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1 **EUCAPNIC VOLUNTARY HYPERPNEA TESTING IN ASYMPTOMATIC**
2 **ATHLETES**

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23

24 *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 FEV₁ 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% O₂, 5% CO₂, balance N₂) 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 \geq 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 (\pm SD) maximum fall in FEV₁ 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 FEV₁) at all time-points post EVH. The mean fall in FEV₁ 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 FEV₁ 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 FEV₁ ($>30\%$, *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 FEV₁ $>10\%$ 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 FEV₁, 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% FEV₁ 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 FEV₁), 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% FEV₁) and more severe (e.g. >30% FEV₁) 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.

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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.

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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.

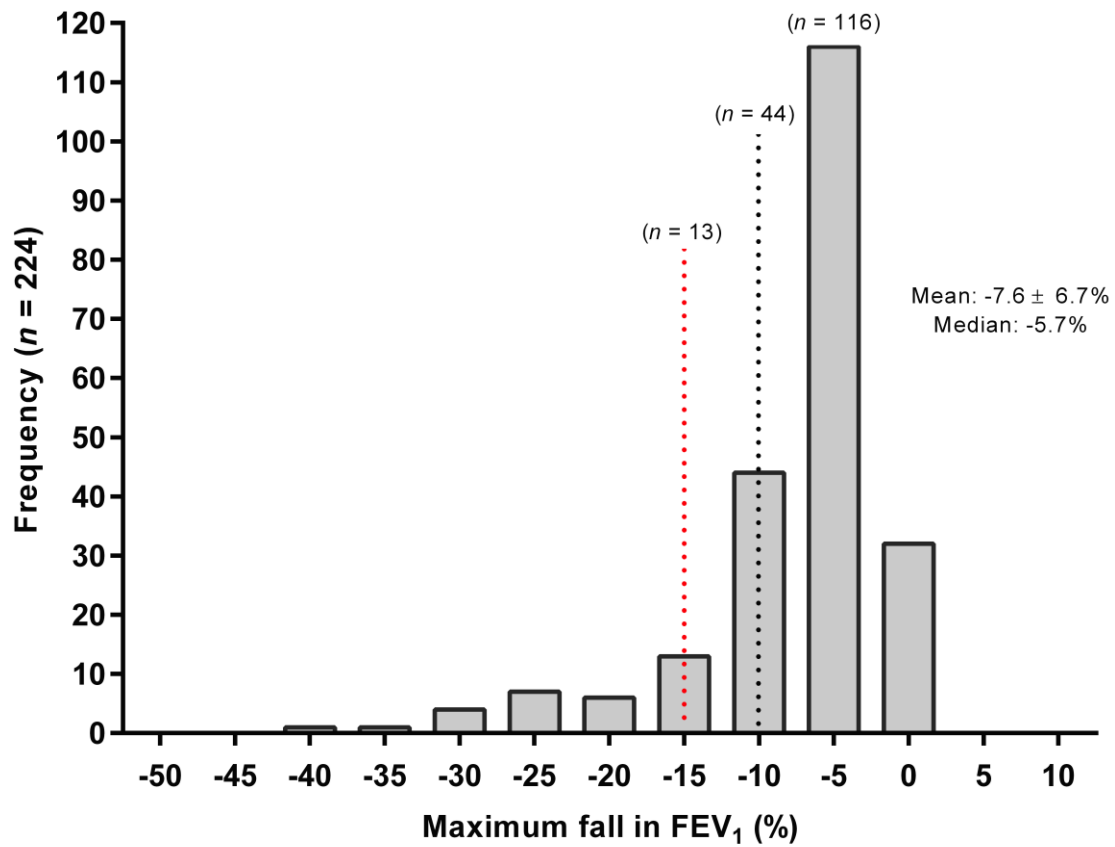


Figure 1. Frequency distribution of the maximum reduction in FEV₁ in asymptomatic athletes post EVH. Broken horizontal line (*black*) represents current diagnostic threshold (i.e. $\geq 10\%$ fall in FEV₁) and broken horizontal line (*red*) represents proposed revised diagnostic threshold (i.e. $\geq 15\%$ fall in FEV₁). Data presented as Mean \pm SD.