1 **EUCAPNIC VOLUNTARY HYPERPNEA TESTING IN ASYMPTOMATIC**

2 **ATHLETES**

3 Oliver J. Price[1] PhD, Les Ansley[4] PhD, Irisz Levai[5] MD, John Molphy[6] PhD, Paul Cullinan[2] PhD,

4 John W. Dickinson*[5] PhD, James H. Hull*[2,3] MRCP, PhD

5 [1]Carnegie School of Sport, Leeds Beckett University, Leeds, United Kingdom (UK).

6 [2]National Heart and Lung Institute, Imperial College London, London, UK.

7 [3]Department of Respiratory Medicine, Royal Brompton Hospital, London, UK.

8 [4]Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria

9 University, Newcastle upon Tyne, UK.

10 [5]Sports Therapy, Physical Activity and Health Research Group, School of Sport and Exercise

11 Sciences, University of Kent, Chatham Maritime, UK.

12 [6]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool,

13 UK.

14 ***Authors contributed equally**

15 **Corresponding author**:

16 Dr Oliver J Price, PhD

17 Carnegie School of Sport, Leeds Beckett University, Leeds,

18 LS6 3QT, UK

19 Tel: 0113 812 0001

20 Email: o.price@leedsbeckett.ac.uk

21 **Word Count:** 1115.

23

To the Editor:

25 The prevalence of exercise-induced bronchoconstriction (EIB) is consistently reported to be greater in

26 athletic individuals than in the general population (1). The reason for this difference remains to be

27 fully determined, but may be explained by the development of airway hyper-responsiveness arising

28 from repeated episodes of exercise hyperpnea when performed in noxious environments (2). Equally

29 however, it is important that the prevalence of EIB is not over-estimated (i.e. false positive) by the

30 application of overly sensitive diagnostic test methodologies. The aim of this study was to determine

31 the normative response to a eucapnic voluntary hyperpnoea (EVH) challenge, in cohort of entirely

32 asymptomatic athletes.

33 Traditionally EIB was diagnosed using an exercise test, accompanied by a spirometric assessment of

34 expiratory airflow. A positive result was typically defined by a 10% pre-post challenge reduction in

35 forced expiratory volume in one second (FEV_1), based largely on population studies evaluating the

36 'normative' response to exercise (3). Although this approach is logical, there are several limitations

37 when employing this methodology in competitive athletes; these include the difficulties inherent to

38 standardizing and controlling both the effective cardiorespiratory workload and environmental

39 conditions (4). On this basis, several surrogate means for securing a diagnosis have been

40 recommended (1), including both direct and indirect bronchoprovocation tests. Of these, EVH testing

41 is cited as one of the best means to confirm or refute a diagnosis of EIB; principally due to its

42 simplicity and the fact that it mimics the desiccating stimulus driving the development of EIB (4).

43 The diagnostic threshold for a positive EVH test was originally established from a cohort of asthmatic

44 army recruits ($n = 90$) and 'normal' healthy controls ($n = 30$). A 10% fall in FEV_1 was recommended

45 as the cut-off on the basis of optimising the relationship between specificity (90%) and sensitivity

46 (63%) and approximates the threshold most commonly utilised with exercise testing (5, 6). The

47 published data in athletes, is however limited and confounded by a selection bias with inclusion of

48 individuals with a prior diagnosis of airways disease, history of respiratory symptoms and/or those

49 prescribed asthma medication (3). Indeed, it is our experience that despite having normal baseline

50 lung function and no respiratory symptoms, the majority of competitive athletes completing an EVH

51 challenge experience a fall in FEV_1 following EVH, frequently close to or beyond the 10% diagnostic

52 cut-off. To describe this further we undertook a retrospective analysis of EVH tests performed in a

53 large cohort of entirely asymptomatic athletes without a prior diagnosis of asthma or use of asthma

54 medication. In accordance with previous methods (4) the EVH protocol consisted of breathing a dry

55 compressed gas mixture (21% O_2, 5% CO_2, balance N_2) at a target ventilation equivalent to 85%

56 maximum voluntary ventilation for 6 min. Spirometry was performed in triplicate at baseline and in

57 duplicate at 3, 5, 7, 10, 15 min post EVH.

58 All athletes assessed ($n = 224$) were competitive at elite (i.e. either national or international standard)

59 ($n = 161$) or recreational level (i.e. training/competing ≥ 6 hours/week) ($n = 63$) from a variety of

60 sporting disciplines: athletics (i.e. competing in track and field events) ($n = 71$); rugby ($n = 61$);

61 badminton ($n = 4$); boxing ($n = 28$); soccer ($n = 22$); hockey ($n = 13$); swimming ($n = 9$); rowing ($n =$

62 8); and biathlon ($n = 8$). All had normal predicted lung function values with no evidence of airway

63 obstruction at rest (Table 1). The majority of athletes (98%) met accepted minimal target ventilation

64 (i.e. minute ventilation $\geq 60\%$ MVV) (4). The mean (+/- SD) maximum fall in FEV_1 was calculated as

65 $-7.6 \pm 6.7\%$ (Figure. 1) with the vast majority of athletes (98.2%) presenting with bronchoconstriction

66 (i.e. reduction in FEV_1) at all time-points post EVH. The mean fall in FEV_1 was greater in elite ($-8.0 \pm$

67 7.2%) than in recreational athletes ($-4.2 \pm 2.0\%$) (P<0.01). In the very few athletes eliciting

68 bronchodilation post challenge (1.8%, $n = 4$), the 'improvement' in FEV_1 was only minor (i.e.

69 approximately 1-2% increase post EVH). When athletes who failed to achieve their target ventilation

70 were excluded from the analysis ($n = 5$), the findings remained unchanged (P>0.05) (data not shown).

71 Likewise, when those with a severe fall in FEV_1 (>30%, $n = 4$) were excluded, the mean fall was not

72 significantly altered ($-7.2 \pm 5.9\%$) (P>0.05).

73 This study reports, for the first time, what may be considered the pattern of response to an EVH test in

74 a cohort of athletes. Approximately 20% ($n = 44$) of this entirely asymptomatic athletic population

75 would be deemed positive for a diagnosis of EIB based on the accepted 10% cut-off value. Although

76 markers of airway inflammation or other pathological profiling for 'asthma' was not performed, the

77 findings highlight that a fall in FEV_1 >10% is encountered in a significant proportion of entirely

78 healthy asymptomatic athletes and thus in many cases may actually represent a variation of the

79 'normative' airway response following exposure to the highly potent stimulus of EVH. Indeed, if an

80 abnormal response is based on a mean + 2 SD change, as has been previously used to define a cut-off

81 for EIB when employing an exercise test (8) our data suggests that a 15% cut-off would be a more

82 appropriate threshold. Of note, in all athletes with >15% fall in FEV_1, a sustained reduction in lung

83 function (i.e. minimum of two consecutive time-points) was observed, thus consistent with current

84 EIB American Thoracic Society committee guidelines (1).

85 The decision to initiate treatment for EIB should clearly be decided following the synthesis of clinical

86 findings and objective test results, however the selection of a 'correct' cut-off value for detection of a

87 condition is vital to guarantee diagnostic accuracy and ensure clinical care is optimised. We have

88 previously highlighted the poor clinical reproducibility of EVH in athletes when a 10% FEV_1 cut-off

89 threshold is employed (7). Whilst some may consider that a low cut-off threshold ensures that EIB is

90 'detected' and the health and performance of an athlete is optimised, it is equally important to balance

91 this consideration with both the deleterious impact of unnecessary beta-2 agonist prescription and the

92 potential for distraction from other potentially important causes of exertional dyspnoea (9).

93 The findings from this study provide evidence that caution should be applied in the interpretation of a

94 mild post challenge reduction in lung function (i.e. 10-15% fall in FEV_1), certainly when applying

95 EVH to screen athletic squads. Further work is required to evaluate differences between athletes with

96 mild (e.g. 10-15% FEV_1) and more severe (e.g. >30% FEV_1) EIB and in comparison with

97 commensurate exercise challenge data. Employing inflammatory biomarker analysis and applying

98 supplementary test methodologies (e.g. impulse oscillometry) would provide additional value in this

99 setting.

100 *Oliver J. Price[1] PhD*

101 *Les Ansley[4] PhD*

102 *Irisz Levai[5] MD*

103 *John Molphy[6] MSc*

104 *Paul Cullinan[2] PhD*

105 *John W. Dickinson[5] PhD*

106   *James H. Hull[2,3]MRCP, PhD*

COMPETING INTERESTS

The authors have no real or perceived conflict of interest in respect of this manuscript.

CONTRIBUTION STATEMENT

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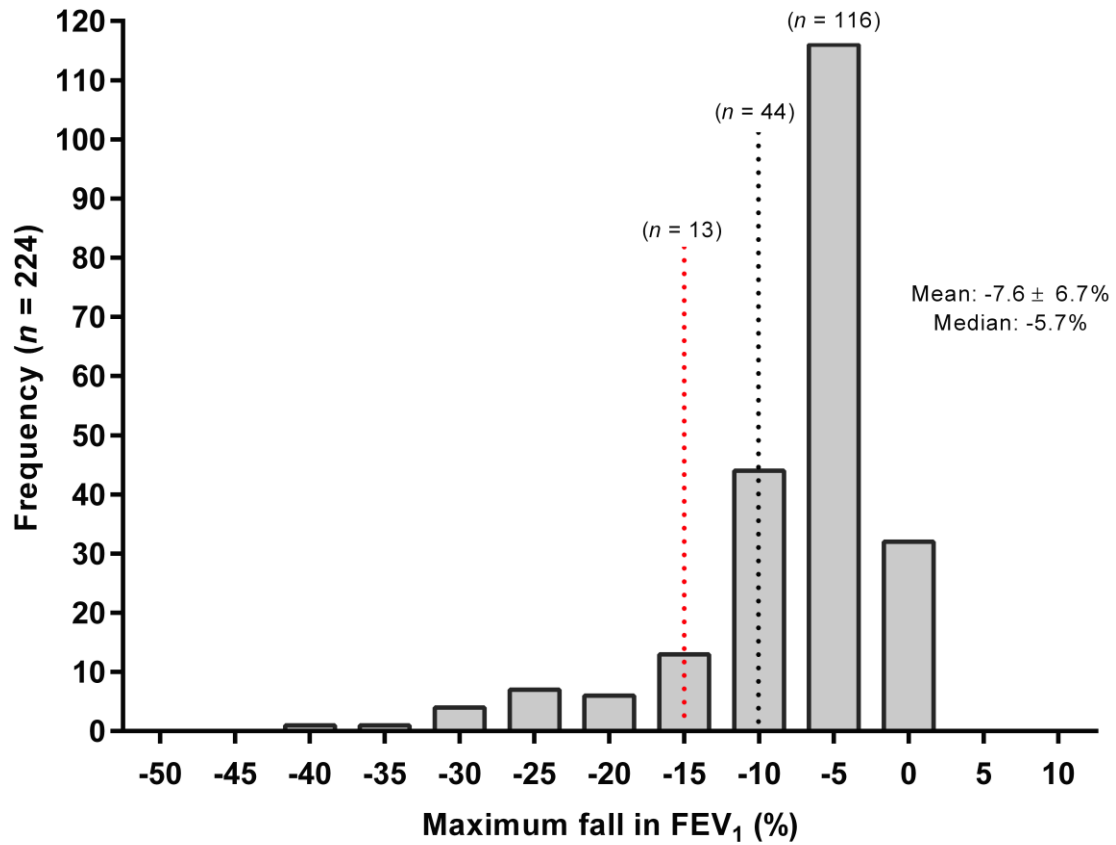
Figure 1. Frequency distribution of the maximum reduction in FEV_1 in asymptomatic athletes post EVH. Broken horizontal line (*black*) represents current diagnostic threshold (i.e. $\geq 10\%$ fall in FEV_1) and broken horizontal line (*red*) represents proposed revised diagnostic threshold (i.e. $\geq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