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Clinical

Asthma and exercise; a testing issue?

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There is an increasing prevalence of allergy and asthma in children in the European population, with most recent estimates in young people showing an atopy prevalence of 20% and an asthma prevalence of 8% (1). This increasing asthma prevalence has resulted in an increasing number of asthmatics entering the workforce, producing new challenges to industries which have traditionally excluded asthmatics from employment (2). It is not surprising then, that asthma continues to be a significant issue for the military in terms of recruitment and employability (3,4). With an increasing tempo of operations in austere and remote environments as well as the risks of barotrauma in physiologically extreme environments the military require a thorough, detailed and reliable testing system.

Asthma remains a clinical diagnosis; central to all definitions is the presence of symptoms (more than one of wheeze, breathlessness, chest tightness or cough) and of variable airflow obstruction demonstrated by either fluctuant peak expiratory flow rates or variation in forced expiratory volume in one second (FEV1). More recent descriptions of asthma in children and in adults have included airway hyper-responsiveness and airway inflammation as components of the disease, but how these features relate to each other, how they are best measured and how they contribute to the clinical manifestations of asthma, remains unclear (5).

Exercise related symptoms occur in up to 50% of asthmatic patients and are often the most incapacitating aspect of the disease in young people and the least responsive to conventional therapies (6). However, evaluation of exercise-induced asthma is not straightforward as exercise related respiratory symptoms are common in all adolescents (7). To complicate matters further, endurance athletes, particularly those habitually exercising in physically challenging environments, commonly report exercise related respiratory symptoms and have a high incidence of airway hyperresponsiveness (8). Thus, within the population of young adults with exercise-related respiratory symptoms, there may be multiple phenotypes of disease, differing in their pathophysiology and treatment response.

Against this background there are controversies in how to effectively diagnose and manage patients with exercise related symptoms. Straightforward pulmonary function testing in fit young people is not sufficient and exercise testing itself is expensive, time consuming and impractical in most settings. This has led to the substitution of specialised airway challenge tests in the diagnosis of exercise-induced bronchoconstriction, working either directly on the airway or indirectly via inflammatory mediators. Varying responses to these challenge tests by individuals with the same symptoms have made the diagnostic challenge even more complex (9).

There are few studies in the published literature that have tried to address this issue in military populations. It has been acknowledged as an issue for some time (10) but most historical studies have been retrospective or cross-sectional (11). In the only large prospective study, 799 recruits who had normal spirometry and normal exercise challenge results on entry to service were followed up for a 30 month period (12). Of concern is the high number (16%) of this cohort that had a documented deterioration in

respiratory health during the 30 month follow up period, with those attached to frontline combat units most affected. The authors did not explore how best to predict who this group may be and how best to screen them out at the point of selection, but they have served to highlight the magnitude of the problem.

With the paucity of real life information we need to extrapolate from other highly studied groups of active, fit young people. Performance level athletes have come under close scrutiny in recent years because of increasing use of asthma medication at elite level (12,13). This has led to the introduction of extensive testing and screening in these individuals with a wealth of generated research. Whilst there are concerns that the highly motivated athlete population, who probably under report their disease and which does not include those who quit (the healthy worker effect), may not be representative of a conscription defence force, they make a reasonable control population for a motivated, professional, voluntary armed service such as that of the UK.

In the general asthma population the consensus remains that the presence of exercise related symptoms reflects poor underlying control of airways inflammation (5). Traditionally this has been called exercise induced asthma (EIA). Usually other symptoms associated with asthma are present, there is objective evidence of eosinophilic inflammation and long-term use of inhaled corticosteroids results in improvement of all these features (14). Within the athlete population there is increasing evidence that symptoms are not good predictors of disease. Symptom responses on questionnaires provide a limited perspective and there is poor agreement between symptoms and objective measures of airway dysfunction (15). Exercise-induced bronchoconstriction (EIB) is often experienced in the absence of other symptoms, suggesting that the mechanisms and underlying pathophysiology may be different. Several lines of evidence support this view. Firstly, the airway inflammation in athletes has been shown to be less steroid responsive (16) and more heterogeneous than that seen in classic asthma (17,18). Secondly, within the population of athletes with exercise-induced bronchoconstriction there are marked differences in atopy between summer and winter athletes and between different sports (19) whereas EIA is closely associated with atopy. Finally, there may be a causal relationship between training intensity and environment (20) and increasing airway inflammation, airway remodelling and airway responsiveness in athletes whereas all the evidence suggest that increasing exercise and physical fitness has beneficial effects in subjects with EIA.

These controversies in diagnosis and disease pathophysiology led the International Olympic Committee Medical Committee (IOC-MC) to introduce the need for challenge testing before athletes could use asthma medications in elite level competition and this has provided some information on the usefulness of the various testing modalities. These different challenge tests have different measurement characteristics which we need to consider when interpreting the results. In particular it is useful to draw a distinction between tests such as inhaled methacholine and histamine, which act directly on airway smooth muscle and assess airways hyperreactivity only, and indirect challenge tests such as exercise, eucapnic voluntary hyperpnoea and mannitol, which involve an intermediary pathway such as mast cells or neuronal pathways and thus may provide a more complete assessment of the asthmatic process.

Methacholine bronchoprovocation test:
The methacholine bronchoprovocation test is usually carried out in a hospital clinical setting. Increasing doubling concentrations of drug are delivered either by the tidal breathing or dosimeter method and the concentration or dose that creates a 20% fall in FEV1 from baseline is expressed as the PC or PD20. The methacholine challenge test has been well validated as a direct challenge to the airways smooth muscle (21). Clinically it is the challenge test of choice in those patients with

an intermediate probability of asthma and normal or near normal spirometry (5). Of all the tests available in this setting it has the best validity, with a sensitivity of greater than 90%, which means that a negative test effectively excludes asthma in a symptomatic patient (22). This test has fallen out of favour as a screening test in athletes due to the large number of false positives in young people (23), but it remains a very useful clinical test because of its high negative predictive value.

Exercise and sports specific exercise testing: Laboratory exercise testing has been well established as an indirect challenge test and has the benefits (and drawbacks) of assessing the individual during the activity in which they complain of symptoms. There needs to be environmental control of both air temperature and relative humidity to standardise results and monitoring of continuous heart rate to determine an appropriate challenge. The test should challenge the athlete to greater than 85% maximum heart rate for a period no longer than 6-8 minutes as longer testing may miss mild bronchoconstriction. A warm up should be avoided to prevent the induction of refractoriness. Traditionally these use either a treadmill or cycle ergometer and assess whole body exercise. However, in fit individuals standard exercise challenge has a low sensitivity for detecting airways dysfunction (24) and in unfit individuals they are often limited by cardiovascular fitness rather than respiratory symptoms. In addition the laboratory environment is not as austere as the environment in which they may be forced to perform (25).

The enhancement of exercise testing with the addition of cold dry air has been felt to improve the sensitivity of this testing modality. In a study carried out on military recruits the numbers testing positive were roughly similar whether the ambient room air or cold dry air was used to supplement the challenge test. Subjects had a more pronounced bronchoconstriction to cold air suggesting that the addition of cold dry air enhances the testing procedure. However, on closer analysis only 12 subjects tested positive to both tests suggesting that the addition of cold dry air has defined a different population (12,26). It is because of these concerns that alternative testing modalities have been developed.

Eucapnic Voluntary Hyperventilation (EVH) The EVH test was developed to imitate the effects of ventilation at high flow rates on the airway surface liquid, creating a drying and osmotic effect (27). It relies on the individual being able to attain and maintain a ventilatory flow equivalent to 85% of maximum voluntary ventilation (approximately 30 x FEV1) for 6-8 minutes breathing a gas mixture containing 5% carbon dioxide to maintain eucapnia. It is a laboratory based test that creates an 'all or nothing' response making it useful in those with normal or supranormal spirometry but questionable in those with abnormal resting spirometry. The diagnostic criteria used by the IOC-MC (ie a 10% drop in FEV1 post challenge) make it a very sensitive test for the diagnosis of airways dysfunction in athletes (28). This has led to the adoption of the EVH test as the 'gold standard' test by the IOC-MC and it has been used as a screening test at elite level in some countries (29). One concern is that the criteria for a positive test have been set too low, meaning that relatively few subjects identified have genuine steroid responsive airway pathology (30).

Mannitol
Mannitol is a dry powder inhalation test that acts by developing an osmotic gradient across the airway epithelium, thereby triggering bronchoconstriction by a mechanism similar to that responsible for EIB (9). In a recent large multi-centre study it was found to be as sensitive and specific as a methacholine inhalation test for the diagnosis of EIB determined on laboratory exercise testing (31). It comes as a standardized test kit, which contains pre-filled mannitol capsules in escalating doses and a hand-held dry powder inhaler device. It can be used safely in most clinical settings and may be useful in the pre-hospital environment. It has been widely used in the diagnosis of EIB and has helped to determine some of the underlying

mechanisms involved, most notably the involvement of mast cells (32,33).

More information is required before we can conclude that these tests are a suitable surrogate for investigating the heterogeneity of exercise-induced airway symptoms. In particular, we know nothing about whether these tests identify patients with clinically important airway pathology, who are going to respond well to corticosteroid treatment. Variable responses to the different tests creates issues, as each defines a different albeit overlapping population and so the choice of test is important and must be pre-determined.

Over recent years there have been significant improvements in the phenotyping of asthma in the clinical population. This approach has aimed to determine the differing levels of airways dysfunction and airways inflammation that are present in an individual presenting with airways disease and to tailor appropriate therapies to treat this effectively. Central to this approach has been the use of 'inflammometry' in the assessment of airways inflammation to phenotype disease in to eosinophilic or non-eosinophilic disease. This is important because we know that the presence of eosinophilic airway inflammation is more closely predictive of a response to corticosteroid therapy than any other marker of disease (34,35) and that there is only a weak correlation between the presence of eosinophilic airway inflammation and either the pattern or severity of airway dysfunction (36). We also know that exhaled nitric oxide is a good predictor of underlying eosinophilic airways disease (37) and this gives us a very practical non-invasive means to assess airway inflammation. The potential to use these techniques for the phenotyping of asthma in fit, active young people has not been investigated to any degree. The usefulness of these tools in screening an asthmatic population has recently been demonstrated (38).

Within the military there are several scenarios where an objective diagnosis of asthma is helpful. At the initial selection phase for training we require a robust means of determining the likelihood that any given recruit has underlying airways disease, how that will affect them in training and whether they are likely to develop airways disease during service life. At present this is done using a symptoms based screening system which may not be ideal and consideration should be given to using a testing system that explores the disease phenotypes. There also needs to be an agreement on testing standard, particularly which challenge test is used. At entry level a primary care based assessment using a safe means to determine airways dysfunction and inflammation would be ideal and the combination of mannitol as a challenge test and exhaled nitric oxide as a marker of eosinophilic airways inflammation would seem promising and is in use in some defence forces around the world (39,40).

Another scenario where testing becomes an issue is at the selection level for specialised training in areas where subjects are exposed to presurised environments, such as divers, submariners and fixed wing pilots. In these individuals there is a safety issue with the risk that bronchoconstriction can lead to problems during pressure changes that may lead to pulmonary barotrauma or in worst case scenarios to cerebral air gas embolisation. How the array of substitute tests relates to real life scenarios for these individuals remains to be clearly defined. However, it would seem sensible to instigate a testing process whereby a generic standard is introduced. The concern here is that the sensitivity and specificity of the test is all important and whilst a highly sensitive test such as EVH would be helpful to determine risk it may lead to a significant level of false positive results which may exclude individuals from shortage branch specialities.

Finally, the testing regime that would best predict the development of asthma or worsening of respiratory health during service life remains to be fully determined. To define this will require a large, detailed prospective study of newly recruited service personnel who have undergone a detailed screening system on entry and who are then followed up for an appropriate time period. Central to this would be the ability to exclude individuals at certain time points throughout service life

should they fail to meet the minimum medical requirements for respiratory health. By clearly defining what these are on entry this should allow for an easy means to assess, treat and if needs be medically discharge patients with asthma by clearly defined, objective criteria.

Conclusions

Exercise related respiratory symptoms are common in young people. Within this group, symptoms are not good predictors of underlying disordered function or pathology and testing for asthma in this group of individuals is complicated by variable responses to the numerous tests available. It is essential for the military to have a robust entry level testing system and this may require the introduction of asthma screening in recruits by objective challenge tests. There needs to be an agreed entry standard both at basic level and also at selection for more specialised employment, but these testing regimes need not be identical and this may involve a different testing regime to answer these very different questions.

Central to this debate will be the redefinition of what level of disease and more importantly disease control is acceptable within the general service population and at what stage airways pathology either excludes service or leads to a re-assessment of employability. Current criteria would exclude a large proportion of elite performance athletes from military service despite these individuals exhibiting some of the highest cardiovascular fitness levels in the population.

Finally we need a large, prospective cohort study of entry level recruits to determine the risk factors that predict the development of asthma during service life. This, over time, will allow the entry standard to be adjusted accordingly so that questions of employability and deployability are dependant on robust, population specific, peer reviewed data.

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