EDITOR'S CHOICE

Airway injury during high-level exercise

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ABSTRACT
Airway epithelial cells act as a physical barrier against environmental toxins and injury, and modulate inflammation and the immune response. As such, maintenance of their integrity is critical. Evidence is accumulating to suggest that exercise can cause injury to the airway epithelium. This seems the case particularly for competitive athletes performing high-level exercise, or when exercise takes place in extreme environmental conditions such as in cold dry air or in polluted air. Dehydration of the small airways and increased forces exerted on to the airway surface during severe hyperpnoea are thought to be key factors in determining the occurrence of injury of the airway epithelium. The injury-repair process of the airway epithelium may contribute to the development of the bronchial hyper-responsiveness that is documented in many elite athletes.

INTRODUCTION
The prevalence of asthma, bronchial hyper-responsiveness (BHR) and exercise-induced bronchoconstriction (EIB) is markedly increased in elite athletes.[1] The influence of water and heat loss in causing the transient bronchoconstriction that occurs shortly after strenuous exercise is now widely accepted.[2] The mechanism responsible for EIB or BHR development over time in elite athletes, however, remains unknown. In 2005, we proposed that repeated injury to the airway epithelium is important to the pathogenesis of respiratory dysfunction in elite athletes.[3] Experimental work has since confirmed that injury-repair of the epithelium occurs during episodes of severe hyperpnoea. The environment has also proven important to the development of postexercise airway injury.

There are several reasons why the airway epithelial cells may get damaged during high-intensity exercise. First, severe hyperpnoea leads to changes in viscosity, tonicity and volume of the airway surface liquid (ASL). Second, the high force generated on the airway epithelial surface during exercise causes shear stress and increases transepithelial pressure gradients. As a consequence, disruption of the epithelial cell layer may occur and an injury-repair response may follow. Plasma exudation, induced by repeated injury and repair process, may change contractile properties of the airway smooth muscle making it hyper-responsive in susceptible athletes.

EVIDENCE OF EXERCISE-INDUCED AIRWAY EPITHELIAL INJURY
Exercise-induced airway epithelial injury was first documented in animal models, but recent studies have confirmed that injury also occurs in exercising human. Exercise intensity and environmental factors have been identified as modulators of loss of airway epithelial barrier integrity during exercise.

Animal models
In the 1990s, Freed and collaborators developed a canine model of hyperpnoea-induced airways obstruction. In this model, insufflation of dry air for 5 min at 2000 ml/min into the peripheral airways of dogs caused a 50% loss of ciliated epithelium.[4] By contrast, hyperpnoea with humid air or hyperpnoea at lower flow (1000 ml/min) was associated with little mucosal injury.[5] Even though mucosal damage may be exaggerated in this model because of the unidirectional airflow, it has since been confirmed that exercise can cause epithelial injury. For example, in thorough bred horses, after a single bout of strenuous exercise in cold conditions, more ciliated epithelial cells were found in the bronchoalveolar lavage of exercising compared with non-exercising horses.[6] In elite sled dogs, abnormal accumulation of intralumenal debris was noticed following a 1100 km endurance race in a cold environment.[7] In mice, a progressive decrease in the number of ciliated cells, together with evidence of active repair was observed following 6 weeks of endurance training.[8]

While some animal studies support the idea of hyperpnoea-induced airway epithelial injury, not all exercise is harmful to the airways. Animal studies based on interventions that mimic training programmes for non-athletes have so far shown no signs of the airway injury-repair process.[9][10] This suggests that intensity, frequency of exercise or both are important determinants for the development of airway epithelial injury, with only the most strenuous/frequent exercise regimens causing damage to the airways.

Human-based studies
Signs of the injury-repair process of the airway epithelium were initially shown in elite athletes under baseline conditions. Young competitive cross-country skiers without a diagnosis of asthma, but 75% with BHR to methacholine, had increased deposition of tenascin, an extracellular matrix protein, in endobronchial biopsy specimens (figure 1 and see commentary on the BJSM blog, http://www.blogs.bmj.com/bjsm).[11] Repeated prolonged exposure of the airways to inadequately condition air may therefore be responsible for the early changes of airway remodelling. Moreover, the increased airway epithelial cell count in sputum of elite swimmers (69% with BHR to methacholine)[12] confirms that airway injury can occur across sports.
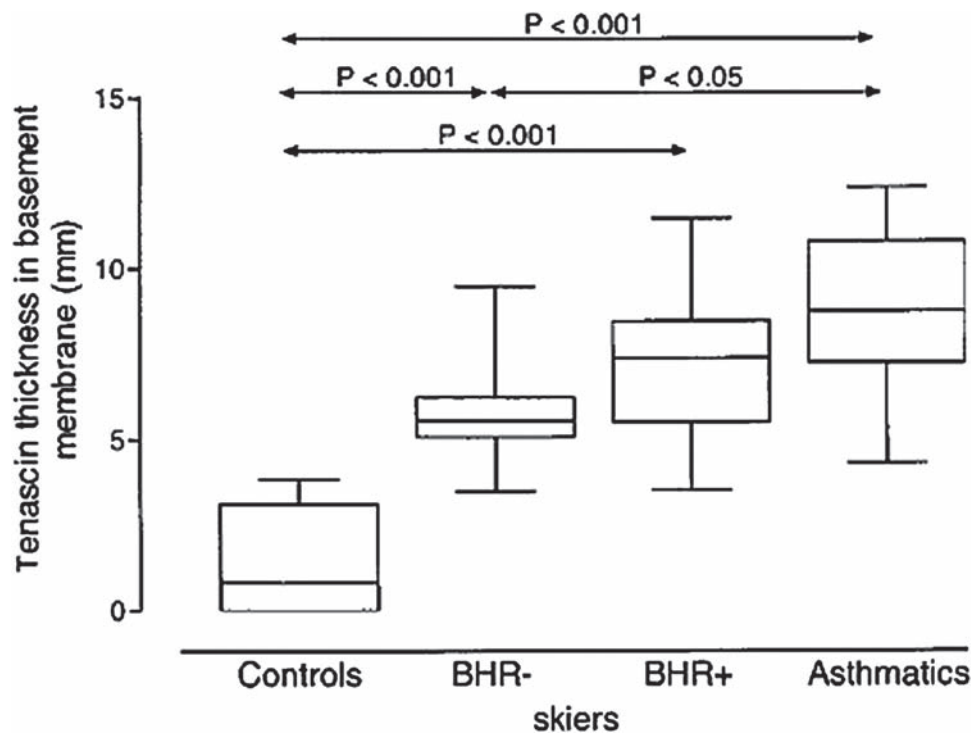
Figure 1 Thickness of tenascin immunoreactive band in subepithelial basement membrane zone in controls, skiers with and without BHR and subjects with asthma. Horizontal bar=median value. Reproduced with permission from Karjalainen *et al.*[11]

Signs of injury-repair of the airway epithelium have also been identified following acute bouts of high-level exercise. Increase in sputum bronchial epithelial cells, apoptotic cells and pro-inflammatory cytokine interleukin 8 (IL-8) were found post half-marathon in male amateur runners who are non-asthmatic.[13] These changes were accompanied by an increase in serum levels of the clara cell protein (CC16) (figure 2), a marker of increased permeability of the peripheral airways.[14] Further results obtained from sputum in recreational athletes who are non-asthmatic support the concept that mild injury occurs after 10 km to 21 km runs[15] and following supramaximal rowing exercise.[16]

Measuring urinary levels of CC16, we recently demonstrated that environmental conditions impact on the degree of airway epithelial disruption during high-level exercise.[17] In male recreational athletes (38% with EIB), an 8 min running test performed in cold dry air caused an increase in urinary CC16. When warm humid air was inhaled, this rise in CC16 was blunted. Similar findings were made following 8 min of voluntary hyperpnoea with dry air[18] supporting that it is the hyperpnoea of dry air rather than exercise per se that causes the airway epithelial injury.

Some studies, however, have failed to show signs of airway epithelial injury following strenuous exercise. This was the case in non-asthmatic recreational athletes who performed a marathon[19] or long-distance swimming trials.[20] Aerobic training in patients with moderate-to-severe asthma was associated with a reduction in inflammatory markers and exacerbations, and an increase in symptom-free days.[21] It is not clear if these inconsistencies are due to methodological issues or to the fact that airway epithelial injury may only occur under specific conditions or in individuals with a particular genetic makeup. Adoption of a particular breathing pattern, the exposure to extreme or polluted environments, or both may explain intersports differences in the occurrence of airway epithelial injury, while mechanical constraints on exercise hyperpnoea,[22] specific genotype-environment interactions[23] or both may explain interindividual differences.

The presence of pollutants, irritants or both in the inhaled air has formerly been identified as a confounding factor in the occurrence of exercise-induced airway epithelial injury. An increase in serum CC16 was observed following moderate exercise in healthy adult cyclists during episodes of photochemical smog[24] and in healthy adults exposed to 0.2 parts per million of ozone in controlled laboratory conditions.[25] Further, the degree of leakage of CC16 across the airway epithelial barrier into the bloodstream during exercise was directly linked to the concentration of ozone in the atmosphere.[24] However, the finding that ozone exposure affects serum CC16 concentrations was not confirmed in exercising children who are non-asthmatic.[26] The possibility of a synergistic effect of ozone and heat stress on the integrity of the airway epithelial barrier during exercise has recently been suggested.[27]

Chlorine used to disinfect swimming pools has been incriminated in the development or exacerbation of allergic and respiratory diseases in children,[28] elite swimmers[29] and indoor swimming pool workers.[30] Nitrogen trichloride (NCl_3), the common byproduct of chlorination, is a well-known irritant that causes acute disruption of the lung epithelial barrier in animals.[31] In young children, subtle changes in a number of markers of airway hyper-permeability were found after swimming in a chlorinated environment.[31] In older children[32] and in adult swimmers,[31] more obvious changes in airway permeability were observed. Those changes seemed mainly dependent upon the intensity of the exercise and the concentration of NCl_3 in the pool atmosphere.[33]

In summary, exercise has the potential to disturb the airway epithelium. The occurrence and extent of injury, however,
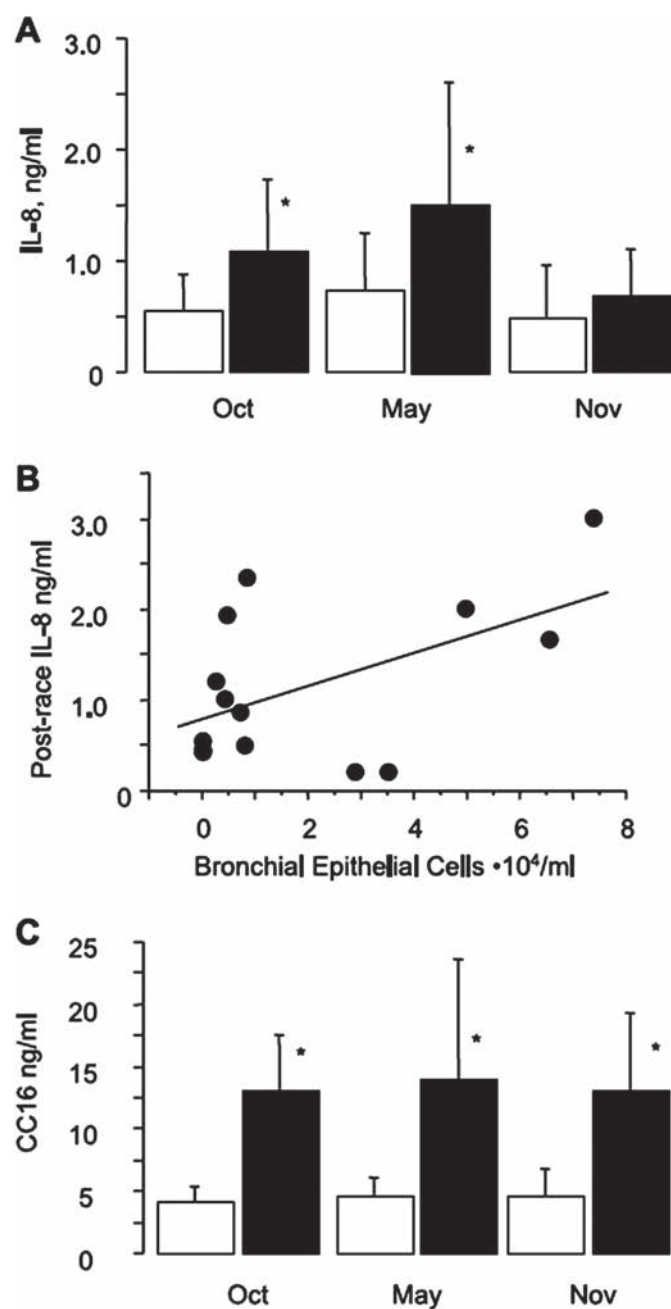
Figure 2 Inflammatory mediators in induced sputum and serum samples obtained from amateur runners who are non-asthmatic before and after the half-marathon races. (A) IL-8 concentrations significantly increased postrace (*p<0.01). (B) IL-8 was positively correlated with bronchial epithelial cell absolute counts post-race. (C) Serum CC16 concentration significantly increased after each race (*p<0.01). Reproduced with permission from Chimenti et al.[13]

seem mainly dependent upon the level of hyperpnoea and on environmental factors.

MECHANISMS OF AIRWAY INJURY

The potential for detrimental effects of various air pollutants and irritants on airway function in athletes is discussed in detail in other sections of this issue (see articles by K Rundell, V Bougault and LP Boulet and M Sue-Chu). For this reason, we will discuss the mechanism by which hyperpnoea alone may cause injury to the airway epithelium.

Hyperpnoea-induced dehydration stress

As a result of inhalation of large volumes of unconditioned air, respiratory water and heat losses occur during exercise.[34] Ventilation of only 60 l/min (far below the 200 l/min that can be reached by elite athletes) has shown in models to require at least 12 generations of airways to heat and humidify temperate air (26.7°C and 8.8 mg l^{-1}) to body conditions.[34] As the volume of ASL in the first 10 generations of airways is limited (<1 ml), the increased rate of evaporative water loss from airway surfaces during exercise is thought to lead to a dehydration of the airway surface volume and a rise in ASL osmolality.[2 35] Evidence of change in the osmolality of the ASL has been obtained in dogs following dry air challenge of the peripheral airways,[36] although not in humans.[37] In asthmatic and healthy subjects, a reduction of mucociliary clearance occurred during hyperpnoea of dry air,[38] a finding consistent with a reduction in ASL volume. The transient reduction in volume/depth of ASL in conditions of high air-flows may be responsible for detachment or sloughing of the epithelium, subepithelial vascular congestion oedema and cellular infiltration, as demonstrated in animals[4 39] and in humans.[40]

Hyperpnoea-induced mechanical stress

During tidal breathing, the epithelium is exposed to complex physical forces, including airflow-induced shear stress and transepithelial pressure gradients. When ventilation increases, when the airways narrow or both happen, those physical forces increase. While transmural pressure gradient is ~8.5 cm H_2O during normal tidal breathing, during forced expiration (such as during exercise) transmural pressure gradients generated within the airways can approach ~20 cm H_2O in the proximal airways.[41] In an in vitro model of airway reopening, high pressure gradients and fluid shear stress have been shown to cause injury to the epithelial cells.[42] During high-intensity exercise, it is therefore likely that elevated airflow-related shear stress and increased transmural pressure gradients contribute to disruption of the epithelial cell layer.

We cannot discount that the repeated stretch or compression of the airway epithelial cells during severe hyperpnoea modulates epithelial cell function. In vitro cyclic stretch has been shown to induce the release of IL-8 by human bronchial epithelial cells.[43] IL-8 is the major chemo-attractant for neutrophils in humans. Furthermore, compressive mechanical stress of airway epithelial cells in culture has been shown to lead to the expression of various mechanoreceptive genes. For example, plasminogen activator genes[44] and epidermal growth factor receptor ligands[45] could contribute to the airway remodelling observed in elite winter athletes.[11]

CONSEQUENCES OF AIRWAY INJURY

Disruption and shedding of the airway epithelial lining cells are rapidly followed by repair. The rapid tissue repair is critical to re-establish the integrity of the damaged barrier. An important potential consequence of the epithelial injury is the release of plasma-derived biological-active molecules, such as cytokines and growth factors.

Short-term effects

One immediate effect of injury to the epithelium is the loss of integrity of the physical barrier. As a consequence, the potential for penetration by pathogens (such as bacteria and
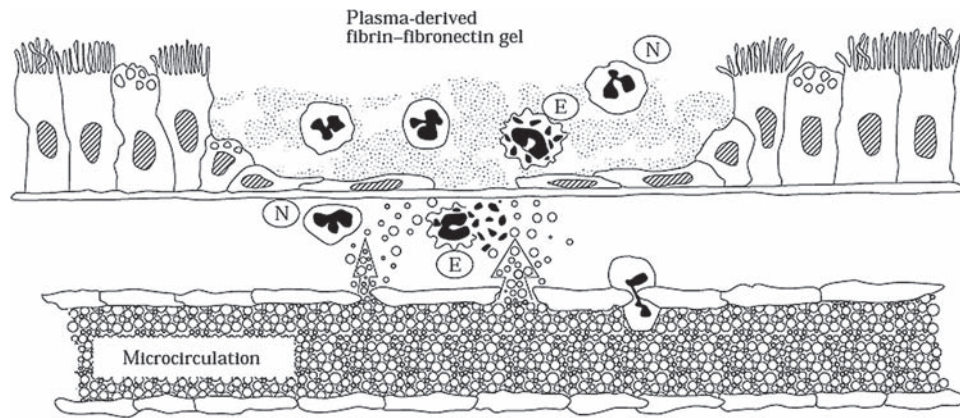
Figure 3 A diagram indicating that after denudation, epithelial restitution occurs speedily under the provisional cover of plasma-derived and leucocyte-rich gel. N, neutrophils; E, oeosinophils. Reproduced with permission from Persson *et al*.[57]

viruses) and pollutants/irritants (including ozone, allergens and chlorine byproducts) is increased. Various reports suggest an increased risk for upper respiratory tract infections in athletes following competitive long-distance events.[46]

In order to fight off infections efficiently, the epithelium requires the assistance of neutrophils. The fact that neutrophil count is increased in sputum samples of elite athletes, at rest[11] [19 47] and following a single bout of heavy exercise.[19] The neutrophil count tended to increase in the morning after 10 km to 21 km races in non-asthmatic male amateur runners,[15] while remaining low shortly after completion of 21 km races[13] suggests that the neutrophilic airway infiltration may be a secondary event. It is likely that osmotic and thermal stress induced by exercise hyperpnoea cause the release of IL-8,[48 49] which then leads to a delayed infiltration of neutrophils into the airways.

Another potential immediate effect of injury to the airway epithelium is a reduction of the release of the bronchoprotective prostaglandin (PG) E_2 by the epithelial cells, as observed in patients with asthma having EIB.[40 50] PGE_2 is known to inhibit mast cell activation and to induce relaxation of the airway smooth muscle,[51] so that a reduction of its release could contribute to the development of postexercise airway narrowing.

Disruption of the airway epithelium could also impact on mucociliary clearance. In patients with asthma having EIB, an increase in the gene expression and release of the secreted or gel-forming mucin 5AC (MUC5AC) was observed after exercise.[52] This mechanism may favour exercise-induced mucus production, as often reported by elite athletes.[53]

Repair of denuded airway epithelial areas occurs very quickly and involves basal cells and Clara cells. These cells have stem-cell-like properties and are capable of self-renewal and proliferation in the affected area.[54] In guinea pigs in the first few minutes after denudation of the airway epithelium, ciliated and secretory epithelial cells at the wound border dedifferentiate, flatten and migrate rapidly over the denuded area to create a new cellular cover.[54] This rapid and efficient restitution process is thought to limit serious damage to the exposed mucosa and seems comparable with the healing process by 'primary intention' that occurs in patients with asthma.[55]

The exercise-induced epithelial injury is a transient event that is supported by in vivo data. In dogs, restitution of the epithelial cell barrier of the bronchial mucosa occurred within 6 to 24 h of a dry air challenge.[4] Further, in male amateur athletes who completed 10 km to 21 km running races, the IL-8 sputum concentrations had returned to baseline 20 h later.[15] Finally, in female amateur athletes, urinary CC16 normalised

within 90 min of completion of an 8 min hyperpnoea challenge with dry air.[18]

Long-term effects
Even though the injured airway epithelial cells are likely to recover rapidly, an important potential consequence of the epithelial injury is the activation of inflammatory mechanisms in the recovering injured or surrounding uninjured cells.[56] The epithelial injury-repair process is associated with many tissue responses, including hypersecretion, plasma exudation, recruitment and activation of leucocytes, and increased proliferation of fibroblasts and smooth muscle cells.[57]

Within minutes after injury, endothelial gaps form which leads to extravasation, lamina propria flooding and entry of bulk plasma into the luminal space (figure 3).[57] This event plays an important role in the immediate defence of the airways and the repair processes by removing cell debris, providing a transient supply of locally acting growth factors and cytokines, and acting as a diluent. However, in elite athletes who train daily, a possible drawback of the repeated release of these molecules in the subepithelial environment is a change of the contractile properties of the airway smooth muscle with, long-term, an increased risk for BHR.[3] Elite cross-country skiers[11 58] and swimmers[29] have a high frequency of BHR to pharmacological agents. In athletes exposed to high concentrations of aeroallergens, the extravasation of bulk plasma may also create an in vivo model of 'passive sensitisation' and favour the development of allergy and EIB.[59] In elite runners, a strong association exists between EIB and allergy.[60 61]

Because seasonal variability of EIB and BHR has been demonstrated in elite athletes,[60 62] it is likely that some aspects of the airway dysfunction are only transient. When swimmers are away from chlorinated pools, the BHR usually resolves.[62 63] Whether the structural changes observed in relatively young cross-country skiers[11] are a more permanent feature is unknown.

In conclusion, severe exercise hyperpnoea either by itself, or in combination with environmental stimuli, is a primary contributor to epithelial stress injury in competitive athletes. Implementation of new prevention strategies should be encouraged in elite sports in order to mitigate the potentially harmful effect of severe hyperpnoea on the airway epithelium.

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