TITLE

ENVIRONMENTAL INFLUENCE IN THE PREVALENCE AND PATTERN OF AIRWAY DYSFUNCTION IN ELITE ATHLETES

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ABSTRACT WORD COUNTS: 244 words
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SUMMARY AT GLANCE

This is the first study to screen the entire elite GB Swimming and Boxing teams using an EVH challenge. The findings support the notion that athletes who train and compete in provocative environments at a sustained high ventilation have an increased susceptibility to airway dysfunction.

ABSTRACT

Background and objective: Elite swimming and boxing require athletes to achieve relatively high minute ventilation. The combination of a sustained high ventilation and provocative training environment may impact the susceptibility of athletes to Exercise-induced bronchoconstriction (EIB). The purpose of the study was to evaluate the prevalence of EIB in elite Great British (GB) Boxers and Swimmers.

Methods: Athletes from Boxing (n=38, Mean age: 22.1±3.1 yrs.) and Swimming (n=44, Mean age: 21.1±2.6 yrs.) volunteered. Athletes completed an exercise-induced respiratory symptoms questionnaire, baseline assessment of exhaled Nitric Oxide (FeNO), maximal spirometry manoeuvres and a Eucapnic Voluntary Hyperpnoea (EVH) challenge. EIB was confirmed if FEV₁ reduced by ≥10% from baseline at two time points post-EVH challenge.

Results: The prevalence of EIB was greater in elite swimmers (30 of 44; 68%) than boxers (3 of 38; 8%) (p<0.001). 22 out of the 33 (67%) EVH-positive athletes had no prior diagnosis of asthma/EIB. Moreover, 12% (6 of 49) of the EVH-negative athletes had a previous diagnosis of asthma/EIB. We found a correlation between FeNO and FEV₁ change in lung function post-EVH challenge in swimmers (r= -0.32; p=0.04), but not in boxers (r= -0.24; p=0.15).

Conclusions: The prevalence of EIB was nine fold greater in swimmers when compared with boxers. Athletes who train and compete in provocative environments at sustained high
ventilation may have an increased susceptibility to EIB. It is not entirely clear whether 
increased susceptibility to EIB affects elite sporting performance and long-term airway health 
in elite athletes.

KEYWORDS
Asthma, Athlete’s care, Exercise-induced bronchoconstriction, Sport, Training environment

SHORT TITLE
EIB in elite boxers and swimmers

LIST OF ABBREVIATIONS
Dx, previous diagnosis; EIB, exercise-induced bronchoconstriction; GB, Great British; EVH, 
eucapnic voluntary hyperpnoea; FeNO, fraction of exhaled nitric oxide; FEV\textsubscript{1}, forced 
expiratory volume in one second; PEF, peak expiratory flow; FVC, forced vital capacity; 
FEV\textsubscript{1}/FVC, FEV\textsubscript{1}:FVC ratio; MVV, maximal voluntary ventilation

MAIN TEXT
INTRODUCTION
Exercise-induced bronchoconstriction (EIB) has been shown to be highly prevalent in 
certain groups of elite athletes (e.g. swimmers, cyclists, cross country skiers); \textsuperscript{1-3} our group 
previously reported that approximately a quarter of the Great British Olympic Team have 
asthma/EIB, \textsuperscript{4} i.e. more than double the national prevalence of asthma. \textsuperscript{5}

This heightened prevalence is thought to arise due to a combination of the deleterious impact 
of training and competition environmental exposures (e.g. pollution, swimming pool
chemicals), coupled with the repeatedly high ventilatory requirements, necessitated by participation in elite level sport. This combination may result in airway injury, leading to a greater propensity to bronchoconstriction, during or following vigorous exercise.

Elite level swimmers, appear to have an alarmingly high prevalence of EIB (41% - 55%). This heightened airway hyper-reactivity appears to resolve in retirement from competitive swimming. It has been proposed that repeated exposure to airborne irritants and sensitizing agents (e.g. halocetic acids and trihalomethanes) may drive a sensitisation process and induce airway inflammation, that increases a propensity to EIB. Despite this, a clear relationship between EIB and airway inflammation has not been determined; with some studies demonstrating no difference in markers of eosinophilic inflammation between pool and non-pool athletes.

In contrast, very little information is currently available on exercise associated respiratory problems in elite level boxing. Although not intuitive, both sports necessitate that athletes reach a similar peak heart rate and minute ventilation, however both the training environment and the duration athletes are exposed to these physiological demands differ significantly.

We therefore undertook this study with the aim of firstly providing an ‘up-to-date’ evaluation of the prevalence of EIB in the Great British (GB) elite swimming squad but also, for the first time, establish the prevalence of EIB in a cohort of screened elite-level boxers. A secondary aim was to compare the Eucapnic Voluntary Hyperpnoea (EVH) challenge response and baseline exhaled nitric oxide (FeNO), as a surrogate of airway inflammation,
between two sports with similar peak ventilatory demands, but with differing training environments.

METHODS

Study design and participants

Adult members (Age >18 years) of the elite GB Boxing and GB Swimming squads, competing regularly in international competition were recruited, as part of a screening study, to assess their airway health. Participants attended the laboratory on a single occasion at various locations between July 2013 and September 2015. Participants were invited to take part in the testing regardless of previous diagnosis (Dx) of asthma/EIB.

Athletes were excluded if they had a chest infection within 4 weeks, did not withdraw from using their prescribed asthma medications or they had a current FEV₁ value of ≤70% predicted. The study was approved by the University Ethics Committee (Reference Number: Prop74_2012_13 and Prop82_2013_14) and all participants provided written informed consent.

Training environment

The boxing squad trained indoors in gymnasiums with moderate temperatures (19-21°C) and relative humidity (40-50%) levels. In contrast, the swimming squad trained in indoor pools with air temperatures of 29°C with relative humidity above 60%. All pools that swimmers trained in followed WHO Guidelines ¹⁵ for use of chlorine-based disinfectants. The free chlorine levels were maintained at 1mg/l or below. Combined chlorine (chloramines) levels were never more than half the free chlorine, and never more than 1mg/l.
Study measurements

Participants initially completed a questionnaire, addressing exercise respiratory symptoms and environmental triggers. They then completed measurements of FeNO and spirometry, followed by an EVH challenge. Participants were requested to avoid high intensity exercise and caffeine for four hours prior to the study. Participants with a Dx of asthma/EIB were required to withhold inhaled asthma medications according to recommendations. 

Fraction of Exhaled Nitric Oxide (FeNO)

A NIOX analyser (NIOX MINO®, Aerocrine AB, Sweden) was used to measure FeNO in the exhaled breath at rest at a flow rate of 50 ml/min. FeNO was performed prior to spirometry manoeuvres and taken as the mean of duplicate measures.

Spirometry

Using digital spirometers (Spiro-USB™ and MicroLab™, CareFusion, Germany), participants completed a minimum of three forced maximal flow-volume manoeuvres. For each maximal flow-volume manoeuvre the following measurements were recorded in accordance to ATS/ERS 2005 Guidelines: forced expiratory volume in one second (FEV₁); peak expiratory flow (PEF); forced vital capacity (FVC) and FEV₁:FVC ratio (FEV₁/FVC).

EVH Challenge

EVH challenge was conducted in accordance to methods outlined by Anderson et al. Briefly, participants were asked to attain a target minute ventilation of 85% of their predicted maximal voluntary ventilation (MVV) rate for 6 minutes and maximal voluntary flow-volume loops were measured at 3, 5, 7, 10 and 15 minutes. The test was deemed positive if the FEV₁ fell by at least 10% from baseline at two consecutive time points.
Statistical Analysis

Normally distributed data were expressed as mean ±SD unless otherwise stated. One-way analysis of variance (ANOVA) was performed to compare baseline spirometric indices between EVH-positive and EVH-negative participants. Chi-squared ($\chi^2$) analysis was used to evaluate the reported symptoms between EVH-positive and EVH-negative participants. To assess the efficacy of self-reported symptoms, sensitivity, specificity and diagnostic accuracy were calculated. Assumptions of normal distribution of FeNO data could not be made therefore Spearman’s correlation was used to demonstrate the strength and the direction of the relationship between mean FeNO values and the maximal fall in FEV$_1$ post-EVH challenge. The results were considered significant if $p\leq0.05$. Statistical analysis was performed using statistical package for social sciences (SPSS, Version 22, IBM).

RESULTS

Participants’ characteristics

Participant characteristics are shown in Table 1. Thirty-eight boxers (5 females; 26 Caucasians) and forty-four swimmers (19 females; 44 Caucasians) completed the study. Ten participants (12%) were excluded (n=6, under age of 18; n=3 resting airflow obstruction; n=1, equipment failure during testing).

Seventeen (21%) of the participants had a Dx of asthma/EIB. Of these, all were prescribed short-acting $\beta_2$-agonist for use pre-exercise, however in addition four (24%) were prescribed inhaled corticosteroid, six (35%) were prescribed an inhaled corticosteroid/long-acting $\beta_2$-agonist combination. One participant (6%) was not using any regular asthma medication.
At baseline, when compared against swimmers, boxers had lower baseline FEV$_1$, percentage predicted FEV$_1$, FVC, percentage predicted FVC and FEV$_1$/FVC (Table 1).

Airway response to EVH Challenge and Dx of asthma/EIB

Eighty-two participants completed the EVH challenge, of which thirty-three (40%) had a positive EVH challenge. Twenty-two (67%) of these subjects (three boxers and nineteen swimmers) had no Dx of asthma/EIB. In contrast, six (12%) participants with Dx of asthma/EIB had a negative EVH result.

Six (12%) EVH-negative athletes (six swimmers) and ten (30%) EVH-positive athletes (ten swimmers) reported having previously been diagnosed with asthma/EIB and were using one or a combination of short-acting β$_2$-agonists, long-acting inhaled β$_2$-agonists and inhaled corticosteroids.

The maximum fall in FEV$_1$ from baseline ranged from -11.6% to -21.3% in EVH-positive boxers and from -12.4% to -56.1% in EVH-positive swimmers. Two boxers and one swimmer presented with a FEV$_1$ fall from baseline of >10% (-10.1% and -10.5% for the boxers and -10.1% for the swimmer) at only one time point, deeming them EVH-negative. Of the thirty-three positive EVH challenges three (7.9%) were elite boxers and thirty (68.2%) were elite swimmers (Figure 1). There was no difference in anthropometric characteristics between EVH-positive and EVH-negative participants (Table 1).
Symptoms

Of the EVH-positive participants, fourteen (43%; all swimmers) reported no exercise-associated respiratory symptoms. However, thirteen (93%) of the fourteen EVH-negative swimmers reported at least one exercise respiratory symptom.

There was an inverse relationship between the maximal fall in lung function following EVH challenge and self-report of exercise-associated chest tightness ($r=-0.25; p=0.02$) and wheezing ($r=-0.25; p=0.02$) in EVH-positive participants. There was also an inverse relationship between the maximal fall in FEV$_1$ and reports that high pollen content increased severity of symptoms ($r=-0.35; p=0.04$).

Ten (23%) swimmers reported increased respiratory symptoms due to “bad pool air and/or high chlorine concentrations” and three (7%) swimmers reported exacerbation of respiratory symptoms due to “hot, humid climate”. There was no difference in likelihood of a positive EVH between these groups; i.e. five were EVH-positive and eight EVH-negative. Thus overall, the precision of symptoms for a positive EVH test in swimmers was poor; specificity values ranging from 19.2% (cough) to 29.4% (breathing difficulty).

Fraction of Exhaled Nitric Oxide (FeNO)

Resting mean FeNO was similar between boxers and swimmers, 40.7±40.9 ppb vs. 28.1±21.9 ppb; $p=0.08$, respectively. EVH-positive boxers had greater FeNO values when compared to their negative counterparts (99.0±86.5 vs. 35.7±32.5; $p=0.01$). There was no difference in FeNO values between EVH-positive and -negative swimmers (32.0±25.0 vs. 19.6±8.7; $p=0.08$). There was a correlation between mean FeNO values and the maximal fall in FEV$_1$ post-EVH challenge in swimmers ($r_s=0.32; p=0.04$), but not in boxers ($r_s=0.24; p=0.15$).
DISCUSSION

It is proposed that the combination of training and performing in noxious environments makes certain groups of elite athletes highly susceptible to the development of airway dysfunction. The findings from our study supports this notion, confirming the very high prevalence of airway hyper-reactivity in elite level swimmers. Indeed, to our knowledge, this is the highest prevalence (68%) of airway dysfunction reported in an elite internationally-competitive squad of athletes, screened using an indirect stimulus for bronchial provocation. In contrast, in a cohort of athletes, who are not exposed to the environmental stress of the pool environment (i.e. boxers), the prevalence of airway dysfunction was found to be nine fold lower (8%).

The training and competition environment that elite swimmers are exposed to clearly differs from that of elite boxers. In this respect, boxers train indoors in gymnasiums with relatively low levels of airborne irritants (e.g. allergens (5-10μm) and ultrafine particles (<0.1μm)), moderate temperatures and moderate humidity levels. In contrast, the elite swimmers we studied trained in high temperature and humidity. Previous studies suggest that athletes who regularly attend indoor swimming pools are acutely and repeatedly exposed to high concentrations of inhaled surface irritants such as chlorine gas derivatives. Repeated exposure to airborne irritants and sensitizing agents can induce an airway inflammation and remodelling process that may lead to the development of asthma/EIB. It has been suggested that the increased occurrence of EIB in swimmers may be caused by the combined effects of the inhalation of by-products arising from disinfection and high number of training hours. Our cohort may have had even greater exposure to triggers, as they were part of an elite squad, in contrast to other studies that have only tested well-trained and/or sub-elite athletes. Indeed, the prevalence of EVH-positive elite swimmers and boxers is
notably greater than the only previous report of the prevalence of asthma and EIB in GB Olympic Swimmers (41%). Although Dickinson et al. used similar methods to confirm asthma/EIB, they did not screen the entire 2004 GB Olympic Team, but only conducted indirect bronchoprovocation challenges with athletes who had a Dx of asthma/EIB or at the request of a team medical officer.

In the entire athletic cohort, we found no significant relationship between FeNO values and the maximal fall in FEV₁ post-E VH challenge. This is in keeping with prior publications and indicates that FeNO is a poor predictor of airway hyper-reactivity and clinical asthma in elite athletes. However, when this association was evaluated in swimmers alone, there was a correlation between FeNO and the maximal fall in FEV₁ post-E VH challenge, indicating that baseline airway inflammation may predict more severe response to EVH.

In total, 22 out of 33 (67%) EVH-positive athletes had no Dx of asthma/EIB. Sixty-three percent (19 of 30) of the EVH-positive swimmers had no previous history of EIB, whilst none of the EVH-positive boxers had a Dx of asthma/EIB. Moreover, reports of exercise-associated respiratory symptoms were not predictive for the presence of a positive E VH test. Taken together these findings continue to confirm and underline the complex relationship between respiratory symptoms in athletes and presence or indeed lack of airway dysfunction.

Conditions such as exercise-induced laryngeal obstruction are commonly misdiagnosed as EIB due to inappropriate initial diagnosis. There were six swimmers who had a Dx of EIB who did not have a positive EVH challenge. Of these six athletes, four were using Salbutamol inhaler exclusively, one was also prescribed inhaled corticosteroid and one was prescribed an inhaled corticosteroid/long-acting β₂-
agonist combination. Although athletes stopped using inhaler therapy prior to the EVH challenge, this may not have been adequate and athlete may still have received some protection from inhalers. Furthermore, a negative indirect airway challenge does not confirm the absence of EIB. An alternate test, such as Mannitol or sport specific exercise, may be appropriate to confirm or reject diagnosis of EIB.

The best approach to manage an asymptomatic aquatic athlete with a positive EVH challenge remains to be determined. There is a lack of data to indicate whether initiating treatment in this context has a beneficial impact for health and performance and indeed the relationship between a positive EVH result and ‘in the field’ airway dysfunction is not straightforward. Castricum et al. reported a discrepancy between different bronchial provocation tests when they were compared to field based exercise challenge tests in the diagnosis of EIB in swimmers. At the current time initiation of treatment in asymptomatic EVH-positive athletes with no previous history of EIB must be taken on a case-by-case basis. The transient nature of EVH positivity can be reduced and/or normalised in swimmers when intense training has ceased for a period of at least 15 days. These observations suggest that the results of bronchial challenges in swimmers may be dependent on training and resting periods.

METHODOLOGICAL CONSIDERATIONS / STUDY LIMITATIONS

Seven athletes (one boxer and six swimmers) did not attain the minimum required percentage of Maximal Voluntary Ventilation (MVV) (60%) during the EVH challenge. Despite this, four had a significant fall in FEV₁ post EVH challenge confirming EIB. Those who did not provide a positive challenge should be offered another opportunity to complete the EVH challenge and achieve >60% MVV. Alternatively, a different indirect challenge or exercise may be preferred.
It is also possible that some athletes, with a positive EVH test on the day of testing, could have a negative EVH result on a subsequent or second test. This acknowledged, the majority of the athletes tested positive had a fall in FEV$_1$ >15% (n=24; 73%) and in prior studies, test repeatability is improved in those with a fall of this severity or above.\(^3\)

The athletes that demonstrated higher FeNO values were tested during summer time. This seasonal variation in FeNO levels could be explained by the variation of ambient pollution or outdoor allergens. FeNO can also be influenced by nitrate intake and anti-inflammatory agents. Future studies would be methodologically strengthened by the inclusion of additional supporting tests such as skin prick test to characterise atopic status, other measures of airway inflammation (e.g. sputum analysis) and data on athlete’s nitrate supplementation.

CONCLUSION

Our results demonstrate a very high prevalence of airway dysfunction in elite swimmers and overall a nine-fold greater prevalence than elite boxers. The findings support the notion that athletes who train and compete, for prolonged periods, in provocative environments have an increased susceptibility to airway dysfunction. Future research should investigate whether increased exposure to provocative environments allied with certain biochemical and genetic components has a long-term health impact in elite athletes and what can be done to ameliorate this risk.

ACKNOWLEDGEMENTS

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REFERENCES


TABLES

Table 1 Participant characteristics

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*a Different from EVH-negative boxers (p<0.05); b Different from GB Swimmers (p<0.05); c Different from GB Swimmers (p<0.001); EVH - Eucapnic Voluntary Hyperpnoea; FeNO – Fraction of Exhaled Nitric Oxide; FEV₁ - Forced Expiratory Volume in 1 second; FVC – Forced Vital Capacity
FIGURE LEGENDS

Figure 1 Maximal fall in FEV\textsubscript{1} post-EVH challenge showing tests that attained 60% MVV (vertical line) and tests, that were above and below the 10% fall in FEV\textsubscript{1} cut-off value (horizontal line) for a positive test. Panel A represents GB Boxing and Panel B represents GB Swimming. EVH - Eucapnic Voluntary Hyperpnoea; FEV\textsubscript{1} - Forced Expiratory Volume in 1 second; MVV - Maximal Voluntary Ventilation; Dx - Previous Asthma/EIB Diagnosis.