at the University of Kent. He also manages the Exercise Respiratory Clinic at the University, which provides services to individuals with exercise respiratory issues. He provides a similar service at the Centre for Health and Human Performance, 76 Harley Street, London.

Email: J.W.Dickinson@kent.ac.uk

Dr Jon Greenwell, MBBS
Dr Jon Greenwell is a specialist in Sport and Exercise Medicine, and splits his time between the National Health Service, and working in professional rugby union and rugby league and high performance swimming, where he regularly sees and treats athletes with exercise induced asthma
Email: jrgreenwell@hotmail.com

Dr Lee Ingle, PhD
Dr Lee Ingle is currently a Senior Lecturer in Sport, Health & Exercise Science at the University of Hull. He has held the title of Honorary Senior Research Fellow in the Department of Academic Cardiology, University of Hull since 2007. Dr Ingle was previously a Reader in Exercise Science for Health & Rehabilitation in the Carnegie Faculty, Leeds Metropolitan University. His personal and collaborative research has focused on the therapeutic benefits of exercise on cardiorespiratory health and disease outcomes.
Email: L.Ingle@hull.ac.uk

Introduction

Exercise-induced bronchoconstriction (EIB) is closely related to asthma and is defined as a transient narrowing of the airways, limiting expiration that usually follows a bout of exercise, and is reversible spontaneously or through inhalation of β_2-agonists[1]. Emerging evidence has demonstrated that susceptible athletes do not recognise that they have EIB[2,5]. Without the intervention of screening programmes, athletes may remain undiagnosed and may continue to suffer from EIB potentially compromising performance and health[5,6]. The risk of acute bronchoconstriction in athletes can be reduced through early detection of EIB and suitable treatment[7]. Diagnosis of EIB should incorporate a medical consultation and an indirect airway challenge. The inclusion of an indirect airway challenge is crucial as diagnosing EIB through symptoms alone can result in a higher prevalence of false positives[8,9]. The eucapnic voluntary hyperpnoea (EVH) indirect airway challenge has a high level of sensitivity and specificity for the identification of EIB[10], and is a suitable airway challenge in athletic populations[4].

The proposed mechanism for the development of EIB is a dehydration of the airway surface liquid caused by the inhalation of large volumes of 'unconditioned' air requiring humidification by the lower airways. The dehydration of the alveolar surfactant causes an osmotic effect that leads to an inflammatory response causing bronchoconstriction[11]. It is possible that if the inflammatory process is not controlled it may lead to damage of the epithelium and resultant airway remodelling. Hence sports that have high minute ventilation demands and take place in cold, dry environments are at risk of airway damage and EIB development. It is crucial therefore that EIB is detected as early as possible in order to control airway inflammation and minimise the potential for airway remodelling. Rugby union is a sport that requires bouts of high minute ventilation and can take place in cold and dry environments. Therefore players can put themselves at increased risk of EIB and EIB development through training and game play. The dry environments encountered either at cold temperatures or at altitude accompanied by high minute ventilation requirements could increase the risk of an acute episode of EIB in susceptible rugby players[12]. Despite a number of studies reporting a high prevalence of EIB in athletes whose sports take place in cold environments[3,12], there is limited data available investigating the prevalence of EIB in rugby union players.

Once diagnosis of EIB has been made the most appropriate prevention strategy has been shown to incorporate regular use of inhaled corticosteroids[13-15]. However, it is unclear whether detection of athletes with previously undiagnosed EIB and appropriately treating them with inhaled corticosteroid therapy results in an improvement in health and performance[16]. At present there are no studies that have investigated the longer-term impact on health and performance of treating athletes with an initial diagnosis of EIB. Accordingly the aim of this study is two-fold: 1) to investigate the prevalence of undiagnosed EIB in rugby union players; 2) investigate the impact of corticosteroid therapy on airway function of susceptible rugby union players and how this impacts on a rugby-specific performance test.

Methods

Participants

Twenty-nine professional male rugby players from the same club in Northern England were approached to participate in the study. All participants agreeing to participate in the study provided written informed consent and ethical approval was provided by Leeds Metropolitan University. All tests were performed during pre-season training. Inclusion and exclusion criteria for the study are outlined in Table 1.

Table 1: Inclusion and exclusion criteria for study participation

Inclusion criteria	Exclusion criteria
Member of the same rugby union club	Recent chest infection (less than four weeks prior to testing)
Male	A current diagnosis of asthma and/or EIB and using inhaler therapy.
Age: 18-30 years	FEV_1 of <70% predicted value at baseline spirometry.
	Participants with injuries which will prevent them from completing maximal fitness testing

The Rugby Football Union (RFU) fitness test

The RFU fitness test[17] was conducted on all participants (Figure 1). The test was familiar and was conducted regularly as part of routine training and fitness assessments. The RFU fitness test is similar to the 20 m multi-stage fitness test[18], involving a number of timed repeated sprints. There are two different RFU fitness tests dependent on whether the player is a forward or back, and participants completed the test according to their playing position.

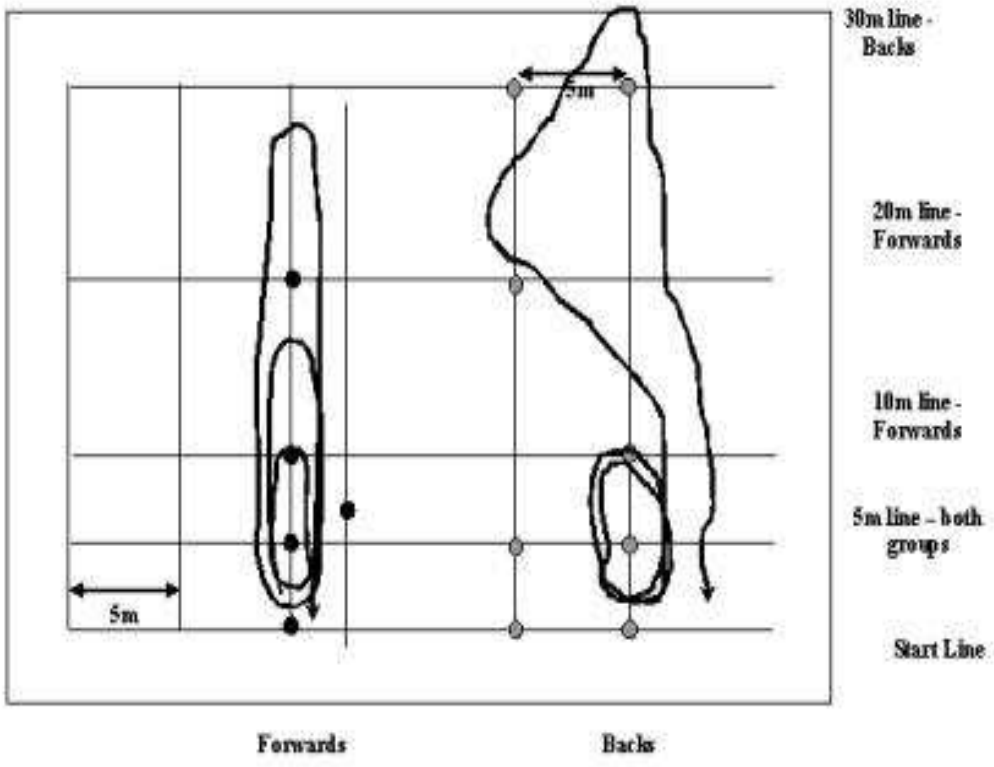

Figure 1: The RFU fitness test for forwards (left panel) and backs (right panel)

EVH challenge

All participants performed an EVH challenge within the same week as the fitness test. Maximal flow volume loops were recorded using a digital spirometer (ML3500 Micro Medical Spirometer, Cardinal Health, UK). The European Community for Coal and Steel (ECCS) reference values were used to predict maximal lung flow-volumes[19]. All maximal flow-volume manoeuvres were performed in accordance with the European Respiratory Society criteria[20]. Prior to the EVH challenge participants completed three maximal flow-volume manoeuvres. The best FEV_1 was recorded and taken as baseline lung function. Other measurements collected included forced vital capacity (FVC), peak expiratory flow (PEF), and mid-expiratory flow rate at 50% of FVC (FEF_{50}).

The EVH challenge was carried out in accordance with methods outlined by Anderson *et al*.[21]. During the EVH challenge each participant was asked to achieve target minute ventilation ($\dot{V}_E$) of 85% of the maximal voluntary ventilation (MVV) for six minutes. Target $\dot{V}_E$ was calculated by multiplying the baseline FEV_1 by 30[21]. The gas inhaled during the EVH challenge consisted of 74% nitrogen, 21% oxygen, and 5% carbon dioxide. At the point of air entering the mouth the gas temperature was 18° C and humidity <2%. During the EVH challenge verbal encouragement and visual feedback was provided. Upon completion of the EVH challenge, two maximal flow- volume loops were recorded at 3, 5, 7, 10 and 15 minutes respectively. At each time point the flow-volume loop with the best FEV_1 was recorded and used to calculate the decrease from the baseline FEV_1 at each time point. If FEV_1 was >10% from baseline at two consecutive time points this was deemed a positive EVH challenge. If participants presented with two consecutive time points where FEV_1 fell $\geq$10% from baseline they were offered 200µg of inhaled salbutamol and a repeat flow-volume loop was measured 10 minutes after inhalation. All participants were asked to remain in the laboratory until their FEV_1 was within 10% of the baseline measure.

Participants were diagnosed with EIB if:

- They had a fall in FEV_1 $\geq$10% from baseline at two consecutive time points following the EVH challenge.
- The participant had an initial low-normal FEV_1 (70-80% of predicted value at baseline spirometry with persistent respiratory symptoms. Following the EVH challenge there was a minimal decrease in the percentage of the FEV_1, yet following use of a salbutamol inhaler there was an improvement of >12% from the baseline FEV_1.
- Each decision about a participant being diagnosed with EIB was taken in consultation with the club's team doctor.

A participant was deemed to be EVH negative if the FEV_1 did not demonstrate a drop of $\geq$10% on two consecutive time points.

Randomisation of participants

Players were all blinded to the results and were also blinded as to whether they received a placebo or beclomethasone inhaler. All players diagnosed with EIB were prescribed beclomethasone inhaler 200µg (two puffs per day). The negative EVH group was randomly selected to either receive a placebo inhaler to be used twice daily or they formed part of the control group that received no treatment. Both groups were shown how to use the inhaler by the club doctor and were sent a daily reminder to use their inhaler, to ensure compliance. All participants completed their regular pre-season exercise training regimens. After twelve weeks, all players underwent re-assessment of the RFU fitness test under identical conditions. The EVH challenge was repeated in players with a positive diagnosis for EIB.

Data analysis

Continuous variables are presented as mean and standard deviation (SD); categorical variables are reported as percentages. A one-way analysis of variance (ANOVA) was used to identify baseline differences between groups. A repeated measures ANOVA with Bonferroni post hoc adjustment was used to identify differences over time (baseline to 12 weeks). An arbitrary level of 5% statistical significance (two-tailed) was assumed. SPSS

software v17.0 (IBM, NY, USA) was used to analyse the data.

Results

Twenty-nine professional rugby union players (mean ± SD; age 22.1 ± 4.1 years; height 1.84 ± 0.07 m, body mass 100.1 ± 12.3 kg) agreed to participate in the study. There were no baseline differences in age, height, and body mass between players with positive and negative EVH results (Table 2). The baseline RFU fitness test was completed by 24 participants; whilst 5 did not participate/did not complete it. However, due to injury and/or illness, only 16 participants completed both the baseline and 12-week post intervention RFU fitness tests.

Table 2: Player characteristics separated by positive and negative EVH results at baseline

Characteristic	EVH positive (n=7)	EVH negative (n=22)	p-value
Age (years)	22.6 ± 3.8	22.0 ± 4.4	0.887
Height (m)	1.87 ± 6.3	1.83 ±7.0	0.189
Weight (kg)	101.9 ± 11.2	99.6 ±12.8	0.713
FEV_1 (l)	4.5±0.7	5.0±0.7	0.76
Percent of predicted FEV_1	94.3±11.1	109.0±11.0	**0.01**
FVC (l)	5.8±0.9	6.0±0.9	0.670
PEF (l/min)	601.9± 69.8	640.7± 88.3	0.299
FEF50 (l/min)	4.3 ±0.8	5.8±1.4	**0.017**
Max FEV_1 decrease post EVH challenge	-11.6 ± 4.6	-6.0±3.6	**0.002**

None of the 29 participants had a previous diagnosis of asthma or EIB. Seven players (24%) were diagnosed with EIB. Of these, five had a positive EVH challenge and two presented with significant reversibility following inhalation of salbutamol. Three other participants demonstrated a fall in FEV_1 of >10%, but only at one time point. There was no significant difference in the baseline maximal flow volume measures between players with positive and negative EVH challenges. However, the baseline percentage of predicted FEV_1 and the FEF50 was significantly higher in the players with negative results (P=0.01, P =0.017 respectively). Seven participants (24%) were diagnosed with EIB. The maximal decrease in FEV_1 was significantly (P=0.002) higher in the EVH positive group (Table 2). There was no significant relationship between the percentage of MVV achieved and the maximum FEV_1 fall post EVH challenge (P=0.74) (Figure 2). Figure 3 illustrates the individual percentage decrease in FEV_1 in players with positive and negative responses.

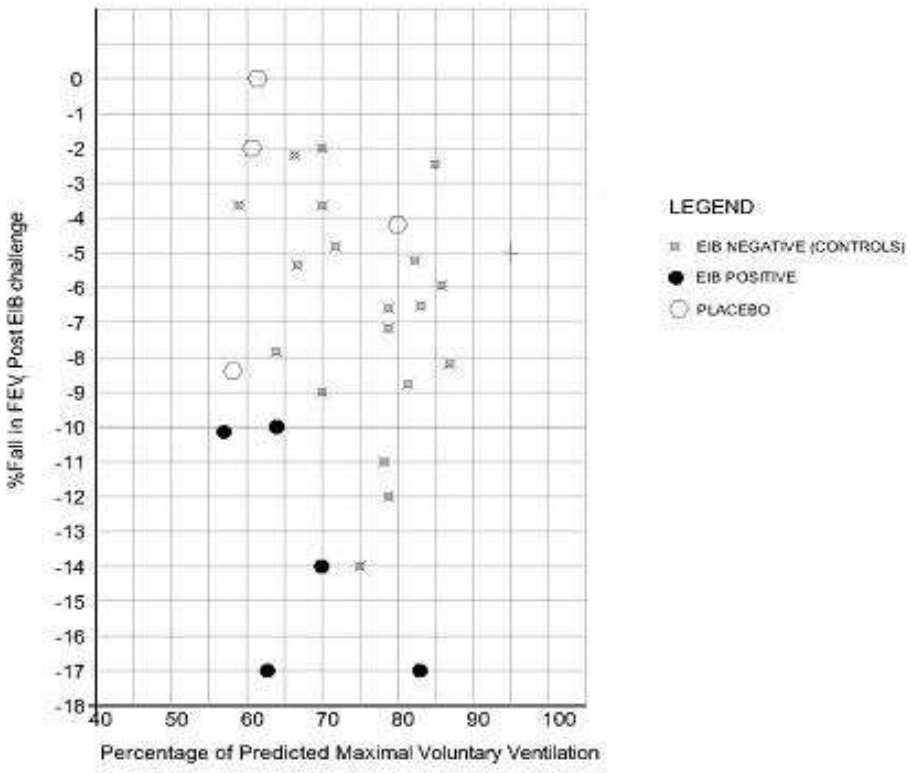

Figure 2: Percentage of MVV achieved during the EVH challenge and the percentage decrease in FEV_1 from baseline following the EVH challenge

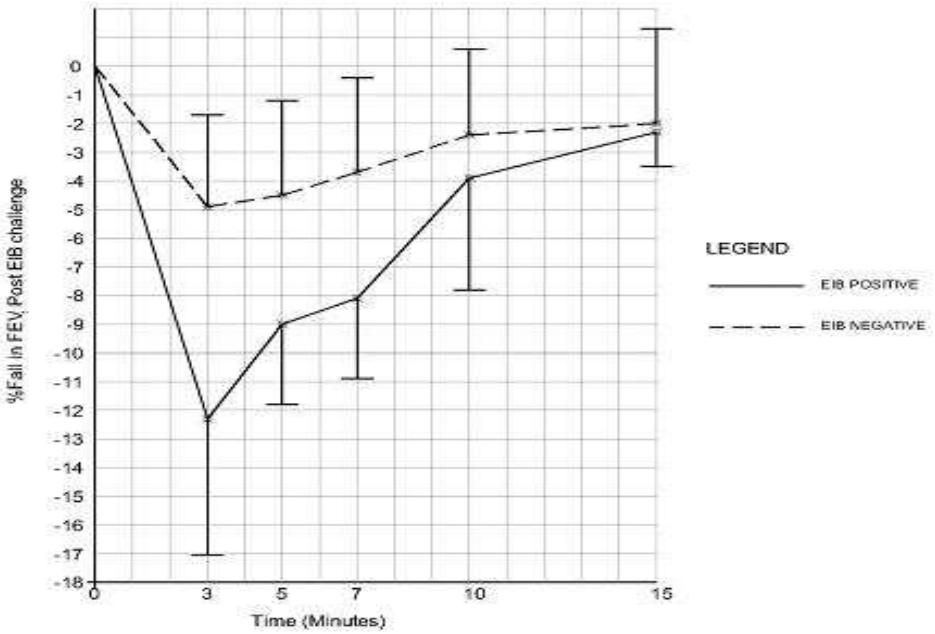

Figure 3: Changes in FEV_1 in rugby union players with positive and negative responses to the EVH challenge

RFU Fitness Test

Sixteen out of twenty-four players completed the baseline and 12 week follow up RFU fitness test. Seven players were found to be EIB positive. All three groups, EIB positive, placebo and control improved their fitness test scores after 12 weeks of training (*P*=0.014).When taken on an individual basis, all participants improved their RFU fitness test performance times over the 12-week period. There was no significant group difference (*P*=0.359) in performance improvement of the RFU fitness test between the EVH positive group (mean Δ: -22.3 seconds; 8.0 ± 2.8% improvement), controls (mean Δ: -12.2 seconds; 5.7 ± 3.5% improvement), and the placebo group (mean Δ: 16.5 seconds; 6.7 ± 1.6% improvement) (Figure 4). A second EVH test was repeated after 12 weeks in players with an initial diagnosis of EIB. A decrease in FEV_1 of >10% continued to remain in all players following the treatment period.

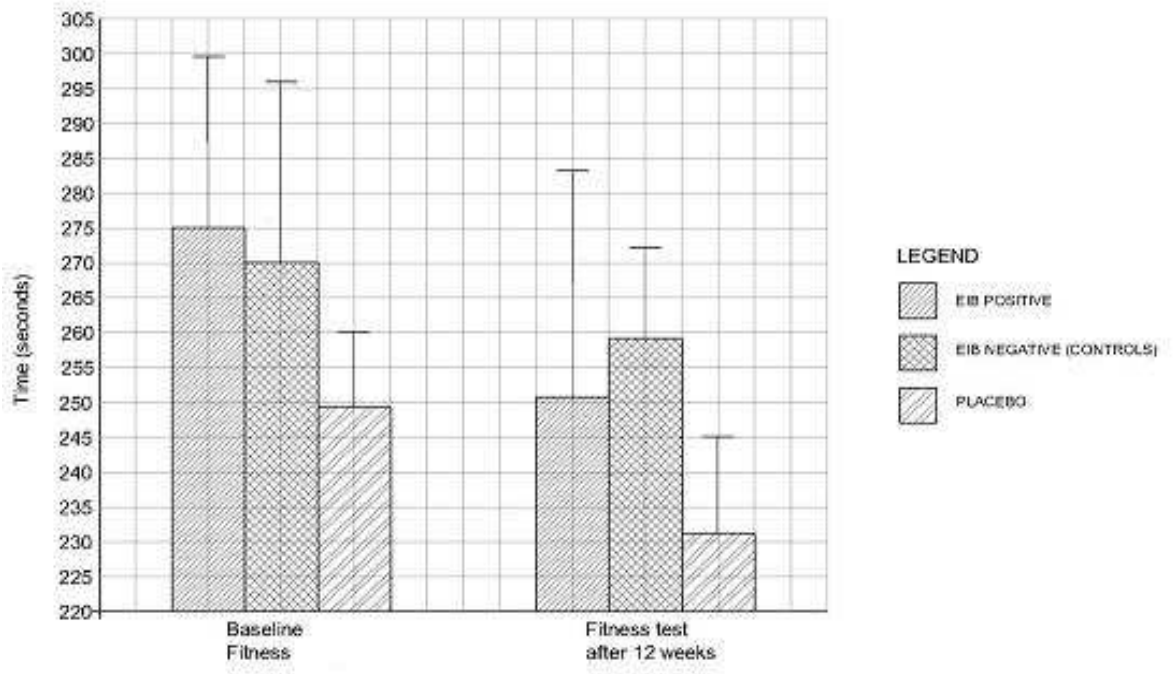

Figure 4: Comparison of the mean time taken to complete the RFU fitness test at baseline and after the 12-week intervention for player5s with a positive EVH, placebo group, and controls

Discussion

This is the first study to screen a team of rugby union players for EIB and track changes in performance in those detected with EIB with no previous diagnosis. This study shows that the prevalence of EIB in rugby union players with no previous history of asthma is 24%. Following 12-week inhalation of prescribed beclomethasone (200µg), the EIB group showed significant improvement in the RFU fitness test. Although the EIB positive group significantly improved their RFU fitness performance from baseline they did not improve at a significantly greater rate than the placebo group or controls. The EIB group demonstrated the greatest fitness improvement over the intervention and this study's findings are similar to previous data from asthmatics recruited to a six-week treatment programme with inhaled corticosteroids[22]. The improvement in fitness was seen across all groups is due to the testing being held during the pre-season training, where the players are in the building up fitness phase after a short layoff from training.

The high airway resistance that occurs during EIB increases the expiratory flow limitation

during exercise[23] predisposing athletes to hypoxaemia during exercise. Haverkamp *et al.*[24] found a significant decrease in arterial oxygen saturation during exercise caused by an increased difference in alveolar to arterial PO_2 pressure and an insufficient ventilatory response resulting in reduced exercise performance. Six weeks of inhaled corticosteroids increased arterial blood oxygen saturation during exercise and exercise performance in asthmatics[24]. It is hypothesised that if these authors had not treated the EIB group they may have had impaired adaptation in fitness over the 12 weeks of training. Due to ethical issues surrounding not treating an athlete for EIB, once a diagnosis has been made these authors were unable to test this hypothesis in their study. The EVH challenge identified 24% of rugby union players with underlying EIB. This is similar to previous findings by Dickinson *et al.*[5] where 32% of rugby players were found to have undiagnosed EIB[5]. There is the potential for EIB to develop in an athlete following over exposure during training and competition to high ventilatory demands, dry air, or poor air quality[12,25,26]. It may take several years of exposure to a provocative environment for EIB to develop in susceptible individuals[27]. This study's group of rugby players were relatively young (mean age 22.6 years), and it is feasible that in an older group of players the number of positive tests may have been greater, providing similar findings to Dickinson and colleagues [5].

These authors found that the maximal flow-volume measures at baseline did not distinguish between players with positive and negative results. FEV_1 is commonly used to help diagnose intrinsic asthma, as it measures the expiratory flow at high and mid-lung volumes. The baseline FEV_1 was within the normal range for all participants (>80% of the predicted FEV_1), hence identification of undiagnosed EIB through analysis of the resting FEV_1 (pre-exercise) was not possible. This is supported by previous findings[4,5]. The exception to this is the % predicted FEV_1 obtained at baseline. Players with a positive diagnosis of EIB had significantly lower (P=0.011) % predicted FEV_1 values compared to healthy controls at baseline. This result is similar to studies conducted on large cohorts of elite athletes that report EIB athletes to have significant lower % of predicted FEV1 measures[4,5]. It is difficult to distinguish players with a positive EVH test by analysis of the % predicted FEV_1 as values are still within the normal range (>80% predicted value). Beck and colleagues[28] demonstrated that baseline spirometry in an athletic population was >20% higher than the predicted values for the general population. Future studies should determine an adjusted 'normal range' for high performance athletes (which may require further sub-specialisation for sporting mode i.e. power vs endurance sports).

In this study, the players diagnosed with EIB were treated with inhaled corticosteroids as per the British Thoracic Society Guidelines[29], with inhaled beclomethasone, as this was found to improve EIB[22]. The option of providing the EIB positive participants with solely β_2-agonists was not feasible, as although β_2-agonists can inhibit mast cell mediator release, this response is susceptible to desensitisation, a process that can be inhibited by corticosteroids. Corticosteroids can increase the transcription of the β_2-receptor gene in the lung and the nasal mucosa. This effect of corticosteroids lessens the reduction in transcription of the β_2-receptors, which would occur as a result of long term β_2-agonist administration[30]. However, when players with positive results for EIB underwent a repeated EVH challenge after 12 weeks of treatment, all participants still demonstrated a decrease in FEV_1 >10%. Thus, other treatment options including fluticasone[30] or leukotrienes may require further consideration, although the latter is not considered a first-line treatment for EIB[32].

There does not appear to be a relationship between respiratory symptoms and the presence/absence of EIB. Rundell and co-workers[3] showed that in athletes experiencing a decrease of ≥10% in FEV_1 post-exercise challenge, respiratory symptoms were reported by 39% of athletes. Conversely, in athletes with EIB, respiratory symptoms were reported by 41%. These authors found a similar trend in their study; 76% of the rugby players without EIB experienced respiratory symptoms, whilst 71% of the players with EIB denied any respiratory symptoms. This finding adds weight to previous studies which indicates that the analysis of signs and symptoms are not a reliable method of diagnosing or rejecting EIB[3]. Thus the diagnosis of EIB must include an objective test of airway function alongside a medical consultation.

Limitations

This study's cohort presented with mild bronchoconstriction following the EVH challenge (decrease in FEV_1 from baseline between 10-25%). The authors may have seen

larger performance gains by using a group of athletes with moderate to severe EIB. In addition, the field-based assessment (RFU fitness test) whilst being ecologically valid and familiar to the rugby players, was less well-controlled than a laboratory testing environment. The EVH challenge is a highly sensitive and specific test for the diagnosis of underlying EIB[4]. However the humidity of the air (2%) is much lower than any athlete is likely to inhale during most sporting situations. Occasionally, this may lead to over-cautious diagnosis of EIB where the impact of inhaled medication may be less significant.

Conclusion

Prevalence of EIB in professional rugby union players was 24%. A 12-week prescription of beclomethasone (200 µg) showed similar improvements in RFU fitness test performance in players diagnosed with EIB compared to players with healthy airway responsiveness.

What is already known?

- Athletes are susceptible to EIB
- Screening athletes with an indirect airway challenge such as EVH testing may result in diagnosis of EIB in previously undiagnosed athletes

What are the new findings?

- The prevalence of EIB in UK-based rugby union players was 24%
- Diagnosing EIB in rugby union players with no previous history and treating them with inhaled corticosteroids for 12 weeks allows them to make similar performance gains as players with healthy airway responsiveness.

How might it impact on clinical practice in the future?

- Increased testing for undiagnosed EIB in high-performance athletes. This will aid to protect airway health and to allow these athletes to perform at their optimal level whilst remaining healthy.

Acknowledgements

The authors would like to thank Charlie Steggles for her support in the recruitment of players, as well as ensuring player compliance to inhaler use throughout the study.

Address for correspondence:

Dr Danica Bonello Spiteri, Leeds General Infirmary, Leeds, UK
Tel.: +44 742 514 8381
Email: danica_spiteri@hotmail.com

References

1. Anderson S. Exericse induced asthma In: Kay A. Ed. Allergy and allergic diseases. Oxford: Blackwell Scientific, 1997:621-711.
2. Lund T, Pederson L, Anderson S, et al. Are asthma-like symptoms in elite athletes associated with classical features of asthma? Br J Sport Med. 2009;43(14):1131-5
3. Rundell K, Im J, Mayers L, et al. Self-reported symptoms and exercise induced asthma in the elite athlete. Med Sci Sports Exerc 2001;33:208-213.
4. Dickinson J, Whyte G, McConnell A, et al. Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. Br J Sports Med . 2006;40:179-183.
5. Dickinson J, McConnell A, Whyte GI. Diagnosis of exercise-induced bronchoconstriction; eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. Brit J Sport Med 2011;45:1126-1131.
6. Holzer K, Brukner P. Screening of athletes for exercise induced bronchoconstriction. Clin J Sport Med. 2004;14:134-138.
7. Carlsen K, Anderson S, Bjermer L, et al. Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. Allergy 2008. 63: 492-505.
8. Rundell K, Jenkinson D. Exercise induced bronchospasm in the elite athlete. Sports Med. 2002;32(9):583-600(18).
9. Ansley L, Kippelen P, Dickinson J, et al. Misdiagnosis of exercise induced bronchoconstriction in professional soccer players. Allergy 2012;67(3):390-5.
10. Holzer K, Anderson S, Chan H, et al. Mannitol as a challenge test to identify exercise induced bronchoconstriction in

elite athletes. Am J Resp Crit Care Med 2003;167:S34-S37.
11. Kippelen P, Larsson J, Anderson S et al. Acute effects of beclomethasone on hyperpnoea induced bronchoconstriction. Med Sci Sport Exerc 2009;42(2):273-280.
12. Helenius I, Tikkanen H, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. Br J Sports Med 1998;32:125-129.
13. O'Byrne P, Barnes P, Rodriguez-Roison R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma. Am J Respir Crit Care Med. 2001;164(8):1392-1397.
14. Pauwels R, Pedersen S, Busse W, et al. Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial. Lancet 2003;361: 1071-1076.
15. Boushey H, Sorkness C, King T, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005;352: 1519-1528.
16. Brukner P, Holzer K, Davies L, et al. The impact of exercise induced bronchoconstriction on exercise performance. Med Sci Sports Exerc 2007; 39:S30.
17. Jenkins D, Reaburn P. Protocols for the physiological assessment of rugby union players. In Australian Institute of Sport Test Methods Manual. Belconnen National Sports Research Centre. 1998:327-333.
18. Belconnen, ACT: Australian Coaching Council. 20m shuttle test: A progressive shuttle run test for measuring aerobic fitness. Australian Sports Commission 1999.
19. Quanjer P, Trammeling G, Cotes J, et al. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests. European Community for Steel and Coal. Official Statement of the European Respiratory Society. Euro Resp J 1993; 6: 5S–40S.
20. Miller M, Hankinson J, Brusasco V, et al. Standardisation of sprirometry. Euro Resp J 2005;26:319-338.
21. Anderson S, Agyros G, Magnussen H et al. Provocation by eucpanic voluntary hyperpnoea to identify exercise induced bronchoconstriction. Br J Sports Med 2001;35:344-7.
22. Heverkamp H, Dempsey J, Pegelows D, et al. Treatment of airway inflammation improves exercise pulmonary gas exchange and performance in asthmatic subjects. J Allergy Clin Immunol 2007;120:39-47.
23. Crimi E, Pellegrino R, Smeraldi A, et al. Exercise induced bronchodilation in natural and induced asthma: effects on ventilatory response and performance. J Appl Physiol 2002;92:2353-2360.
24. Haverkamp H, Miller J, Romer L, et al. Gas exchange during exercise in habitually active asthmatic subjects. J Appl Physiol 2005;99:1938-50.
25. Weiler J, Layton T, Hunt M. Asthma in United States Olympic athletes who participate in the 1996 Summer Games. J Allergy Clin Immunol 1998;102:722-726.
26. Deveouassoux G, Saxon A, Metalfe D et al Chemical constituents of diesel exhaust particles induce IL-4 production and histamine release by human basophils. J Allergy Clin Immunol 2002;109:847-853.
27. Karjalainen E, Laitinen A, Sue-Chu M, et al. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. Am J Respir Crit Care Med 2000;161:2086-91.
28. Becker J, Rogers G, Rossini H. et al. Asthma deaths during sports: report of a 7-year experience. J Allergy Clin Immunol2004;113:264-267.
29. British Thoracic Society, British guideline to the management of asthma. May 2011. http://www.brit-thoracic.org.uk/guidelines/asthma-guidelines.aspx.
30. Black J, Oliver B, Roth M. Molecular mechanisms of combination therapy with inhaled corticosteroids and long acting β-agonists. Chest .2009;136(4):1095-1100.
31. Acuna A, Gabrijelcic J, Uribe E. et al. Fluticasone propionate attenuates platelet activation factor induced gas exchange defects in mild asthma. Eur Respir J. 2002;19:872-878.
32. Ribeiro J, Toro A, Baracat E. Antileukotrienes in the treatment of asthma and allergic rhinitis. J Paedr 2006;82(5): S213-21.