Title: **Is there a need to improve asthma diagnosis in young athletes?**

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Nature and extent of the problem

Since the late 1990's, many studies have highlighted that, compared to the general population, the prevalence of respiratory disorders is markedly increased in elite sport [1]. Notwithstanding other frequent respiratory ailments (e.g., exercise-induced laryngeal obstruction or dysfunctional breathing), asthma/airway hyper-responsiveness (AHR) is the most common chronic medical condition in elite athletes; the prevalence in Olympians being 8% [2]. Whilst the majority of data have been obtained in athletes aged 18 or over, it has been recognized that up to 50% of young elite athletes could suffer from asthma/AHR [3].

Athletes the most at risk for asthma/AHR are the ones competing in endurance and winter sports, and in swimming [2]. The AHR is thought to reflect injury to the epithelium of the lower airways, as a result of the need to condition large volumes of air repetitively during training [4]. Inhalation of cold air or of noxious airborne agents (allergens, pollutants or chlorination by-products) could contribute and/or amplify the damage, and add to the chronicity of the airway inflammation [4].

In the sporting field, AHR often expresses itself in the form of exercise-induced bronchoconstriction (EIB) – i.e., a transient narrowing of the airways that occurs during and/or shortly after strenuous exercise – [5]. As such, serial measurements of forced expiratory volume in 1 sec (FEV_1) – an index of airway caliber – are recommended for objective assessment of EIB [6]. The use of respiratory symptoms alone is strongly discouraged for diagnostic purpose, in that symptoms are neither sufficient, nor essential to confirm the presence of asthma/EIB in young athletes [3,7-9]. Further, resting spirometry measurements are poor predictors of variable airflow obstruction in athletes [10].

Reasons for the problem

Despite the scientific recognition of an increased risk for asthma/AHR in sub-groups of young elite athletes, little is currently done to allow early diagnosis, and to improve the level of respiratory care delivered to the athletes.

In the United Kingdom, athletes with suspected EIB (i.e., those experiencing respiratory symptoms during and/or shortly after exercise) will typically be assessed and treated in primary care. Yet, as demonstrated by Hull and colleagues [11], British family practitioners rarely employ the recommended (and most accurate) diagnostic tools for EIB (i.e., indirect bronchial provocation challenges with exercise or its surrogates [6]). Hence, it does not come as a surprise that almost half of professional English soccer players are misdiagnosed for asthma/EIB [12].

Similarly, in the United States of America, only those patients seen by pulmonologists are likely to have a bronchial provocation test and, when they do, it is likely to be methacholine [13]. Caution should be taken when interpreting methacholine tests in athletes; in winter sports, a positive result can reflect airway epithelial injury rather than asthma/EIB, whilst in summer sports, a negative result does not preclude the presence of EIB.

The common practice whereby only symptomatic athletes get referred for a respiratory check-up is flawed, in that those young athletes not reporting symptoms will never be seen by health professionals. It is however well recognized that a significant number of young asymptomatic athletes with no previous history or diagnosis of asthma/EIB have AHR [3,7,9]. As with untrained children, this pre-clinical form of AHR could be a precursor of asthma requiring treatment; hence the need for early detection. It remains unclear as to whether asymptomatic athletes i) fail to perceive a change in the caliber of their airways, ii) consider their symptoms as a

'normal' response to exercise, or iii) prefer to hide the presence of symptoms (probably in fear of being dropped from their team). Minimal difference in the perception of bronchoconstriction-related symptoms was recently observed between athletes and non-athletes (aged 14 to 35), but worse perception was noticed in the young and in males [14]. Since fatal asthma exacerbations during sporting activities mainly occur in male athletes aged 10 to 20 years [15], this further emphasizes the need for early and accurate diagnosis.

Recommendations

Many scientists have advocated the use of screening programs for asthma/AHR in elite sport. Yet, it is worth reflecting if such a preventive approach is warranted in young athletes. A sound screening program is characterized by the following: the condition causes a significant burden of suffering; a good screening test is available; the preventive intervention or treatment is effective, safe and economically viable.

Acknowledging the burden of suffering

While the number of deaths directly attributed to sport is fortunately low, the burden of the condition is substantial. In sports like swimming, 25 to 50% of young competitive athletes could suffer from asthma/AHR [3,7-9]. In soccer and basketball, the prevalence in 12-14 year old players has recently been estimated at ~20% [3]. However, not all sports are associated with increased risk for asthma/AHR [2]; hence, athletes at higher risk should be identified before implementing a screening program.

Asthma/AHR has potential to compromise performance of the high-performing athlete. Many athletes worry that their respiratory symptoms [16] or EIB [17] affects their performance. While there is limited evidence of a direct impact of asthma/AHR on sporting performance in athletes (young or older), data from habitually active asthma patients highlight that (steroid-based) anti-inflammatory treatment improves exercise pulmonary gas exchange and performance [18]. Over half of children with EIB have early onset of airway narrowing during exercise (so called 'breakthrough' EIB) [19]. It can therefore be speculated that the benefits of anti-inflammatory treatment on performance may be greater in the young compared to the older athletes (the latter typically developing bronchoconstriction *after* exercise).

Choosing the appropriate screening test(s)

A variety of bronchial provocation tests are available to help with the diagnosis of asthma/AHR in (young) athletes [5]; all being safe, well accepted, and relatively inexpensive. However, the airway response to bronchial challenge may vary with the stimulus used, the sport the athlete competes in, the age of the athlete, and the time of the year/sporting season when the test is conducted. Hence, there is no 'gold standard' and a simple 'one-test-fits-all' approach cannot be advised.

With a high ecological validity and a high specificity, exercise is an obvious first, and recommended choice [6] for investigation of young athletes with suspected EIB. However, if poorly standardized (e.g., if humidity of the inhaled air is not controlled), its sensitivity to detect EIB can be significantly reduced. Further, two separate tests are often necessary to exclude or diagnose EIB [20]. The highly standardized and sensitive eucapnic voluntary hyperpnoea (EVH) test has been recommended for over 15 years for EIB detection in elite (adult) athletes [21]. However, when conducted in

young athletes, the target ventilation of 85% of maximum voluntary ventilation may need adjustment [3]. Further, as for exercise testing, two EVH tests may be required [22]. Due to its high potency, EVH is not recommended in athletes with a history of severe clinical asthma; for those, the progressive osmotic challenge tests (i.e., 4.5% saline or dry powder mannitol) should be preferred. Because athletes inhale air that is completely dry during EVH, and the ventilation achieved during EVH can at times exceed ventilation attained in the field, some investigators have argued that EVH could give false positive results. To address this issue, in those asymptomatic athletes with no history of asthma/EIB but a mild response to EVH (i.e., 10-15% fall in FEV_1), complementary measures of exhaled nitric oxide may be recommended to ascertain the presence of airway inflammation.

Improving treatment

As for their adult peers [5], the pharmacological treatment of young elite athletes with documented asthma/AHR should follow the international recommendations on asthma management. However, due to the high heterogeneity in the airway response to beta2-agonists in children [23], not all young athletes may gain bronchoprotection from this class of drugs. Further, due to the high frequency of training (often daily), and to avoid possible side-effects of chronic use of inhaled beta2-agonists [23], daily preventive treatment with inhaled corticosteroids (ICS) should be considered even in those athletes with mild asthma/AHR. Whilst the effectiveness of ICS at controlling asthma and reducing AHR is well established, the potential for ICS to alter the natural course of asthma in young (and older) athletes remains to be established. Further, one difficulty when treating asymptomatic athletes is poor adherence. Education

(including up-to-date information on anti-doping regulations [24]) should therefore be at the cornerstone of asthma/AHR management in all athletes [5].

Conclusion

There is a need for better provision of respiratory care in young elite athletes; that service should come in the form of improved detection and better management. Thus, moving away from symptom-based diagnosis of asthma/EIB and incorporating objective testing *via* indirect bronchial provocation with exercise or its surrogates are warranted. To ensure success of new initiatives, the changes should be driven by policies; either through anti-doping programs, or mandatory, sport-specific screening programs. The implementation of more stringent regulations for inhaled beta2-agonists usage stands up as an exemplar for a successful (albeit no longer ongoing) anti-doping policy [25,26]. Importantly, new policies should be complemented by educational programs devised both, for young athletes and for their support staffs (including coaches, team doctors, physiotherapists, etc.). It is only when all stakeholders fully appraise the nature and extent of the problem that young athletes will finally get the level of respiratory care they deserve.

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