EUCAPNIC VOLUNTARY HYPERPNEA TESTING IN ASYMPTOMATIC ATHLETES

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To the Editor:

The prevalence of exercise-induced bronchoconstriction (EIB) is consistently reported to be greater in athletic individuals than in the general population (1). The reason for this difference remains to be fully determined, but may be explained by the development of airway hyper-responsiveness arising from repeated episodes of exercise hyperpnea when performed in noxious environments (2). Equally however, it is important that the prevalence of EIB is not over-estimated (i.e. false positive) by the application of overly sensitive diagnostic test methodologies. The aim of this study was to determine the normative response to a eucapnic voluntary hyperpnoea (EVH) challenge, in cohort of entirely asymptomatic athletes.

Traditionally EIB was diagnosed using an exercise test, accompanied by a spirometric assessment of expiratory airflow. A positive result was typically defined by a 10% pre-post challenge reduction in forced expiratory volume in one second (FEV_1), based largely on population studies evaluating the 'normative' response to exercise (3). Although this approach is logical, there are several limitations when employing this methodology in competitive athletes; these include the difficulties inherent to standardizing and controlling both the effective cardiorespiratory workload and environmental conditions (4). On this basis, several surrogate means for securing a diagnosis have been recommended (1), including both direct and indirect bronchoprovocation tests. Of these, EVH testing is cited as one of the best means to confirm or refute a diagnosis of EIB; principally due to its simplicity and the fact that it mimics the desiccating stimulus driving the development of EIB (4).

The diagnostic threshold for a positive EVH test was originally established from a cohort of asthmatic army recruits (n = 90) and 'normal' healthy controls (n = 30). A 10% fall in FEV_1 was recommended as the cut-off on the basis of optimising the relationship between specificity (90%) and sensitivity (63%) and approximates the threshold most commonly utilised with exercise testing (5, 6). The published data in athletes, is however limited and confounded by a selection bias with inclusion of individuals with a prior diagnosis of airways disease, history of respiratory symptoms and/or those prescribed asthma medication (3). Indeed, it is our experience that despite having normal baseline lung function and no respiratory symptoms, the majority of competitive athletes completing an EVH challenge experience a fall in FEV_1 following EVH, frequently close to or beyond the 10% diagnostic cut-off. To describe this further we undertook a retrospective analysis of EVH tests performed in a large cohort of entirely asymptomatic athletes without a prior diagnosis of asthma or use of asthma medication. In accordance with previous methods (4) the EVH protocol consisted of breathing a dry compressed gas mixture (21% O_2, 5% CO_2, balance N_2) at a target ventilation equivalent to 85% maximum voluntary ventilation for 6 min. Spirometry was performed in triplicate at baseline and in duplicate at 3, 5, 7, 10, 15 min post EVH.

All athletes assessed (n = 224) were competitive at elite (i.e. either national or international standard) (n = 161) or recreational level (i.e. training/competing ≥6 hours/week) (n = 63) from a variety of sporting disciplines: athletics (i.e. competing in track and field events) (n = 71); rugby (n = 61); badminton (n = 4); boxing (n = 28); soccer (n = 22); hockey (n = 13); swimming (n = 9); rowing (n = 8); and biathlon (n = 8). All had normal predicted lung function values with no evidence of airway obstruction at rest (Table 1). The majority of athletes (98%) met accepted minimal target ventilation (i.e. minute ventilation ≥60% MVV) (4). The mean (+/- SD) maximum fall in FEV_1 was calculated as -7.6 ± 6.7% (Figure. 1) with the vast majority of athletes (98.2%) presenting with bronchoconstriction (i.e. reduction in FEV_1) at all time-points post EVH. The mean fall in FEV_1 was greater in elite (-8.0 ± 7.2%) than in recreational athletes (-4.2 ± 2.0%) ($P<0.01$). In the very few athletes eliciting bronchodilation post challenge (1.8%, n = 4), the 'improvement' in FEV_1 was only minor (i.e. approximately 1-2% increase post EVH). When athletes who failed to achieve their target ventilation were excluded from the analysis (n = 5), the findings remained unchanged ($P>0.05$) (data not shown). Likewise, when those with a severe fall in FEV_1 (>30%, n = 4) were excluded, the mean fall was not significantly altered (-7.2 ± 5.9%) ($P>0.05$).

This study reports, for the first time, what may be considered the pattern of response to an EVH test in a cohort of athletes. Approximately 20% (n = 44) of this entirely asymptomatic athletic population would be deemed positive for a diagnosis of EIB based on the accepted 10% cut-off value. Although markers of airway inflammation or other pathological profiling for 'asthma' was not performed, the findings highlight that a fall in FEV_1 >10% is encountered in a significant proportion of entirely healthy asymptomatic athletes and thus in many cases may actually represent a variation of the 'normative' airway response following exposure to the highly potent stimulus of EVH. Indeed, if an abnormal response is based on a mean + 2 SD change, as has been previously used to define a cut-off for EIB when employing an exercise test (8) our data suggests that a 15% cut-off would be a more appropriate threshold. Of note, in all athletes with >15% fall in FEV_1, a sustained reduction in lung function (i.e. minimum of two consecutive time-points) was observed, thus consistent with current EIB American Thoracic Society committee guidelines (1).

The decision to initiate treatment for EIB should clearly be decided following the synthesis of clinical findings and objective test results, however the selection of a 'correct' cut-off value for detection of a condition is vital to guarantee diagnostic accuracy and ensure clinical care is optimised. We have previously highlighted the poor clinical reproducibility of EVH in athletes when a 10% FEV_1 cut-off threshold is employed (7). Whilst some may consider that a low cut-off threshold ensures that EIB is 'detected' and the health and performance of an athlete is optimised, it is equally important to balance this consideration with both the deleterious impact of unnecessary beta-2 agonist prescription and the potential for distraction from other potentially important causes of exertional dyspnoea (9).

The findings from this study provide evidence that caution should be applied in the interpretation of a mild post challenge reduction in lung function (i.e. 10-15% fall in FEV_1), certainly when applying EVH to screen athletic squads. Further work is required to evaluate differences between athletes with mild (e.g. 10-15% FEV_1) and more severe (e.g. >30% FEV_1) EIB and in comparison with commensurate exercise challenge data. Employing inflammatory biomarker analysis and applying supplementary test methodologies (e.g. impulse oscillometry) would provide additional value in this setting.

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Conception and design: OP, JD, JH; Analysis and interpretation: OP, JD, JH; Drafting the manuscript for important intellectual content: OP, LA, IL, JM, PC, JD, JH.

GUARANTOR STATEMENT

OP confirms full responsibility for the content of the manuscript.

REFERENCES

1. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, Storms WW, Weiler JM, Cheek FM, Wilson KC. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *American journal of respiratory and critical care medicine* 2013; 187: 1016-1027.

2. Price OJ, Ansley L, Menzies-Gow A, Cullinan P, Hull JH. Airway dysfunction in elite athletes–an occupational lung disease? *Allergy* 2013; 68: 1343-1352.

3. Dryden DM, Spooner CH, Stickland MK, Vandermeer B, Tjosvold L, Bialy L, Wong K, Rowe BH. Exercise-induced bronchoconstriction and asthma. *Evidence Report/Technology Asssessment* 2010; 189.

4. Anderson S, Argyros G, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnea to identify exercise induced bronchoconstriction. *British journal of sports medicine* 2001; 35: 344-347.

5. Hurwitz KM, Argyros GJ, Roach JM, Eliasson AH, Phillips YY. Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. *CHEST Journal* 1995; 108: 1240-1245.

6. Argyros GJ, Roach JM, Hurwitz KM, Eliasson AH, Phillips YY. Eucapnic voluntary hyperventilation as a bronchoprovocation technique. *Chest* 1996; 109: 1520-1524.

7. Price OJ, Ansley L, Hull JH. Diagnosing Exercise-Induced Bronchoconstriction With Eucapnic Voluntary Hyperpnea: Is One Test Enough? *The Journal of Allergy and Clinical Immunology: In Practice* 2014.

8. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *British journal of sports medicine* 1998; 32: 125.

9. Walsted NE, Hull JH, Backer V. High Prevalence of Exercise-Induced Laryngeal Obstruction in Athletes. *Medicine and science in sports and exercise* 2013; 45: 2030-2035.

Table 1. Clinical characteristics and baseline lung function.

Variables	
Sex (M:F)	178 : 46
Age (years)	23 ± 4
Height (cm)	179.6 ± 10.2
Weight (kg)	83.7 ± 17.5
BMI ($kg \bullet m^{-2}$)	22.0 ± 4.0
FEV_1 (L)	4.52 ± 0.78
FEV_1 (% predicted)	101.9 ± 11.2
FVC (L)	5.36 ± 1.03
FVC (% predicted)	102.2 ± 12.5
FEV_1/FVC (%)	85.1 ± 7.6
Target ventilation (L/min)	135.7 ± 23.4
Achieved ventilation (L/min)	121.0 ± 25.2
Predicted ventilation (%)	89.6 ± 14.4
Total fall in FEV_1 (%)	-7.6 ± 6.7%
-Elite athlete; fall in FEV_1	-8.0 ± 7.2%
-Recreational athlete; fall in FEV_1	-4.2 ± 2.0%

Data presented as mean ± SD. *n* = 224.

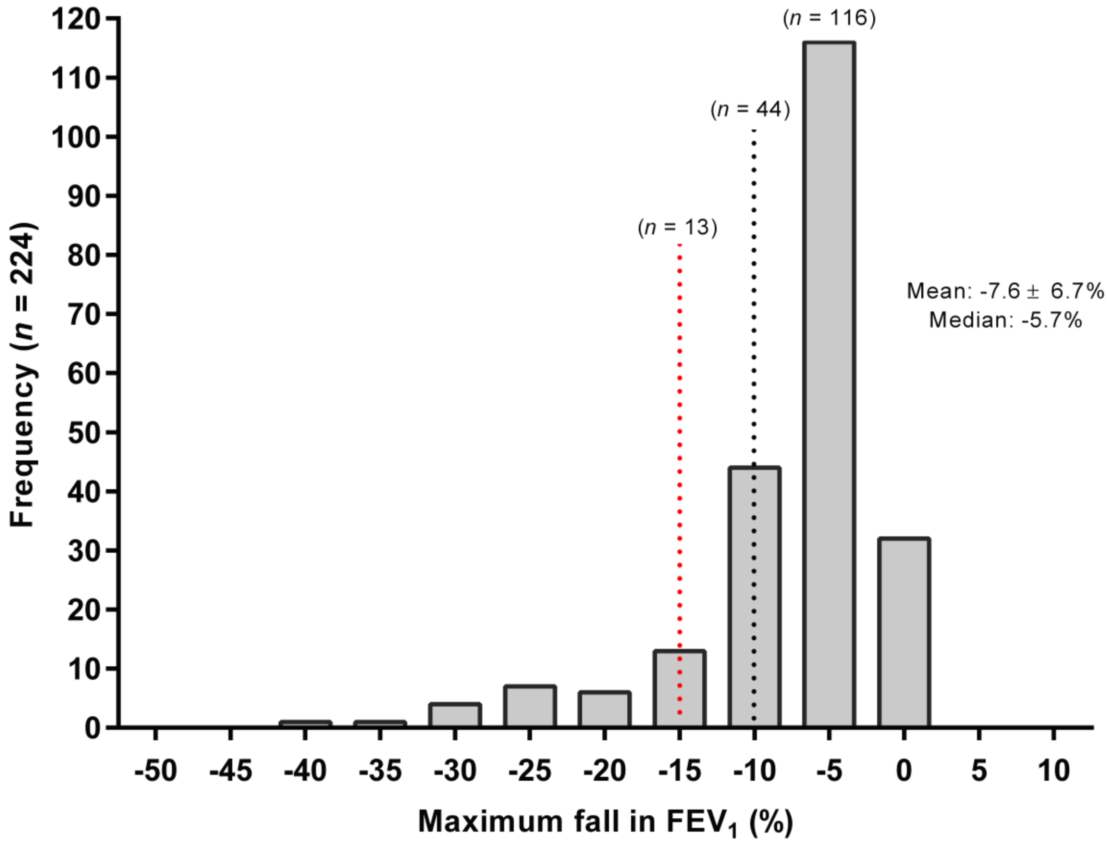

Figure 1. Frequency distribution of the maximum reduction in FEV_1 in asymptomatic athletes post EVH. Broken horizontal line (*black*) represents current diagnostic threshold (i.e. ≥10% fall in FEV_1) and broken horizontal line (*red*) represents proposed revised diagnostic threshold (i.e. ≥15% fall in FEV_1). Data presented as Mean ± SD.