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Exercice-induced bronchoconstriction among athletes: Assessment of bronchial provocation tests

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ABSTRACT

Diagnosis of exercise-induced bronchoconstriction (EIB) requires the use of bronchial provocation tests (BPTs). We assessed exercise-induced respiratory symptoms (EIRS), EIB and asthma in athletes and evaluated the validity of BPTs in the diagnosis of EIB. Rhinitis and atopy were also assessed.

Athletes with (n = 55) and without previous asthma diagnosis (n = 145) were tested by skin prick tests, lung function and eNO measurements. EIRS were recorded and EIB was assessed by methacholine (Mch), eucapnic voluntary hyperpnoea (EVH), mannitol and exercise test.

EIRS were highly reported and history of asthma was common among athletes. A high prevalence of atopy (48.7%) and allergic rhinitis (30.5%) was found. Athletes with asthma had a higher response rate to Mch and to EVH, as compared with athletes without a previous asthma diagnosis (P = 0.012 and P = 0.017 respectively). Report of EIRS, rhinitis and atopy were not associated with a positive BPT response.

Screening athletes for EIB using BPTs is suggested, irrespective of reported EIRS or a previous asthma diagnosis.

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1. Introduction

Exercise-induced bronchoconstriction (EIB) describes the transient airway narrowing that occurs after exercise, a phenomenon that ensues frequently among athletes who may not have a diagnosis of asthma or any respiratory symptoms (Parsons and Mastronarde, 2009). EIB is more common among endurance athletes, particularly swimmers and winter sport athletes, than in the general population (Langdeau et al., 2000).

Diagnosing EIB or asthma in elite athletes is important given its potential detrimental impact on health and performance. Previous reports in athletic populations highlight that EIB and asthma are associated with increased morbidity and mortality (Becker et al., 2004). In terms of performance, EIB and asthma may reduce exercise capacity (Stensrud et al., 2007). Many studies support the need for screening for EIB and asthma in elite sport competitors.

Exercise-induced respiratory symptoms (EIRS) have poor predictive value for making a diagnosis of EIB in athletes whilst documentation of variable airway obstruction is a requirement for the diagnosis of EIB in elite athletes (Fitch et al., 2008; Bougault et al., 2010) Use of direct or indirect bronchial provocation tests (BPTs) is recommended. However, there are many issues that need to be addressed before such a policy could be feasible, including adoption of a standardized and reproducible test that is universally accepted, agreement on interpretation of test results, and cost-effectiveness (Hull et al., 2007).

Allergic rhinitis has also been observed as common among elite athletes (Carlsen and Kowalski, 2008) and the history of rhinitis should suggest the possibility of concomitant asthma or airway hyperresponsiveness(AHR) (Carlsen et al., 2008). Of interest is also the association of physical exercise with the development of allergic sensitization in summer sport athletes. Zwick et al (Zwick et al.,

Abbreviations: EIB, exercise-induced bronchoconstriction; BPT, bronchial provocation test; AHR, airway hyperresponsiveness; Mch, methacholine; EVH, Eucapnic Voluntary Hyperpnoea; EIRS, exercise-induced respiratory symptoms; FEV_1, forced expiratory volume in 1 s; PD_{20}, provocative dose inducing a 20% decrease in FEV_1; PD_{15}, provokative dose inducing a 15% decrease in FEV_1; ICS, inhaled corticosteroids.

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1990) showed that in highly competitive swimmers the frequent exposure to chlorine and chlorine by-products in swimming pools during training and competition may facilitate sensitization to airborne allergens and AHR.

The aim of the present study was to test in elite athletes for the presence of exercise induced respiratory symptoms (EIRS), EIB, asthma, atopy and allergic rhinitis and to further evaluate the validity of direct and indirect BPTs in the diagnosis of AHR in this population.

2. Methods

2.1. Subjects and study design

A group of 200 elite athletes, competing at high level at national, international and Olympic Games participated in the study. Recruitment was through national sporting teams. The study was performed in collaboration with the Global Asthma and Allergy European Network (GA^2LEN), the European Network of Centres of Excellence in Allergy and it was approved by the hospital and University Ethics Committee.

At the outset of the study a demographic questionnaire on history of past and current respiratory symptoms, on asthma diagnosis, allergic rhinitis or existence of other allergies, training and sport habits, was completed by all athletes. The AQUA questionnaire (Bonini et al., 2009) (Allergy Questionnaire for Athletes) with supplement of some questions from the ECRHS questionnaire (Burney et al., 1994) was used. According to previous history the population was subdivided in two groups; Group A: athletes with a previous physician-based diagnosis of asthma and Group B: athletes without a previous diagnosis of asthma. Asthma was based on recent doctor diagnosis before entering the study (as ever diagnosed asthma). EIRS were defined as respiratory symptoms reported during or after exercise.

Atopy, lung function and airway inflammation assessed by a non invasive index as exhaled Nitric Oxide (eNO), were assessed on the same day. All athletes had skin prick tests (SPT) according to European standards (Dreborg and Frew, 1993) to common allergens with the GA^2LEN Pan-European panel of allergen extracts (Heinzerling et al., 2005). Spirometry was performed according to the ERS recommendations (Miller et al., 2005), using a dry wedge spirometer (Masterscreen, Jaeger, Hoechberg, Germany). Exhaled NO was measured using the portable Nitric Oxide Analyzer (NIOX MINO;Aerocrine, Solna, Sweden), according to ATS guidelines (American Thoracic Society and European Respiratory Society, 2005).

During the second phase of the study and in order to further investigate the validity of BPTs in detecting EIB, 111 athletes who voluntarily participated and were tested by direct and indirect BPTs [with methacholine, eucapnic voluntary hyperpnoea (EVH), mannitol and exercise test] were studied. Elite athletes were asked to refrain from using short-acting β_2-agonists, long-acting β_2-agonists and inhaled corticosteroids (ICS) within 8, 48 and 24 h of testing, respectively (Crapo et al., 2000). Each test was performed with at least 24 h time frame from the other BPT. No test was performed if there was an upper or lower respiratory tract infection for the last 8 weeks. Elite athletes with at least one positive BPT were defined as EIB positive.

2.2. Bronchial provocation tests

2.2.1. Methacholine challenge

Methacholine chloride was dissolved in normal saline solution to produce doubling concentrations range of 0.39–200 mg/ml and immediately used for bronchial challenge. The first nebulisation administered was normal saline solution, and the post-saline solution FEV_1 was used as the baseline for the calculation of subsequent percentage fall in FEV_1. After challenge with saline solution, doubling concentrations of methacholine chloride was inhaled (Crapo et al., 2000). An acceptable-quality FEV_1 was obtained at each time point; otherwise the FEV_1 manoeuvre was repeated. The challenge test was followed up to the dose of Mch that caused a 20% drop from baseline of FEV_1 or until the maximum dose was inhaled. The cumulative dose causing a 20% fall in FEV_1 (PD_{20}) was automatically calculated by interpolation of the logarithmic dose response curve.

2.2.2. Mannitol challenge

A dry powder preparation of mannitol was delivered in gelatine capsules containing 0, 5, 10, 20 or 40 mg (Osmohale, Pharmaxis Pharmaceuticals Ltd, UK). Consecutive doses of 0, 5, 10, 20, 40, 80, 160, 160 and 160 mg (to a maximum cumulative dose of 635 mg) were administered via an inhalator and a controlled deep inhalation to total lung capacity with 5 s of breath holding (Brannan et al., 2005). A positive test was defined by a $\geq$15% fall in FEV_1 at $\leq$635 mg. The response was expressed as the cumulative dose that provoked a 15% fall in FEV_1 (PD_{15}) and as response-dose ratio (RDR; final percentage fall FEV_1/total dose of mannitol administered).

2.2.3. EVH challenge

The EVH challenge was performed according to the method described by Anderson and Brannan (Anderson and Brannan, 2003). Briefly, athletes were required to breathe a dry gas mixture (21% O_2, 5% CO_2 and 74%N_2) at room temperature for 6 min at a target ventilation rate equivalent to approximately 85% maximal voluntary ventilation (MVV). Target minute ventilation was calculated as 30xFEV_1 (Anderson and Brannan, 2003). FEV_1 was measured before and at 3-, 5-, 10-, 15- and 20-min after EVH, with the best FEV_1 recorded at each time point. The test was considered positive if a fall in FEV_1 of $\geq$10% was observed over two consecutive time points compared with baseline. Ambient conditions in the laboratory were 21 °C and 2% humidity

2.2.4. Exercise test

The laboratory cycle test used the stepped protocol recommended by the ATS (Crapo et al., 2000). Athletes were required to cycle for 8 min on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, USA). Exercise intensity was set to elicit a heart rate greater than 85% of maximum for the final four minutes of exercise. Post-exercise spirometry was conducted in duplicate at 3-, 5-, 10-, 15- and 20-min recovery, with the best FEV_1 recorded at each time point. The test was considered positive if a fall in FEV_1 of $\geq$10% was observed over two consecutive time points compared with baseline.

3. Statistical analysis

Comparisons of variables of interest between athletes in Group A (i.e.: athletes with a previous physician-based diagnosis of asthma) and in Group B (i.e.: athletes without a previous diagnosis of asthma) were performed either by chi-square statistics of *t*-test as appropriate. Multivariate analysis (logistic regression model) assessed the existence of positive bronchial provocation challenge adjusted for EIRS, diagnosis of asthma, rhinitis and atopy. All tests were 2-sided and the level of statistical significance was set at 5%. The magnitude of association is indicated by the respective Odds Ratio followed by the 95% Confidence Interval (CI). All variables related to the airway responses to bronchial provocation challenges, pulmonary function tests and eNO levels were transformed into the natural logarithms in order to reduce the within subjects

Table 1
Demographic characteristics and respiratory symptoms based on the AQUA/ECRHS Questionnaire.

	All Participants (n = 200)	No previous diagnosis of Asthma (n = 145)	Previous diagnosis of Asthma (n = 55)
Sex (male)	100 (50%)	64 (44.1%)	36 (65.5%) *
Age(years)	21.6 (20.7–22.5)	22.1 (21.1–23.11)	20.4 (18.4–22.3)
BMI (kg/m^2)	21.9 (21.5–22.3)	21.8 (21.3–22.3)	22.1 (21.4–22.8)
Smoking(yes)	16 (8%)	12 (8.3%)	4 (7.3%)
Aquatic Sport	150 (70.5%)	95 (65.5%)	46 (83.6%) *
>3 h of training/day	73 (36.5%)	53 (36.6%)	20 (36.4%)
EIRS	114 (57%)	64 (44.1%)	50 (90.9%) **
Asthma like symptoms			
Shortness of breath	88 (44%)	50 (34.5%)	38 (69.1%) **
Wheezing	43 (21.5%)	20 (13.8%)	23 (41.8%) **
Cough	92 (46%)	53 (36.6%)	39 (70.9%) **
Night Symptoms	28 (14.1%)	10 (7%)	18 (32.7%) **
Rhinitis symptoms	61 (30.5%)	40 (27.6%)	21 (38%)
Positive Skin Prick Tests	96 (48.7%)	63 (43.8%)	33 (62.3%) *
eNO, mean, 95%C.I.	16.0 (14.53–17.62)	15.70 (14.09–17.50)	16.85 (13.64–20.81)
Use of β_2-agonists	38 (19%)	0	38 (69.1%)
Use of ICS	26 (13%)	0	26 (47.3%)
FEV_1 (L), Gmean, 95%C.I	4.12 (4.01–4.24)	4.29(4.05–4.51)	4.07 (3.94–.20)
FVC(L), Gmean, 95%C.I	4.95 (4.81–5.11)	5.07 (4.83–5.32)	4.91(4.66–5.00)
FEV_1/FVC ratio, Gmean, 95%C.I	83.23(82.16–84.35)	84.61 (83.31–85.90)	82.89 (81.75–84.89)

Values are in mean, 95%Confidence Intervals or N (%).
BMI: Body Mass Index, EIRS: exercise-induced respiratory symptoms, SPTs: skin prick tests, eNO: exhaled Nitric Oxide, ICS: Inhaled Corticosteroids, FEV_1: Forced expiratory volume in 1 s, FVC: Forced Vital Capacity.
*: indicates statistically significant difference between athletes with no previous diagnosis of asthma and athletes with previous diagnosis of asthma.
Gmean: Geometric Mean, CI: Confidence Interval.

variability. The dependence of airway response to bronchial provocation challenges and eNO to baseline characteristics, EIRS and asthma like symptoms, rhinitis, atopy, aquatic

sports and treatment were assessed by linear regression analysis model. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

4. Results

4.1. Subject characteristics and screening phase assessment

The demographic characteristics of the study population participated in the 1st phase of the study are presented in Table 1. In total we studied 100 male and 100 female elite athletes. Fifty five (27.5%) athletes had a previous diagnosis of asthma (Group A) and 145 athletes had no previous history of respiratory disease (Group B). Asthma diagnosis was more common in males compared with female elite athletes. Aquatic sport competitors had greater prevalence among elite athletes of Group A. Baseline spirometry data for the 2 Groups of athletes and asthma treatment for athletes of Group A are presented in Table 1. No other differences in characteristics for age, smoking status and BMI were found between the two groups.

Exercise-induced respiratory symptoms (EIRS) were reported to correspond to 57% of the whole study population; 90.9% in Group A and 44.1% in Group B. Other asthma-like symptoms like shortness of breath, wheezing, cough and night respiratory symptoms were reported by a high proportion of Group A, but they were also stated by Group B. Specifically, shortness of breath and cough were reported by 34.5% and 36.6%, respectively in Group B.

Rhinitis symptoms were reported by 30.5% of the participants with no statistical difference being observed between the two groups. Surprisingly, a high proportion of atopy (48.7%) was also detected in our population with a higher percentage (62.3%) in Group A. Chi square analysis showed a statistically significant association between EIRS and atopy (P = 0.01) and between EIRS and rhinitis symptoms (P = 0.02) in the whole population.

According to history the athletes from Group A had mild severity of the disease.

There was no difference observed regarding the levels of eNO between the two groups (Table 1). Higher levels of eNO were related (P = 0.01) with the presence of atopy and with rhinitis symptoms (P = 0.049). Smoking was associated with lower levels of eNO (P = 0.029).

4.2. Airway hyperresponsiveness assessments and correlations

Among the 111 elite athletes who participated in the 2nd phase of the study 51 elite athletes had a previous physician-based diagnosis of asthma (Group A) and 60 elite athletes had no previous history of respiratory disease (Group B). The participants were matched for age, sex, BMI and smoking status. Direct and indirect BPTs were performed without any complications by all participants. The methacholine (Mch) test was performed by all participants, the EVH test by 82 athletes, the mannitol test by 73 athletes and the exercise test by 58 athletes. The responses to BPTs are presented in Table 2a.

As it was expected elite athletes from Group A had more frequently a positive response to Mch and EVH challenges, as compared with athletes from Group B (P = 0.012, P = 0.017, respectively). However no statistically significant difference was recorded for mannitol or exercise test between the two groups of athletes (Table 2a). A high percentage (63.3%) of Group B had a positive Mch challenge and 66.7% of that group had at least one positive response to direct or indirect challenges. Furthermore, 10 (27.8%) athletes from Group B had a positive response to EVH test and 8 (25%) athletes had a positive response to mannitol challenge.

The existence of reported EIRS or any other asthma-like symptoms, or rhinitis and atopy were not associated with a positive BPT response (Table 2b). Seventeen (15%) elite athletes have reported EIRS but they did not have any positive BPT response, whereas 9 (8.1%) athletes had at least 1 positive BPT response without reporting any EIRS.

Linear regression analysis showed a good correlation of the airway response to Mch (PD_{20}) with wheezing (P < 0.005, regression coefficient: −1.343) and of the airway response to EVH (ΔFEV_1)

Table 2a
Bronchial Provocation Tests in study population group.

	No Previous diagnosis of Asthma(n = 60) N (%)	Previous diagnosis of Asthma(n = 51) N (%)	P-value
Methacholine (positive)	38 (63.3%)	44 (86.3%)	0.012[a]
EVH (positive)	10 (27.8%)	26 (56.5%)	0.017[a]
Mannitol (positive)	8 (25%)	12 (29.3%)	0.888
Exercise (positive)	1 (4%)	3 (9.1%)	0.815
At least one positive BPT	40 (66.7%)	46 (90.2%)	0.006*

[a] Indicates statistically significant difference between athletes with no previous diagnosis of asthma and athletes with previous diagnosis of asthma.

Table 2b
Association of a positive bronchial provocation test and respiratory symptoms.

	OR (95% Confidence Interval)	p-value
EIRS	2.977 (0.739–11.989)	0.125
Breathlessness	1.272 (0, 371–4,364)	0.702
Wheezing	1.693 (0.514–5.569)	0.386
Cough	2.714 (0.978–7.532)	0.055
Night symptoms	0.842 (0.139–5.096)	0.852
Allergic Rhinitis	1.460 (0.488–4.373)	0.499
Atopy	0.866 (0,301–2,486)	0.789

EIRS: exercise-induced respiratory symptoms.
Night symptoms: Respiratory symptoms that awake the athlete during the night.

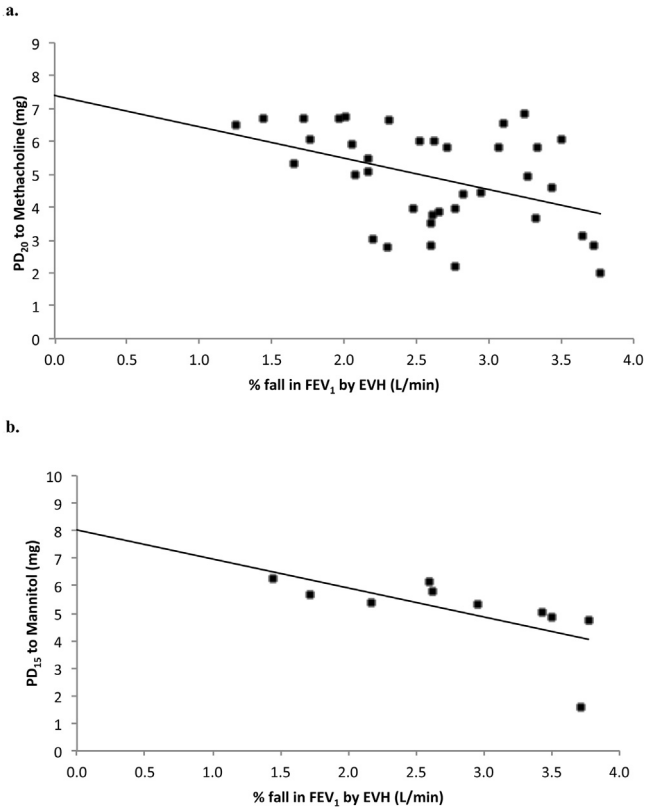

Fig. 1. Scatterplot of percentage fall in FEV_1 by EVH in Group A vs. a) PD_{20} to methacholine challenge (mg) (r_p: −0.424, p = 0.009, n = 37) and b) PD_{15} to mannitol challenge (mg) (r_p: −0.659, p = 0.038, n = 10). EVH: Eucapnic Voluntary Hyperpnoea, FEV_1: Forced expiratory volume in 1 s, PD_{20}: provocative dose inducing a 20% decrease in FEV_1, PD_{15}: provocative dose inducing a 15% decrease in FEV_1.

with cough (P = 0.017, regression coefficient:,764). Other factors such as age, gender, BMI, smoking status were not related with a positive response to BPTs.

Correlations among BPTs in our study population are shown in Fig. 1a and b. EVH response (%drop in FEV_1) was well correlated with Mch response (PD_{20}) (r = – 0.424, P = 0.009, Fig. 1a) and with mannitol response (PD_{15}) (r = – 0.659, P = 0.038, Fig. 1b) in Group A. Mannitol test was correlated with% drop of FEV_1 to Mch test both in Group A (r = 0.440, P = 0.006) and in Group B (r = 0.425, P = 0.019). Not any other relevant correlation was found in Group B.

There was no concordance observed between the tests but only between the existence of a positive test response between mannitol and exercise BPT. More specifically, there was no concordance observed between the existence of a positive test result between the Mch provocation with the EVH test (P < 0.001), the mannitol test (P < 0.001) and the exercise test (P < 0.001). Likewise, there was no concordance observed between the existence of a positive test result between the EVH testing with the mannitol test (P = 0.035) and the exercise (P < 0.001) test.

5. Discussion

This is the first study investigating the prevalence of EIRS and EIB in elite athletes who are competing at high standard national and international sport events. Furthermore information regarding history of asthma, atopic sensitization and allergic rhinitis has been recorded for the first time in this population.

Previously reported diagnosis of asthma was common among the study population of Greek elite athletes (55 subjects out of 200) with male predominance. This is an important finding considering that the prevalence of asthma in Greece ranges from 7.7% to 11.5% (Papadopoulou et al., 2011). This might be explained by the young age of the participants and the fact that a high percentage of athletes have started training in swimming since childhood. As the diagnosis of asthma is more prevalent among boys in the childhood (Mallol et al., 2013) they might have been encouraged to engage in aquatic sports, such as swimming, at an early age. The high percentage of referred asthma among this population of athletes supports the notion that athletes with asthma can also compete at high standards.

A very interesting finding of our study is that a high proportion of elite athletes, without a previous asthma diagnosis, reported EIRS or other asthma-like symptoms compete unaware that they might have EIB or a misdiagnosis of asthma. Although the high prevalence of EIRS is not specific for establishing the diagnosis of EIB, it raises questions regarding a possible misdiagnosis of EIB. Previous reports have shown that the use of self-reported respiratory symptoms to establish a diagnosis of EIB results in a high-frequency of both false-positive and false-negative diagnoses in endurance sport athletes (Bougault et al., 2010). Furthermore it has been shown that airway narrowing may occur in the absence of symptoms; thus an isolated symptom-based diagnosis of EIB is considered by some researchers to be unreliable (Rundell et al., 2001).

The presence of EIRS was associated with atopy and with rhinitis symptoms in our study population. Allergic rhinitis has been previously shown to have negative effects on performance scores (ability to train and compete) (Katelaris et al., 2002). A high percentage of elite athletes tested had atopy (48.7%) and rhinitis symptoms (30.5%). It has previously been reported that the presence of atopic sensitization could be a risk factor for the development of AHR and asthma (Bonini et al., 2007). Moreover allergic athletes experience symptoms of upper and lower airways disease on exposure

to both outdoor and indoor aeroallergens (Bonini et al., 2006). The overall prevalence of atopy and rhinitis in Greece (Papadopoulou et al., 2011) ranges from 16% to 25.2% and from 21.3% to 24.2%, respectively.

Previous studies (Bougault et al., 2010; Ansley et al., 2012), highlight the need for screening elite athletic populations for the presence of EIB using BPTs, regardless of existence of a previous asthma diagnosis or reported EIRS, in order to improve athlete's health and performance. Therefore, we further investigated our population for EIB by objective testing with direct and indirect BPTs. Based on our results regarding the BPTs, it is important to consider that athletes may have a positive response to only one of these types of BPTs; therefore more than one type of tests may be required. Testing of our population of elite athletes with BPTs was performed during a period of intense training (Boulet and O'Byrne, 2015), as it has been shown by Bougault et al (Bougault et al., 2011) that AHR is reduced or even normalized in elite swimmers when intense training is stopped for 15 days. Our findings on the BPTs are in line with previously reported studies (Bougault et al., 2010; Rundell et al., 2001) since 15% of our study population reported EIRS but they did not have a positive BPT response and 8% of elite athletes did not report EIRS but they had at least one positive BPT response. Furthermore, we found no association between EIRS and asthma-like symptoms with objective evidence of EIB.

Among all the BPTs that were performed for the diagnosis of EIB, the Mch provocation tests exhibited the highest positive response in both groups of elite athletes. High positive response to Mch has previously been reported in winter athletes who did not present bronchoconstriction when exposed to indirect stimuli such as exercise, EVH or mannitol (Sue-Chu et al., 2010). In contrast, in summer sport athletes, as it has been reported by Pedersen et al (Pedersen et al., 2008) and Holzer et al (Holzer et al., 2002), there was a lower prevalence of AHR to Mch provocation with a higher prevalence of AHR to indirect stimuli. Nevertheless, in our study population, that has included many swimmers, AHR to Mch had the highest response rate as compared to AHR to the indirect BPTs, and a positive response to Mch detected a positive response to the indirect BPTs in the majority of the athletes. Thus, Mch provocation test is an easy test to be used in the laboratory and it should be in the first line of assessment of EIB in elite athletes. However, reliance on a negative Mch test would frequently result in under-diagnosis of EIB (Holzer et al., 2002; Anderson et al., 2009). In order to avoid misdiagnosis of EIB, a second line of investigation, using indirect BPTs, for accurate diagnosis of EIB is recommended.

EVH is a test that is recommended for the diagnosing of EIB in athletes by the International Olympic Committee (IOC) Medical Commission (Anderson et al., 2003). In our study, airways positive response to the EVH test was found in higher rates among all the indirect BPTs that were performed, especially in athletes from Group A. This EVH challenge response correlated well with all other BPTs (direct and indirect) in this group.

Mannitol provocation testing serves as a surrogate to exercise to identify EIB in elite athletes (Holzer et al., 2003). Inhaling dry powder mannitol increases the osmolarity of the airway surface and causes release of the same inflammatory mediators as EVH and exercise (Brannan et al., 2006; Larsson et al., 2011). A positive response to mannitol has been shown to identify individuals with asthma and with EIB (Brannan et al., 1998). On the other hand, some other previously reported studies have shown that 30% of subjects with mild EIB are not identified with a mannitol test (Anderson et al., 2009). In our study, we found a lower percentage of airway response to mannitol as compared with the response to EVH testing in elite athletes from Group A. In contrast, a similar percentage of positive response to mannitol and to EVH test was observed in elite athletes from Group B, indicating that in this group of athletes any of the two indirect BPTs may be used for the diagnosis of EIB.

In the present study the percentage of a positive airways response to exercise test performed in the laboratory was very low in both groups of elite athletes. One of the most important reasons for this low positive response rate found is the failure of the exercise stimulus to be intense enough in order to increase the ventilatory load to the necessary level for triggering bronchoconstriction. The exercise test was performed according to the protocol on an ergometer bicycle and the majority of subjects were limited by leg fatigue rather than by ventilatory restriction. Sport-specific exercise that reproduces the symptoms reported in the field, is probably the most relevant for testing elite athletes (Rundell et al., 2000). Furthermore other factors associated with environmental conditions, such as humidity and temperature levels, pollen count and pollution level may also greatly affect the response of possible EIB in the field (Anderson and Kippelen, 2012).

No concordance was found between the pairs of BPTs, suggesting that Mch, EVH, mannitol and exercise challenge are not mutually interchangeable. This latter finding also implies that a negative result to e.g. EVH challenge should not deem an elite athlete negative for the presence of EIB and a second line of investigation should follow with another BPT.

According to our results, BPT with Mch should be in the first line for evaluation of EIB in all elite athletes, regardless of a previous asthma diagnosis. As a second line of investigation and according to the facilities of each laboratory, a mannitol or a EVH test should be performed in elite athletes without a previous asthma diagnosis. However in elite athletes with a previous asthma diagnosis the EVH should be preferred over the mannitol test, in order to confirm or exclude the diagnosis of EIB.

Thus, early detection of previously unrecognized EIB by selecting a direct with Mch and/or either by EVH or mannitol indirect BPT can be performed in a specialized laboratory field by trained personnel without any complications.

We acknowledge that there are potential limitations regarding the methodology of the present study. Firstly, a possible limitation relates to the fact that asthma diagnosis was based on previous history and was self reported but not documented, prior to the division of the study population into two groups. Although the percentage of athletes from Group A which reported no EIRS (9.1%) and had no positive BPT (9.8%) was small, it raises the question as to whether these athletes might have mild or well controlled asthma as 47.3% of the athletes from this Group were under treatment. We did not perform a reversibility test in Group A, in order to confirm the self-reported asthma diagnosis, for two reasons. Firstly, it is already known that a reversibility test in a population of elite athletes is of limited value (Kurowski et al., 2016). Secondly, the main objective of the study was to assess the diagnostic value of the BPTs in elite athletes. The study required the conduct of four BPTs across four different occasions; which limited the willingness of the coaching team to allow additional testing (i.e. a reversibility test) to be performed on elite athletes.

A further limitation of our study is that the relatively short ICS washout period in athletes receiving therapy in Group A may have led to some false-negative results. Our approach to the duration of the washout period was dictated by practical and ethical considerations with respect to withholding asthma medications and is in line with recommendations (Crapo et al., 2000). More studies are needed, with a larger number of steroid-naïve athletes with a previous diagnosis of asthma, for a more accurate evaluation of the diagnostic value of bronchial challenges in this population.

Another limitation of the study relates to the failure to carry out all the bronchial challenges to all athletes. As previously mentioned, elite athletic populations have tight schedule regarding their sporting commitments and compliance to the study was difficult. Despite this, a sufficient number of elite athletes with and without a previous asthma diagnosis were tested with BPTs, per-

mitting comparison of BPTs and assessment of their diagnostic value in this population.

6. Conclusions

High prevalence of asthma, allergic rhinitis and atopy was found among elite athletes who are participating and competing at International Level Sport Events, as are Olympic Games. This finding supports the notion that adults and children with mild asthma, they can participate in high standard sports activities. Furthermore the results of this study confirm that EIRS and EIB are common among elite athletes and there is critical need for screening elite athletes by using objective bronchial provocation tests (BPTs) irrespective of a previous asthma diagnosis. More studies are needed in order to establish that early diagnosis of EIB or asthma by BPTs may lead to improvements in athlete's health and better exercise performance.

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