Exercise-Induced Bronchoconstriction among Greek elite athletes: Assessment of the validity of bronchial provocation tests

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Abstract

Background: Diagnosis of exercise-induced bronchoconstriction (EIB) requires objective documentation with bronchial provocation tests (BPTs), since exercise-induced respiratory symptoms (EIRS) have poor diagnostic value. We aimed to assess EIRS, EIB and asthma in elite Greek athletes and evaluate the validity of BPTs in the diagnosis of airway hyperresponsiveness (AHR) in this population. Furthermore rhinitis and atopy were also assessed.

Methods: Two hundred elite athletes (55 with a previous asthma diagnosis) completed a questionnaire. Skin prick tests, exhaled Nitric Oxide and spirometry were consecutively performed. EIB was objectively assessed by the methacholine test, the eucapnic voluntary hyperpnoea (EVH) test, the mannitol test and the exercise test.

Results: EIRS and asthma-like symptoms were highly reported by athletes in both groups. Atopy was found in 43.8% of athletes without a previous asthma diagnosis and in 62.3% of athletes with asthma. AHR to methacholine had the highest prevalence among all the BPTs that were performed in athletes without a previous asthma diagnosis (63%) and in athletes with asthma (86%). Athletes with asthma had more frequently a positive result in methacholine and EVH challenges, as compared with athletes without a previous asthma diagnosis(P=0.012, P=0.017, respectively), whilst AHR to mannitol had a similar prevalence between the two groups. Report of EIRS, asthma-like symptoms, rhinitis and atopy were not associated with a positive BPT response.

Conclusion: Screening elite athletes for EIB using BPTs is suggested irrespective of report of EIRS or a previous asthma diagnosis.

Conflicts of interest: None of the other authors has any conflict of interest related to the present manuscript

Keywords: asthma, exercise-induced bronchoconstriction, bronchial provocation tests, athletes, rhinitis

Abbreviations used: EIB: exercise-induced bronchoconstriction, BPT: bronchial provocation test, AHR: airway hyperresponsiveness, Mch: Methacholine, EVH: Eucapnic Voluntary Hyperpnoea, EIRS: Exercise-induced respiratory symptoms, 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

Exercise-induced bronchoconstriction (EIB) describes the transient airway narrowing that occurs after exercise, a phenomenon that occurs frequently among athletes who may not have a diagnosis of asthma or even have any respiratory symptoms.[1] EIB is more common among endurance athletes, particularly swimmers and winter sport athletes, than in the general population.[2]

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.[3] In terms of performance, EIB and asthma may reduce exercise capacity.[4] Many studies support the need for screening for EIB and asthma in elite sport.

As exercise-induced respiratory symptoms (EIRS) have poor predictive value for making a diagnosis of EIB in athletes, documentation of variable airway obstruction is a requirement for the diagnosis of EIB in elite athletes[5,6] and 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.[7]

Rhinitis has an added importance in the frequent report of combined nasal and asthmatic symptoms in patients with allergic rhinitis[8] and the history of rhinitis should make the physician to test the possibility of concomitant asthma or airway hyperresponsiveness(AHR).[9] Allergic rhinitis has been observed as common among elite athletes.[10] Of interest is also the association of physical exercise with the development of allergic sensitization in summer sport athletes. Zwick et al[11] 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 investigate the presence of EIRS, EIB, asthma, atopy and allergic rhinitis in Greek elite athletes for the first time and secondly to further evaluate the validity, sensitivity and specificity of direct and indirect BPTs in the diagnosis of airway hyperresponsiveness in this population.

Methods

Subjects and study design

A group of 200 elite athletes, competing at high level National 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^{2}LEN), the European network of centres of excellence in allergy and it was approved by the hospital and University Ethics Committee.

All athletes completed a demographic questionnaire on past and current respiratory symptoms, history of asthma, allergic rhinitis or other allergies, training and sport habits. The AQUA questionnaire[12] (Allergy Questionnaire for Athletes) with supplement of some questions from the ECRHS questionnaire was used (see Appendix).[13] According to history the population was subdivided in two groups; Group A: athletes with asthma and Group B: athletes without a previous diagnosis of asthma. Asthma was based on previous doctor diagnosis before entering the study (as ever diagnosed asthma). EIRS were defined as symptoms during or after exercise.

Atopy, lung function and airway inflammation were assessed by skin prick tests to common allergens, spirometry and exhaled Nitric Oxide (eNO) respectively. All athletes had skin prick tests(SPT) according to European standards[14] with the GA^{2}LEN Pan-European panel of allergen extracts.[15] Spirometry was performed according to ERS recommendations,[16] 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.[17]

To further investigate the validity of BPTs in detecting EIB we studied 111 athletes who voluntarily participated in the second phase of the study and they were tested by direct and indirect BPTs [Eucapnic voluntary hyperpnoea (EVH), mannitol and exercise test]. The tests were performed by at least 24h but less than 10 days. No test was performed if there was an upper or lower respiratory tract infection 8 weeks before entering the study. Elite athletes with at least one positive bronchial challenge were defined as EIB positive.

Bronchial Provocation Tests

Methacholine Challenge: Methacholine chloride were dissolved in normal saline solution to produce doubling concentrations range of 0.39-200mg/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 were inhaled. An acceptable-quality FEV_1 was obtained at each time point; otherwise the FEV_1 manoeuvre was repeated. The challenge test was continued 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 calculated automatically by interpolation of the logarithmic dose response curve.

Mannitol Challenge: A dry powder preparation of mannitol was delivered in gelatine capsules containing 0, 5, 10, 20 or 40mg (Osmohale, Pharmaxis Pharmaceuticals Ltd, UK). Consecutive doses of 0, 5, 10, 20, 40, 80, 160, 160 and 160mg (to a maximum cumulative dose of 635mg) were administered via an inhalator and a controlled deep inhalation to total lung capacity with 5 seconds of breath holding.[18] A positive test was defined by a ≥15% fall in FEV_1 at ≤ 635mg. 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).

EVH Challenge: The EVH challenge was performed according to the method described by Anderson and Brannan.[19] 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.[19] 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 ≥10% was observed over two consecutive time points compared with baseline. Ambient conditions in the laboratory were 21^{o}C and 2% humidity

Exercise test: The laboratory cycle test used the stepped protocol recommended by the ATS.[20] The athletes were asked to bike for 8 minutes in an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, USA). Exercise intensity was set to elicit a heart rate of more 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 ≥10% was observed over two consecutive time points compared with baseline.

Statistical analysis

Comparisons of variables of interest between Group A and Group B athletes 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, asthma like symptoms, 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. 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 variability. The dependence of airway response to bronchial provocation challenges and eNO to baseline characteristics, EIRS and asthma like symptoms, rhinitis, atopy, water sports and treatment were assessed by linear regression analysis model. The diagnostic value of bronchial provocation tests over the asthma diagnosis was assessed by sensitivity ($\frac{\text{true positive BPT}}{\text{true positive BPT+ false negative BPT}}$) and specificity ($\frac{\text{true negative BPT}}{\text{true negative BPT+ false positive BPT}}$). All statistical analyses were performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Subject Characteristics

The demographic characteristics of the study population in the 1st phase of the study are presented in Table 1a. We have studied 100 male and 100 female elite athletes. Fifty five (27.5%) had a previous diagnosis of asthma (Group A) and 155 athletes had a free history (Group B). Asthma diagnosis was more common in males compared with female athletes. Water sports were more common among athletes of Group A. No other differences in characteristics for age, smoking status and BMI were found between the 2 groups.

Exercise-induced respiratory symptoms (EIRS) were reported by 57% of the whole study population; 90.9% of Group A and 44.1% of 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 referred by Group B. Specifically, shortness of breath and cough were reported by 34.5% and 36.6% respectively by Group B.

Rhinitis symptoms were reported by 30.5% of the participants with no statistical difference being observed between the 2 groups. Surprisingly a high proportion of atopy (48.7%) was detected in our population with a higher percentage (62.3%) in Group A. A statistically significant association between EIRA and atopy atopy (P=0.01) and between EIRS and rhinitis symptoms (P=0.02) was found in the whole population.

According to history the athletes with asthma had mild severity of the disease and they received treatment; 47% were under inhaled corticosteroids (ICS) or combination treatment and 69% were under β_2-agonists monotherapy.

There was no difference observed regarding the levels of eNO between the 2 groups (Table 1a). Higher levels of eNO were related with the presence of atopy (P= 0.01) and with rhinitis

symptoms (P= 0.049). The report of smoking was associated with lower levels of eNO (P= 0.029).

2nd phase of the study: Bronchial Provocation Tests for Airway Hyperresponsiveness

From the 111 elite athletes who participated in the 2nd phase of the study 51 elite athletes were from Group A and 60 athletes from 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 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.

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). 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, 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 has shown a relation of the airway response to Mch (PD_{20}) with wheezing (P<0.005) and of the airway response to EVH (ΔFEV_1) with cough (P=0.017). 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 Figures 1a, 1b, 2a and 2c. EVH response (%drop in FEV_1) was well correlated with Mch response (PD_{20}) (r=-0.424, P=0.009, Figure 1a) and with mannitol response (PD_{15}) (r=-0.659, P=0.038, Figure 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, Figure 2a) and in Group B (r=0.425, P=0.019, Figure 2b). 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.

The sensitivity and specificity of each BPT for asthma diagnosis are presented in Table 3. Methacholine was the most sensitive and exercise test was the most specific challenge for the diagnosis of asthma in elite athletes.

Discussion

This is the first study investigating the prevalence of EIRS, EIB and the history of asthma, atopy and allergic rhinitis in Greek elite athletes who are competing at high standard national games. The important finding of our study is that a high proportion of Greek elite athletes without a previous asthma diagnosis report EIRS or other asthma-like symptoms without being tested with BPTs and they are competing being unaware that they might have EIB. Our findings are in line with previous studies,[6,21] and highlight the need for screening elite athletic populations for the presence of EIB using BPTs, regardless of a previous asthma diagnosis or

report of EIRS, in order to improve athlete's health and performance. It is important to notice that athletes may have a positive response to only one of these types of BPTs; therefore more than one type of test may be needed. Furthermore, as shown by Bougault et al, AHR is reduced or even normalized in elite swimmers when intense training is stopped for 15 days.[22] Consequently, ideally the testing of athletes with BPTs should be performed during a period of intense training.[23]

The diagnosis of asthma is common among Greek elite athletes (55 out of 200). This is an important finding if we consider that the prevalence of asthma in Greece ranges from 7.7% to 11.5%.[24] The high prevalence of asthma in our study could be related to the fact that a high percentage of athletes from Group A were male (65.5%). As the diagnosis of asthma is more prevalent among boys in the childhood[25] they might be encouraged to engage in water sports, such as swimming, at an early age. Consequently, it is important to highlight that asthmatics can do exercise and compete at high standard national games.

We showed that a high percentage of athletes from Group B and the majority of athletes from Group A reported EIRS and asthma-like symptoms, like cough and shortness of breath. 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 sports athletes.[6] Self- reported symptoms are not specific enough for the diagnosis of AHR or EIB in athletes. 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.[26] Our study is in line with the previously reported studies, 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. However, the high prevalence of EIRS and asthma-like symptoms among Greek elite athletes raises questions regarding misdiagnosis of EIB and suboptimal treatment of asthma among elite athletes.

According to our study, a high percentage of athletes had atopy (48.7%) and rhinitis symptoms (30.5%). The overall prevalence of atopy and rhinitis in Greece[24] range from 16% to 25.2% and from 21.3% to 24.2%, respectively. The high prevalence of atopic sensitization in our study population could be explained by the fact that we evaluated elite athletes mainly from water sports who train mostly outdoors, whereas exposure to airborne allergens is high. It has been previously reported that the presence of atopic sensitization could be a risk factor for the development of AHR and asthma.[27] Moreover allergic athletes experience symptoms of upper and lower airways disease on exposure to both outdoor and indoor aeroallergens.[28] We found no association between AHR with atopy and with rhinitis symptoms, but 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)[29] and pollen monitoring may help allergic athletes to achieve peak performance under prophylactic measures.

Among all the BPTs that were performed in our study for the diagnosis of EIB, AHR to methacholine provocation test had the highest prevalence, in both groups of athletes. Regarding the diagnosis of EIB, a high prevalence of AHR to Mch has been reported only in winter athletes who however did not bronchoconstrict when exposed to indirect stimuli such as exercise, EVH or mannitol.[30] In contrast, in summer sport athletes reported by Pedersen et al[31] and Holzer et al[32] there was a lower prevalence of AHR to Mch provocation and a higher prevalence of AHR to indirect stimuli. Nevertheless, in our study population, AHR to Mch

had the highest prevalence as compared to AHR to the indirect BPTs, and also a positive response to Mch detected almost all of the athletes with AHR to the indirect BPTs. However, reliance on a negative Mch test would frequently result in under-diagnosis of EIB.[32,33] On the other hand a positive response to Mch test, in the absence of a positive response to an indirect stimulus may be an indicator of airway injury or remodeling, rather than currently active asthma or EIB.[34] Mch provocation test is an easy to use test in the laboratory and it should be in the first line of assessment of EIB in elite athletes. In order to avoid over-diagnosis of EIB, a second line of investigation, using indirect BPTs, for accurate diagnosis of EIB is recommended.

The EVH is the test recommended by the International Olympic Committee Medical Commission when diagnosing EIB in athletes.[35] In our study, AHR to the EVH test had the highest prevalence among the other indirect BPTs that were performed, especially in athletes from Group A. We showed that elite athletes from Group A had more frequently a positive response to EVH challenge, as compared with athletes from Group B. Furthermore, the EVH challenge correlated well with all other BPTs (direct and indirect), only in athletes from Group A. Consequently, we may hypothesize that, in contrast to the suggestion of Haantela et al[36] regarding the two different clinical phenotypes of asthma in athletes, the EVH test might be the optimal indirect test for the diagnosis of EIB in elite athletes with a previous asthma diagnosis. In contrast, a similar percentage of AHR to mannitol and to EVH test was observed in elite athletes from Group B, thus concluding that in this group of athletes any one of the two indirect BPTs may be used for the diagnosis of EIB.

Inhaling dry powder mannitol increases the osmolarity of the airway surface and causes release of the same inflammatory mediators as EVH and exercise.[37,38] A positive response to mannitol has been shown to identify individuals with asthma with EIB.[39] On the other hand, previous studies have reported that some 30% of subjects with mild EIB are not identified with a mannitol test.[33] In our study, in elite athletes from Group A we found a lower percentage of AHR to mannitol test as compared with AHR to EVH test. This latter finding might be explained by the fact that…

The prevalence of AHR to exercise test was very low in both groups of athletes. One of the most important reasons why exercise testing can lack the sensitivity for detecting EIB or asthma in elite athletes is the failure of the exercise stimulus to be intense enough to increase the ventilatory load to the necessary level in order to trigger bronchoconstriction.[40] In our study, an ergometer bicycle was used and it seems that the majority of subjects were limited by leg fatigue rather than from ventilatory restriction. Sports-specific exercise that produces the symptoms, performed either in the laboratory or in the field, is probably the most relevant for testing elite athletes.[41] However, environmental conditions, such as humidity and temperature levels, pollen count and pollution level may greatly affect the response to the field.[42]

A limitation of our study is that all the BPTs were not performed by all subjects. A further important limitation of our study is that almost half of athletes from Group A were under treatment with ICS and the relatively short ICS washout period (<3 days) may have led to some false-negative test results. Our approach to the duration of ICS washout was dictated by practical and ethical considerations with respect to withholding asthma medications.

Conclusion

The high prevalence of EIRS and asthma-like symptoms among Greek elite athletes, although they are not specific for establishing the diagnosis of EIB, raises questions regarding misdiagnosis of EIB and suboptimal treatment of asthma in Greek elite athletes. The high proportion of EIB-positive elite athletes highlights the critical need for screening elite athletes for EIB using BPTs, irrespective of report of exercise-induced symptoms or a previous asthma diagnosis. We found no concordance 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. The authors suggest that Mch should be in the first line for evaluation of EIB in 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. 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. The detection of previously unrecognized EIB may lead to improvements in athlete's health and performance.

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Table 1. Demographic characteristics and respiratory symptoms based on Questionnaire

	All Subjects (n= 200)	Non-asthma (n= 145)	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%)
Water Sport	150 (70.5%)	95 (65.5%)	46 (83.6%) *
>3 hours 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 SPTs	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%)

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
*: indicates statistically significant difference between non-asthma and asthma athletes.
Gmean: Geometric Mean, CI: Confidence Interval

Table 2a. Bronchial Provocation Tests in study population group

	Without asthma (n=60) N (%)	**Previous Asthma diagnosis (n=51) N (%)**	**P-value**
Methacholine (positive)	38 (63.3%)	44 (86.3%)	0.012*
EVH (positive)	10 (27.8%)	26 (56.5%)	0.017*
Mannitol (positive)	8 (25%)	12 (29.3%)	0.888
Exercise (positive)	1 (4%)	3 (9.1%)	0.815
At least 1 BPT positive	40 (66.7%)	46 (90.2%)	0.006*

*: indicates statistically significant difference between non-asthma and asthma athletes.

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
Rhinitis	1.460 (0.488 - 4.373)	0.499
Atopy	0.866 (0,301-2,486)	0.789

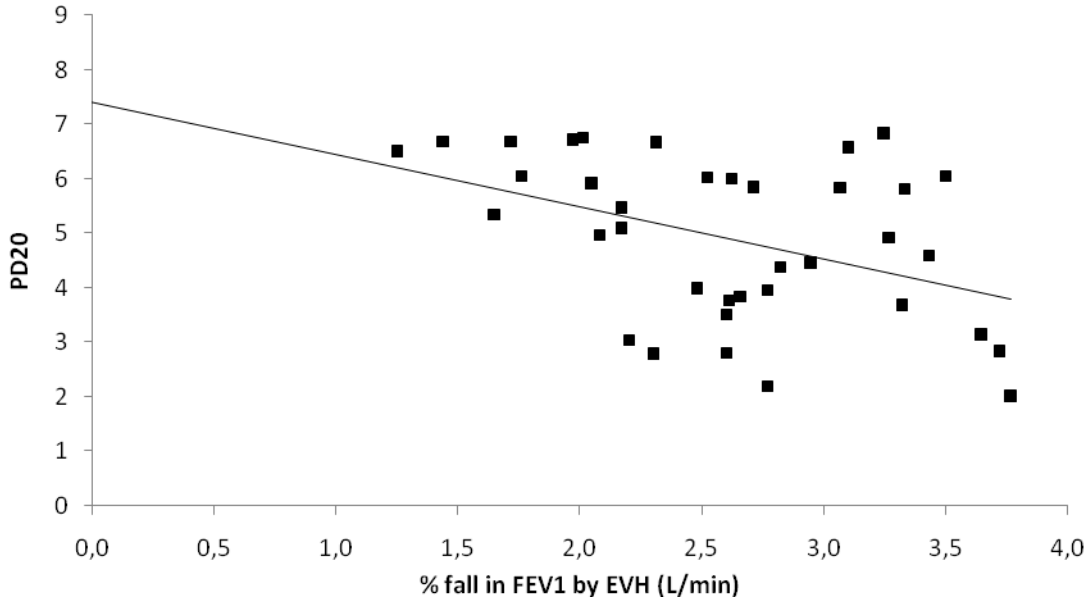
EIRS: exercise-induced respiratory symptoms

Night symptoms: Respiratory symptoms that awake the athlete during the night

Table 3. Sensitivity and Specificity of Bronchial Challenges, based on previous diagnosis of asthma

Bronchial Challenges	Sensitivity (%)	Specificity (%)
Methacholine	86.3	36.7
EVH	56.5	72.2
Mannitol	29.3	75
Exercise	9.1	96

1a.



1b.

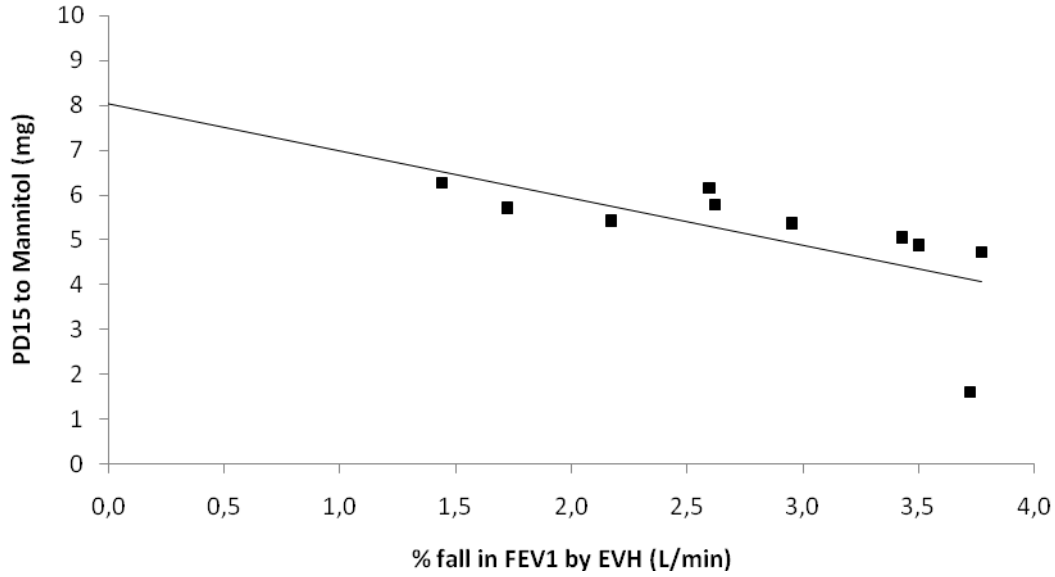
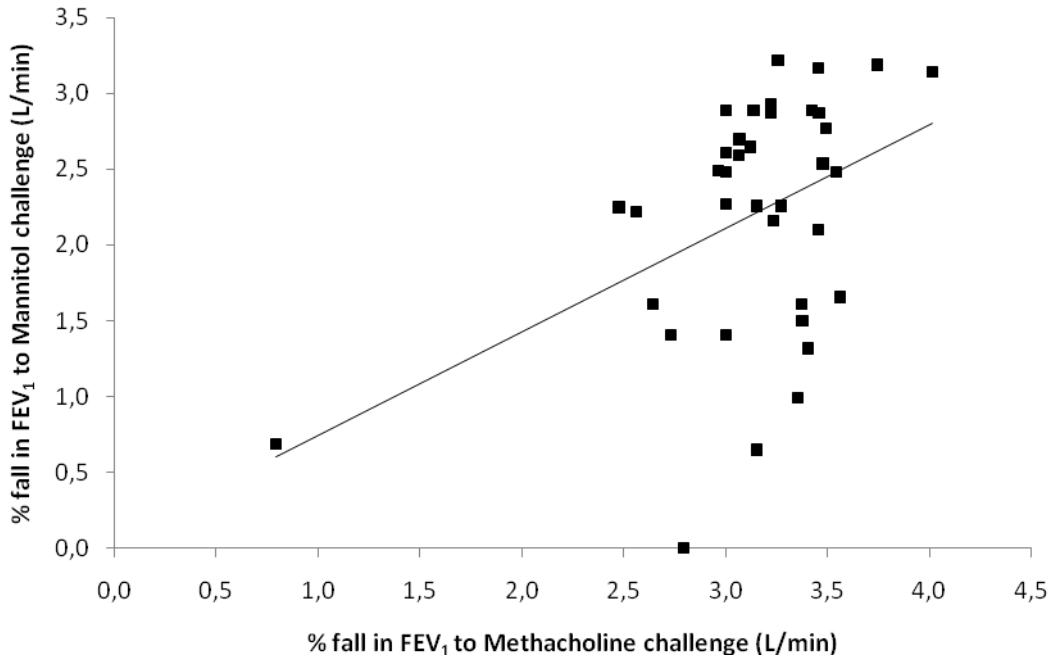


Figure 1. Scatterplot of percentage fall in FEV_1 by EVH in Group A vs. a) PD_{20} to methacholine challenge (mg) (r_p: -0.424, p=0.009, n=37) and b) PD_{15} to mannitol challenge (mg) (r_p: -0.659, p=0.038, n=10)

2a.



2b.

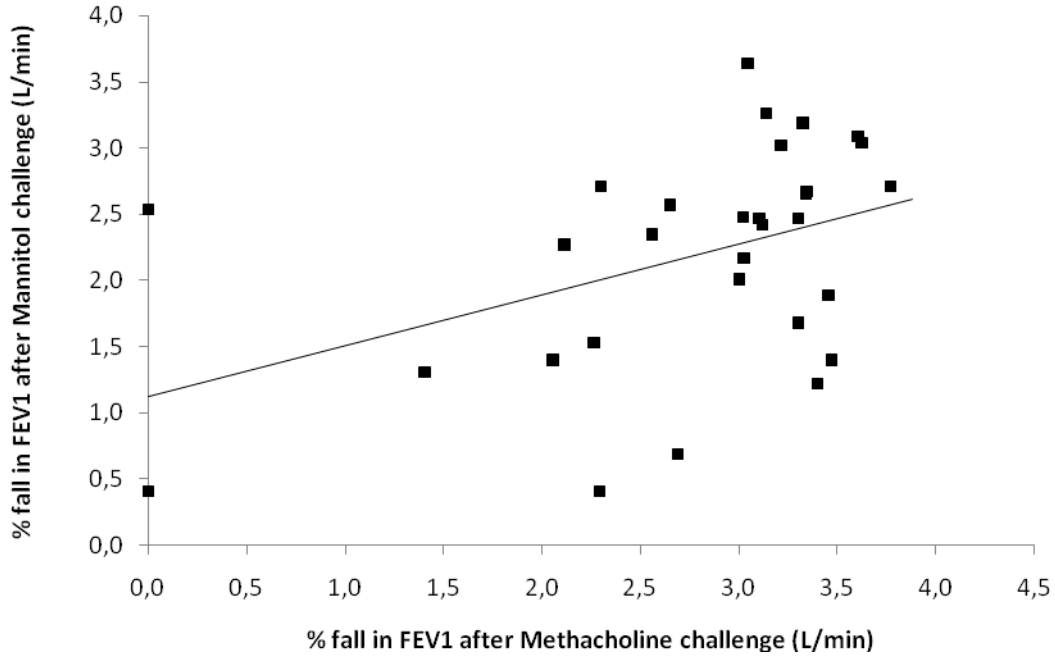


Figure 2. Scatterplot showing the correlation between the percentage fall in FEV_1 for mannitol vs. methacholine challenges in a) Group A (r_p: -0.440, p=0.006, n=38) and b) Group B (r_p: -0.425, P=0.019, n=30)

APPENDIX

Questionnaire GA^{2}LEN