AJRCCM Letter-to-the-editor

Price, O. J.; Ansley, L.; Levai, I.; Molphy, J.; Cullinan, P.; DIckinson, J. W.; Hull, J. H.

Response to Professor Mastronarde: Eucapnic voluntary hyperpnea testing in asymptomatic athletes

We appreciate Professor Mastronarde's interest and comments concerning our cross-sectional analysis of eucapnic voluntary hyperpnea (EVH) testing in a cohort of elite and sub-elite asymptomatic athletes (1). We agree that self-report respiratory symptoms (e.g. wheeze, dyspnea, and cough) provide limited value when confirming or refuting a diagnosis of exercise-induced bronchoconstriction (EIB) or asthma in athletes. Indeed we have recently published both quantitative (2) and qualitative data in support of this concept (3). Moreover, there is currently no 'gold standard' objective test to diagnose EIB in athletes (4); thus classifying athletes as 'healthy' from a respiratory point of view, is a significant challenge.

Our analysis excluded athletes with a prior objective diagnosis of airways disease and/or those prescribed asthma medication (1). However, as Professor Mastronarde (5) quite rightly highlights, we did not perform comprehensive airway inflammatory profiling and this is an important study limitation. Future work should focus on addressing this deficiency, and as previously mentioned, a comparison between EVH and commensurate exercise challenge airway response (ventilation matched) is certainly an important research priority.

Regardless, it is important to recall that many of the original diagnostic cut-off values for surrogate bronchoprovocation challenges used in the diagnosis of EIB in athletes have been established based largely on data derived from non-athletic cohorts +/- prior diagnosis of asthma +/- perceived symptoms +/- previously treated. In our previous study, where we screened British-based elite athletes using EVH, the mean fall in EIB-negative athletes was −4.6 ± 2.9% (n = 150) (6). The normal response to an EVH challenge in elite athletes therefore appears to be a small reduction in FEV_1 when compared with baseline measurements. However, using a population, who report no symptoms and have no prior history of EIB allows us to investigate an abnormal threshold (1).

It is important to highlight that if we limit our population to those that have a maximum fall in FEV_1 post EVH <10% (i.e. EVH negative athletes based on current guidance) the threshold at which we

suggest an abnormal response is set at 10%. To put this into context, if we re-analyse the dataset from our study, and exclude any athlete with ≥10% fall in FEV_1 post EVH, based on the remaining athletes (n = 134), the mean fall in FEV_1 would be calculated as -4.9 ± 2.6%. However, this approach is artificially impacting the upper limit of a normal response. It is therefore only appropriate, when re-evaluating a diagnostic threshold, to analyse and interpret data from the entire cohort (n = 224), rather than classifying athletes as having a normal or abnormal airway response based on existing criteria (4).

Overall, we thank Professor Mastronarde (5) for highlighting important deficiencies in our current work and concede our approach may have overlooked the potential inclusion of asymptomatic athletes who had mild forms of undetected airway dysfunction and/or active airway inflammation. Irrespective of these limitations, we consider the data provided in a population of highly-trained athletes to add to the evidence-base in the field. Further research should be conducted prior to modifying the American Thoracic Society (ATS) clinical practice guideline statement (4).

Oliver J. Price[1] PhD - on behalf of all co-authors.
Les Ansley[4] PhD
Irisz Levai[5] MD
John Molphy[6] PhD
Paul Cullinan[2] PhD
John W. Dickinson[5] PhD
James H. Hull[2,3] FRCP, PhD

Word count: 527.

Note:

- Our original letter has been incorrectly cited as Hull et al. rather than Price et al.
- The prevalence estimates provide by Professor Mastronarde are incorrect:

  5. Parsons JP, Cosmar D, Phillips G, Kaeding C, Best TM, Mastronarde JG. Screening for exercise-induced bronchoconstriction in college athletes. J Asthma 2012 Mar; 49 (2):153-7.

References

1. Price OJ, Ansley L, Levai IK, Molphy J, Cullinan P, Dickinson JW, Hull JH. Eucapnic Voluntary Hyperpnea Testing in Asymptomatic Athletes. *American journal of respiratory and critical care medicine* 2016; 193: 1178-1180.

2. Price OJ, Ansley L, Bikov A, Hull JH. The role of impulse oscillometry in detecting airway dysfunction in athletes. *Journal of Asthma* 2015: 1-7.

3. Price OJ, Hull JH, Ansley L, Thomas M, Eyles C. Exercise-induced bronchoconstriction in athletes–A qualitative assessment of symptom perception. *Respiratory Medicine* 2016; 120: 36-43.

4. 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.

5. Mastronarde JG. Response to letter: Eucapnic Voluntary hyperpnea testing in asymptomatic athletes. *American journal of respiratory and critical care medicine* 2016.

6. Dickinson J, McConnell A, Whyte G. Diagnosis of exercise-induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. *British journal of sports medicine* 2011; 45: 1126-1131.