Asthma: An Untoward Consequence of Endurance Sports?

Endurance sports are an excellent means to promote overall health and well-being. However, practicing endurance sports at a competitive level requires a substantial increase in daily ventilation. Although a sedentary individual breathes ~11,000 L of air per day, this amount often triples in endurance athletes. Depending on the training environment, the inhaled load of irritants, pollutants, and allergens can increase significantly. Thus, an untoward consequence of endurance sports participation is an increased risk of developing or aggravating preexisting lung disorders such as asthma that are triggered by offending air contaminants.

It might be useful to distinguish between asthma among athletes and exercise-induced bronchoconstriction (EIB), which is defined as an airflow obstruction after an exercise challenge (1). EIB is extremely prevalent among athletes, ranging from 30% to 70%, depending on the sport, and can be associated (or not) with respiratory symptoms (2). Thus, many athletes with EIB are not considered to have asthma, although some believe that it may be a milder or earlier form of asthma.

The pathogenic mechanisms of EIB were recently reviewed (3, 4). The prevailing theory implicates the high ventilatory demand of endurance sports, which either inflicts a shear stress that causes subtle damages to the airway epithelium or provokes airway dehydration. These then prompt the release of inflammatory and contractile mediators from immune cells, leading to airway edema and an increased activation of airway smooth muscle. Bronchoconstriction and respiratory distress are usually manifested only after exercise, because the attenuating effect of airway wall strain (imparted by breathing large V_T during exercise) on the contraction of airway smooth muscle quickly vanishes after exercise (5). Obviously, genetic susceptibility or other predisposing factors are probably required, because not all athletes have EIB. Perhaps the repeated insults caused by repetitive bouts of exercise lead to the development of typical features of asthma in some individuals, such as thickening of the airway wall. This would, in turn, increase the propensity for developing ventilation defects upon bronchoconstriction after exercise and thereby severely amplify dyspnea (5). If this is the case, then thickening of the airway wall would need to be chronic but not necessarily permanent, because EIB often recedes during the off-season or once the athlete retires (6).

Progress in the field of EIB and asthma among athletes has been seriously hampered by the lack of animal models. To recapitulate the typical training of a competitive athlete, a proper animal model should develop progressive changes over the course of repeated bouts of exposure to a relevant stimulus. In this issue of the *Journal*, Ueno and colleagues (pp. 57–66) present a murine model of exercise-induced asthma that genuinely re-creates the physiological anomalies and some of the features of airway remodeling that are commonly seen in athletes with asthma (7).

Specifically, Ueno and coworkers subjected female BALB/c mice to 45 minutes of running five times per week for periods varying from 1 to 5 weeks. They demonstrate that periods exceeding 3 weeks led to airway hyperresponsiveness (AHR), airway smooth muscle enlargement, and submucosal fibrosis without causing cellular inflammation. They also show an increased expression of cysteinyl-leukotrienes (cys-LTs) in the whole-lung lavage, together with an increased expression of phospholipase A_2 (PLA_2) and leukotriene C_4 synthase in the airway epithelium. Concordantly, treating mice with montelukast or with a PLA_2 inhibitor during the last 2 weeks of a 5-week period of running reduced all these features.

The biological significance of this new model of exercise-induced asthma in the understanding of asthma among athletes is supported by previous studies showing increased expression of PLA_2, predominantly in epithelial cells, and cys-LTs in induced sputum of patients with EIB after an exercise challenge (8, 9). In fact, leukotriene receptor antagonists are now strongly recommended by the American Thoracic Society for the treatment of EIB because of their proven efficacy (1). This suggests that this new murine model mimics some features of asthma among athletes, and the model also shows that the underlying mechanisms through which they occur may be similar.

The study of Ueno and coworkers also comes at a time when it has been demonstrated that exercise protects against the development of several features of asthma, as well as reverses established features of asthma, in classical murine models of allergic airway inflammation (10–16). This has been shown in various strains, both sexes, and different ages of mice using different allergens and different exercise forms, including running and swimming, as well as for highly variable training regimens in terms of duration, frequency, and exercise intensity and in terms of timing and length of the period over which they were performed (10–16). These animal studies are also consistent with human studies showing the salutary effects of physical exercise on asthma symptoms, quality of life, exercise capacity, lung function, and AHR (17, 18). Together, they seem to contradict the findings of Ueno and coworkers. Perhaps a prolonged period of running leads to features that are reminiscent of asthma in naive (nonasthmatic) mice in a genetically susceptible background, but maybe regular exercise still exerts an overall desirable effect in the context of asthma. More studies are clearly needed to sort this out.

In conclusion, the fact that mice subjected to repeated bouts of running develop pathognomonic features of asthma may lead to the impression that participation in endurance sports is detrimental. However, it is important to emphasize that the benefits of engaging

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in endurance sports undoubtedly outweigh the potential risk of developing or aggravating asthma. The world's experts in EIB and in asthma among athletes strongly encourage the practice of endurance sports for people with or without asthma, including nonathletes (2). Yet, an increased risk of developing or aggravating asthma is one possible adverse consequence of endurance sports that absolutely needs to be addressed. The murine model developed by Ueno and coworkers may help us explore the molecular mechanisms underlying AHR and airway remodeling caused by endurance sports and may expedite the testing of pharmacological or interventional means to prevent and/or reverse these features. It may also turn out to be a useful model to study the effects of some remodeling features on respiratory mechanics in the absence of cellular inflammation. Therefore, the work they present is relevant not only for athletes with asthma but also for all individuals with respiratory disorders exhibiting AHR and airway remodeling. ■

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