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Impact of detecting and treating exercise-induced bronchoconstriction in elite footballers

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ABSTRACT Our aim was to evaluate the prevalence of exercise-induced bronchoconstriction (EIB) in elite football players and assess subsequent impact of therapy on airway health and exercise performance.

97 male professional football players completed an airway health assessment with a eucapnic voluntary hyperpnoea (EVH) challenge to diagnose EIB. Players demonstrating a positive result (EVH⁺) were prescribed inhaler therapy depending on severity, including inhaled corticosteroids and inhaled short-acting β_2 -agonists, and underwent repeat assessment after 9 weeks of treatment. Eight players (EVH⁺ n=3, EVH⁻ n=5) completed a peak oxygen uptake ($\dot{V}O_{2peak}$) test at initial and follow-up assessment.

Out of the 97 players, 27 (28%) demonstrated a positive EVH result. Of these, 10 had no prior history (37%) of EIB or asthma. EVH outcome was not predictable by respiratory symptoms. Seven (24%) of the 27 EVH⁺ players attended follow-up and demonstrated improved post-challenge spirometry (forced expiratory volume in 1 s pre-test $-22.9 \pm 15.4\%$, post-test $-9.0 \pm 1.6\%$; $p=0.018$). At follow-up $\dot{V}O_{2peak}$ improved by $3.4 \pm 2.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in EVH⁺ players compared to $0.1 \pm 2.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in EVH⁻ players. Magnitude of inference analysis indicated treatment was possibly beneficial (74%) for exercise capacity.

Elite football players have a high EIB prevalence. Treatment with inhaler therapy reduces EIB severity.



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Screening and treating EIB in elite football players improves airway health and may improve exercise performance <http://ow.ly/ngE530iWGJh>

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Introduction

Exercise-induced bronchoconstriction (EIB) is now recognised to be highly prevalent in some groups of elite athletes [1, 2] and can impair their health and exercise performance [3–6]. The nature of elite-level football suggests that EIB may be relevant and pose a particular risk to this group of athletes. Specifically, elite football players regularly sustain high ventilation rates [7] from a young age [8], while often training and competing in an asthmogenic environment, *i.e.* in cold air, high pollen and areas of high pollution. Despite this, little is currently known regarding the nature of EIB in professional football players.

Previous studies suggest that football players are often misdiagnosed or incorrectly labelled as having EIB or asthma [9], highlighting that respiratory symptoms are poorly predictive in the diagnosis of EIB and therefore limit the accuracy of a symptom-based approach to diagnosis [10]. However, there have been no prospective studies evaluating the prevalence of EIB, or indeed the benefits of treating EIB in this group of elite athletes.

It is recognised that EIB has deleterious effects on the efficiency of gas exchange [4], and therefore can impair performance. Indeed, STENSURD *et al.* [5] report impaired oxygen uptake in individuals with EIB, and an improvement in peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) was reported in players of Australian Rules football following the initiation of treatment for previously undetected EIB [6].

Football clubs have a duty of care for their players; to protect their health while at the same time optimising their performance. There are rigorous medical guidelines in place which include screening players for certain medical conditions (*e.g.* cardiac abnormalities) [11]; however, clubs do not routinely assess players for EIB. Some authors have called for screening for EIB to be implemented [12, 13]; however, before a screening programme can be put in place, a number of stringent criteria must be met, including demonstrating prevalence, ability to detect the condition of interest and an understanding of the impact of intervention in the population of interest [14, 15].

The aim of this work was to address these deficiencies by using robust objective tests to provide a comprehensive assessment of the impact of EIB in professional football players by: 1) determining the prevalence of EIB in elite footballers; 2) assessing the impact of appropriate therapy on airway inflammation and EIB control; and 3) investigating the effect of treating players with EIB on exercise performance. In order to achieve this aim with a standardised and widely accepted approach, we utilised the bronchoprovocation methodology of eucapnic voluntary hyperpnoea (EVH) [16] testing to establish the presence of airway dysfunction and EIB. We hypothesised that EIB would be highly prevalent and that initiation of standard asthma therapy would be beneficial for airway health, as assessed by physiological measures of airway hyperreactivity and inflammation, and potentially for exercise performance.

Methods

Study population

Male professional football players from the English Football Premier League, Championship and League One were invited to participate in a detailed respiratory health assessment, as a component of their preseason medical examination in July, prior to their preseason training period.

Study design

All players attended for a detailed respiratory assessment, including screening for EIB using EVH challenge [17] (part 1). Subsequently, players with EIB were treated for 9 weeks, after which they had a follow-up respiratory assessment (part 2). A subgroup of players completed maximal exercise testing at both baseline and follow-up (part 3). All players were free from illness in the 2 weeks prior to assessment, and were requested to avoid exercise and caffeine for ≥ 4 h before assessment. Ethical approval for the study was obtained from the University of Kent School of Sport and Exercise Sciences Research ethics committee (144-2014_2015) and participants provided written consent.

Part 1: baseline assessment

Players completed a detailed respiratory assessment and initially completed a questionnaire to determine their medical history and evaluate presence of respiratory symptoms. Players previously prescribed medication for asthma/EIB ($n=7$) were asked to withhold treatment at the time of assessment, in accordance with guideline recommendations [1].

Respiratory assessment

Airway inflammation was assessed by determining exhaled nitric oxide fraction (F_{eNO}) (NIOX VERO; Aerocrine, Uppsala, Sweden) [18] and lung function was assessed by maximal flow volume spirometry (Spiro-USB and MicroLab; CareFusion, Hoechst, Germany) [19].

An EVH challenge was then conducted, as described previously [1]. In brief, players were required to inspire medical-grade air (21% oxygen, 5% carbon dioxide and 74% nitrogen with <2% humidity) for 6 min at a target ventilation rate of 85% maximal voluntary ventilation (MVV). Target MVV was calculated as 30× forced expiratory volume in 1 s (FEV₁) [20] and minute ventilation was recorded. Maximal flow volume loops were measured in duplicate at 3, 5, 7, 10 and 15 min post-EVH, with the flow loop with the best FEV₁ accepted at each time point. A test was considered positive for EIB if FEV₁ fell by ≥10% from baseline at two consecutive time points. At this point, 4×100 µg of inhaled salbutamol was administered using a metered dose inhaler and maximal flow volume loops were recorded 15 min post-inhalation.

Severity of EIB was classified as mild, moderate or severe, dependent on the fall in FEV₁ post-EVH (10–<25%, 25–<40% and ≥40%, respectively) [21]. Players with a positive EVH challenge (EVH⁺) test were then prescribed medication by their team physician, in accordance with recommendations [22], with a spacing device and inhaler technique advice [23].

Treatment

Medication was prescribed according to EIB severity; players with mild EIB were prescribed a daily inhaled corticosteroid (ICS), in conjunction with an inhaled short-acting β₂-agonist (SABA), as needed. Those with moderate EIB were prescribed a combination inhaler containing ICS and a long-acting β₂-agonist, with a SABA as needed. Finally, players with severe EIB were prescribed the combination inhaler with the addition of a daily montelukast and a SABA as required.

Part 2: follow-up assessment

Players continued with their usual preseason training and no change was made to training load. After 9 weeks, EVH⁺ players underwent a further respiratory assessment (as detailed earlier).

Part 3: performance assessment

A subgroup of players (n=8) completed a V'_{O₂peak} test on a motorised treadmill with simultaneous gas analysis (Oxycon Pro; Jaeger, Hoechberg, Germany). Initial running speed was set at 11 km·h⁻¹ and a gradient of 1%. Speed increased 1 km·h⁻¹ every 3 min to 16 km·h⁻¹, at which point the gradient was increased by 1% every minute until volitional exhaustion. V'_{O₂peak} was determined as the single highest 30-s average in V'_{O₂}.

Statistical analysis

Data are presented as mean±SD unless otherwise stated. Players were grouped according to the result of their EVH challenge (EVH⁺, EVH⁻). Group differences and pre- to post- data were analysed using independent or paired t-tests or the non-parametric equivalent and symptom data were analysed using Chi-squared analysis and Fisher's exact test. Given the small number of subjects completing performance assessment, magnitude-base inference analysis was utilised, using the spreadsheet from HOPKINS [24] to assess the clinical impact of detection and treatment of EIB. All other analyses were conducted using SPSS software (version 23; SPSS, Chicago, IL, USA) with significance accepted at p<0.05.

Results

98 players (age 24±4 years, height 183±7 cm, mass 80.3±7.2 kg) completed the initial respiratory assessment; however, one player was subsequently excluded due to his inability to perform reliable spirometry (table 1). 17 players reported a previous diagnosis of asthma and/or EIB, of whom only seven were currently prescribed medication. 16 players reported troublesome respiratory symptoms, including cough, wheeze and dyspnoea at a frequency of 5%, 3% and 8%, respectively.

Part 1: baseline assessment

Pulmonary function, inflammation and EIB

Lung function was normal in all players at the baseline assessment, with no evidence of significant airflow obstruction (FEV₁ >70% predicted). In 39 (40%) players FeNO was raised above normal (>25 ppb), with 19 (20%) players having a value >50 ppb (table 1).

A positive EVH result was found in 27 (28%) players, of which the majority (n=21, 78%) were classified as having a mild response and fewer having a moderate (n=4, 15%) or severe (n=2, 7%) response (figure 1). All EVH⁺ players demonstrated a subsequent improvement in FEV₁ following administration of bronchodilator treatment (change in FEV₁ 20.6±11.6%, range 6–40%; p<0.001). There was a weak inverse relationship between FeNO and percentage fall in FEV₁ post-EVH (r_s -0.24, p=0.02), i.e. the greater the FeNO the larger the reduction in lung function post-EVH.

TABLE 1 Player characteristics and baseline respiratory assessment data for the 97 players who performed the baseline eucapnic voluntary hyperpnoea (EVH) challenge

	All players	EVH ⁺	EVH ⁻	p-value EVH ⁺ versus EVH ⁻
Subjects	97	27	70	
Age years	24±4	24±4	24±4	0.56
Height cm	182.6±6.8	183.0±6.7	182.5±6.9	0.77
Weight kg	80.3±7.2	80.7±6.3	80.2±7.5	0.73
F_eNO ppb	21.0 [24.6]	36.0 [63.0]	18.8 [17.3]	<0.01 [#]
FEV₁ L	4.71±0.65	4.51±0.55	4.78±0.68	0.07
FVC L	5.67±0.76	5.68±0.64	5.67±0.81	0.95
PEF L·min⁻¹	630.0 [135.0]	616.0 [102.0]	635.0 [148.8]	0.29 [#]
FEV₁/FVC	82.7±6.8	79.3±8.0	84.1±5.8	0.01
MVV during EVH % predicted	77.68±11.76	83.07±10.88	75.54±11.48	<0.01
Fall FEV₁ from EVH %	-8 [5.5]	-13 [10.0]	-6 [4.0]	<0.01 [#]

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. F_eNO: exhaled nitric oxide fraction; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; MVV: maximal voluntary ventilation. [#]: data analysed using Mann-Whitney U-tests.

Relationship between EVH result and prior diagnosis and symptoms

Only 10 (37%) of the EVH⁺ players reported a history of asthma and/or EIB and four (15%) of those were currently prescribed asthma medication. Although respiratory symptoms were reported frequently, there was no relationship between the presence of symptoms and likelihood of a positive EVH result (table 2). Moreover, the most severe EVH result (49% reduction in FEV₁) was observed in a player with no prior history of airways disease or current respiratory symptoms.

Part 2: follow-up assessment

After 9 weeks, only 11 of the 27 (41%) EVH⁺ players attended for the follow-up visit. Reasons for not attending included club not permitting time for the medical team to schedule follow-up, not believing it was necessary, away for international competition, injured, and not wanting to repeat the EVH test. A further four players were excluded from follow-up analysis due to them not taking medication as prescribed.

No difference was seen in resting FEV₁ between baseline and follow-up visits (table 3); however, F_eNO was lower at follow-up (p=0.043) (table 3, figure 2a). In addition, there was a reduction (p=0.02) in the percentage fall in FEV₁ following EVH and this was apparent despite players achieving a similar total ventilation during the challenge tests (table 3, figure 2b). Moreover, all but two players had a negative EVH test at the second visit (*i.e.* fall in FEV₁ <10% post-challenge). Despite these findings, two (29%) of the seven players reported an increase in symptoms.

Part 3: performance assessment

All treated EVH⁺ players (n=3) showed an improvement in V_{O₂peak} (pre 50.60±5.65 mL·kg⁻¹·min⁻¹, post 53.98±2.80 mL·kg⁻¹·min⁻¹) (figure 3); however, the magnitude of this change was not significant

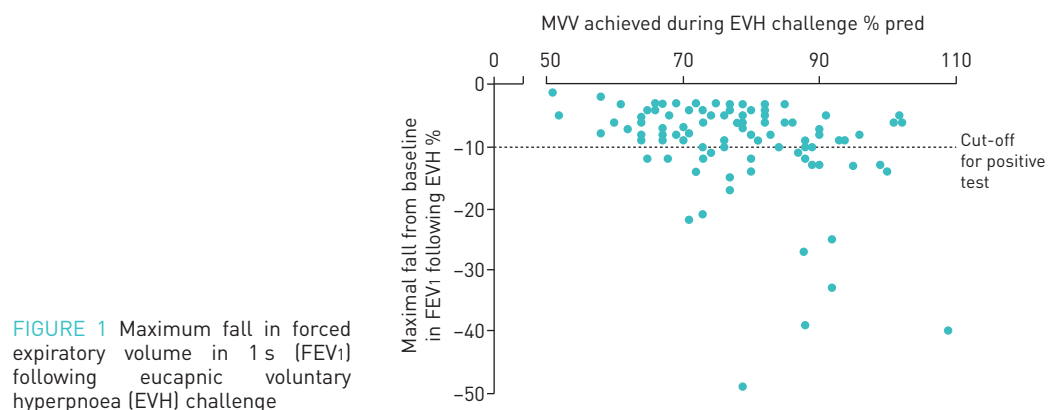


TABLE 2 Respiratory symptoms reported by players

	No symptoms	≥1 symptom	Coughing	Excessive mucus production	Chest tightness	Difficulty breathing	Wheezing
EVH ⁺	19 (70)	8 (30)	1 (4)	1 (4)	2 (7)	4 (15)	1 (4)
EVH ⁻	60 (89)	8 (11)	4 (6)	1 (1)	2 (3)	4 (6)	2 (3)
p-value	0.06	0.06	1.00	0.50	0.32	0.22	1.00

Data are presented as n (%), unless otherwise stated. n=95; n=2 did not complete questionnaires. EVH: eucapnic voluntary hyperpnoea.

($p=0.184$). Three EVH⁻ players had a decrease in $V'O_{2peak}$ and two demonstrated an improvement (pre 53.06 ± 2.14 mL·kg⁻¹·min⁻¹, post 53.15 ± 2.38 mL·kg⁻¹·min⁻¹). No significant difference was found in the change in $V'O_{2peak}$ between the two groups ($p=0.13$); EVH⁺ players had an improvement of 3.38 ± 2.93 mL·kg⁻¹·min⁻¹ and EVH⁻ players improved by 0.09 ± 2.30 mL·kg⁻¹·min⁻¹; however, the effect of treatment on maximal exercise capacity, from magnitude-base inference analysis, was found to be possibly beneficial (74.1%).

Discussion

In a cohort of elite football players completing a preseason medical screening we found a high prevalence of both respiratory symptoms and airway dysfunction. Indeed, by employing a widely accepted bronchoprovocation methodology [17], namely EVH testing, we found that approximately one-third of this prospectively screened cohort of elite football players had evidence of EIB. Moreover, subsequent treatment with appropriate therapy was associated with a clear attenuation in airway dysfunction and improvement in markers of airway inflammation and hyperreactivity. In addition, all treated players demonstrated an improvement in peak exercise capacity.

The high prevalence of EIB in elite footballers observed in this study concurs with previous smaller-scale studies that have reported a prevalence of between 29% [25] and 51% [9] in this group of athletes. DICKINSON *et al.* [25] included only a small sample of one elite football team (n=21), while ANSLEY *et al.* [9] studied a highly selected population of football players using inhaler therapy. Thus, this is the first study to truly assess prevalence in a prospective “medical screening”-type scenario across several elite football teams.

The study findings are consistent with other studies demonstrating a heightened prevalence of airway dysfunction in running-based sports [1]. In addition, they highlight again the poor predictive value of symptoms in the diagnosis of EIB [10, 26]. Indeed “undetected” EIB was found in 63% of players, and no single symptom or combination of symptoms was predictive of the presence of EIB. Accordingly, it is concerning that there appears to be a high proportion of professional footballers currently training and playing with undiagnosed and uncontrolled EIB. Moreover, in keeping with our previous study [9], we found evidence of players with a prior diagnosis of EIB/asthma that was incorrect and not supported by the objective test findings. Indeed 71% of players with a prior diagnosis and treatment plan were either over- or under-medicated.

TABLE 3 Differences before and after treatment in eucapnic voluntary hyperpnoea (EVH)⁺ players on medication

	Pre-treatment	Post-treatment	p-value
F_eNO ppb	85.1±60.7	27.5±10.91	0.04
Baseline FEV₁ L	4.41±0.55	4.25±0.32	0.23
MVV during EVH % predicted	85.29±13.61	87.81±13.58	0.38
Fall in FEV₁ post-EVH %	14 (28.0)	8 (9.0)	0.02[#]

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. Bold type represents statistical significance. F_eNO: exhaled nitric oxide; FEV₁: forced expiratory volume in 1 s; MVV: maximal voluntary ventilation. [#]: data analysed using sign exact tests.

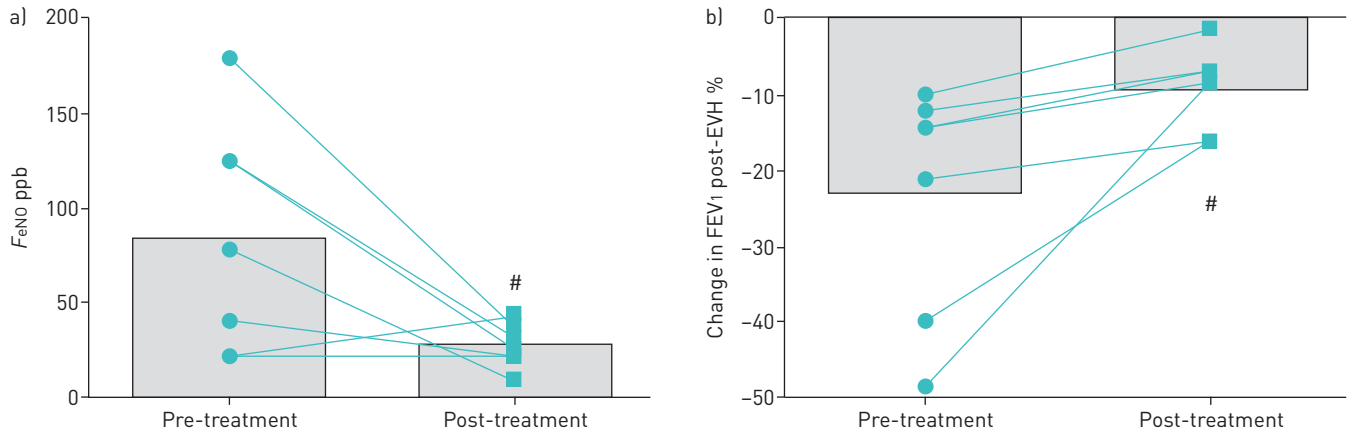


FIGURE 2 a) Exhaled nitric oxide fraction (F_{eNO}) before and after 9 weeks of treatment; b) percentage change in forced expiratory volume in 1 s (FEV₁) following eucapnic voluntary hyperpnoea (EVH) challenge before and after 9 weeks of treatment. Data are presented as mean and individual values. #: $p < 0.05$ versus pre-treatment.

In addition, it is apparent that respiratory symptoms are not useful in predicting the airway response following treatment [27]. Specifically, we found that despite a reduction in the fall in FEV₁ post-EVH challenge, almost one-third of players with EIB reported an increase in symptoms at the follow-up assessment. This is in keeping with the findings of SIMPSON *et al.* [28], who reported that half the athletes assessed reported at least one ongoing respiratory symptom despite their fall in FEV₁ post-EVH being blunted by the use of inhaled terbutaline. Indeed, in this study 28% had a higher symptom score when this fall was blunted. These findings act to emphasise the poor relationship between the presence of respiratory symptoms and airway dysfunction and highlight our current limited understanding of the pathophysiological mechanisms underpinning airway-centric symptoms in athletes [29]. Furthermore, it serves to promote the importance of other conditions, such as exercise-induced laryngeal obstruction, which may coexist with EIB and cause symptoms [30, 31].

In the current study, we repeated objective testing 9 weeks after EIB therapy was initiated to ensure adequate control of EIB [17]. Data from this follow-up assessment reveals that standard asthma therapy can improve EIB and airway inflammation. Although treatment was recommended for all 27 EVH⁺ athletes, only seven took the medication as prescribed. This represents an attrition rate of 74%, which suggests a degree of resistance to football players engaging in therapy for this condition. Certainly, anecdotally, EIB often appears to be discounted as medically relevant by medical staff in football squads and viewed as of secondary importance to cardiac screening [32]. Hopefully, our findings challenge this presumption and provide the supporting basis to educate both players and team clinicians regarding the importance of EIB in elite football players. Our work acts to address some of the concerns regarding screening athletes for airway dysfunction [15] and certainly suggests that focus on airway health is

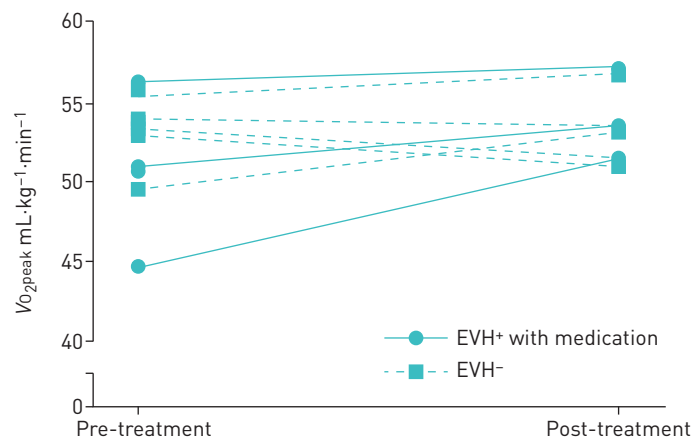


FIGURE 3 Peak oxygen uptake ($V_{O_{2peak}}$) before and following 9 weeks of treatment. EVH: eucapnic voluntary hyperpnoea.

important in football players, given the work suggesting that EIB in endurance athletes could be considered akin to an occupational lung disease [33].

A key driving factor in elite sport is the impact of any intervention (*e.g.* screening or new treatment) on athlete performance, and in addition to improving airway health, treating EIB may be beneficial for performance. Studying performance impact at the elite level is clearly complex, with multiple potential confounding factors and very few footballers completed this component of our study for the above-mentioned reasons, meaning this section of our data is difficult to interpret. Although not statistically significant, EVH⁺ players had mean increase in $\dot{V}O_{2peak}$ of 7.2%, whereas EVH⁻ players had only a 0.24% increase over the same time period, with the observed increases in $\dot{V}O_{2peak}$ bringing the performance of the EVH⁺ players in line with EVH⁻ players. As previously stated, due to the small sample size, these results should be interpreted with caution and future research should aim to follow this up with an adequately powered study. Similar findings have been reported in sports with similar demands. BRUKNER *et al.* [6] found that players of Australian Rules football with newly diagnosed EIB had a significant improvement (9%) in the $\dot{V}O_{2peak}$ following 6 weeks of treatment compared to controls. In addition, SPITERI *et al.* [34] demonstrated that appropriately medicating elite rugby players with previously undiagnosed EIB improved their performance in a rugby-specific aerobic exercise challenge by 8% over the course of 12 weeks compared to 6% in the control group; however, this was not a significant finding. It has been hypothesised that this impact on performance may be due in part to bronchoconstriction during and following exercise resulting in reduced alveolar ventilation and efficiency of alveolar-to-arterial blood oxygen exchange [4].

Methodological considerations

A key limitation of this study is that our findings represent the result of a cross-sectional assessment. Specifically, players were not studied in a prospective randomised placebo-controlled fashion and thus our results have to be interpreted in view of their pragmatic limitations. Due to the elite nature of the football players involved, clubs would not allow us to withhold medication from those who needed it, or provide a placebo medication to those who did not. Moreover, players are subject to antidoping regulations and need to know exactly what they are taking at all times. In addition, we recognise that diagnosis of EIB from a one-off test is not entirely robust [35]; however, due to time restraints imposed by the clubs and the large numbers of players to screen, it would not have been practical to perform multiple tests. Our report replicates how a screening programme would work in “real-life”, and is similar to the way football players are currently screened for cardiac conditions.

During the EVH test, the %MVV achieved was significantly lower among EVH⁻ players than among EVH⁺ players; however, both groups achieved a MVV >60% which is required for an adequate test [36], and we think it is most unlikely that the mean difference of 8% between groups would explain the major findings of this study.

The study was initially powered based on ~30% of players being found to have evidence of EIB. Initial power calculations showed that 15 EVH⁺ players were required to detect a 10% change in FEV₁ in follow-up assessments. To accommodate for an anticipated high dropout rate in this population, we deliberately over-recruited. However, even with a sample size of 97 players, the high dropout rate meant that our study was under-powered.

As discussed, it was difficult for us to follow-up EVH⁺ players and clearly it would have been desirable to significantly increase the number of players undergoing repeat assessment, including performance assessment. It may be possible to reduce the attrition rate by working with subelite cohorts or academy players; however, this limits potential generalisation to the elite population. Players and medical staff at clubs are under huge pressures from clubs and it is hard for them to allocate time for follow-up testing. At the follow-up assessment, it became evident that despite support from coaching and medical staff, many players had decided not to take the inhalers, and there was some confusion among these players regarding what they should be taking and when. MILLER *et al.* [37] highlights the importance of educating coaching staff in the management of asthma and this may be an area which needs to be addressed when establishing a screening programme. For a screening programme to be effective in elite-level football, time needs to be invested in educating players about EIB and its treatment. Although there is a lack of evidence in the athletic population, it is clear that educational interventions can have a positive effect on clinical patients' asthma management [38]. Therefore, it is vital to have the cooperation of players at the start of the treatment.

Conclusion

In conclusion, this study revealed that approximately one-third of a cohort of elite football players appear to have EIB when screened for respiratory dysfunction at a preseason medical assessment, which in the

majority of cases was not predictable by symptom-based assessment. Treatment of screen-detected EIB⁺ players resulted in improved airway inflammation and reduced airway hyperresponsiveness. Overall, the findings support the use of improved diagnostic testing for airway dysfunction in elite football players and highlight the importance of educating both players and football medical staff regarding this condition.

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Conflict of interest: None declared.

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