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Effects of Exercise on the Airways

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1. Introduction

In the last ten years, the effects of exercise on bronchial epithelial cells and inflammatory cells in the airways have been studied in detail, and such new information has been combined with previous knowledge on bronchial reactivity and asthma evoked by exercise in asthmatic patients and athletes. The resulting picture is very complex, and the potential clinical consequences are often contradictory, suggesting the opportunity to define different phenotypes of exercise-associated airway changes (Lee & Anderson, 1985; Haahtela et al., 2008; Moreira et al., 2011a).

Studies in asthmatic athletes in the 90' had began to explore the possibility that airway inflammation might be involved in exercise-associated respiratory symptoms. However, studies in non-asthmatic athletes also found increased number of inflammatory cells not only at rest, but also after strenuous endurance exercise (Bonsignore et al., 2001). It was therefore hypothesized that endurance exercise may physiologically cause influx of inflammatory cells into the airways, associated with low or absent inflammatory activation (Bonsignore et al., 2003a). Subsequent studies in athletes and animal models have extended these finding, but the mechanisms of inflammatory cell recruitment into the airways and the tight control of inflammatory activation physiologically associated with exercise remain poorly understood.

Exercise is a known cause of bronchoconstriction in asthmatic patients (Cabral et al., 1999) and athletes (Parsons & Mastronarde, 2005). A large number of asthmatic elite athletes participate to international top-level competitions, and guidelines regarding management of asthmatic athletes (Fitch et al., 2008) and rules on the use of anti-asthmatic drugs have been issued (World Anti-Doping Agency, WADA, Oct. 18 2010 report). However, exercise is a powerful physiologic stimulus for bronchodilatation, and some reports underlined that exercise training may actually downmodulate bronchial reactivity in normal subjects (Scichilone et al., 2005, 2010), asthmatic children (Bonsignore et al., 2008) and animal models of asthma (Hewitt et al., 2010).

This chapter will summarize the changes induced by acute exercise and training in bronchial reactivity and airway cells in both humans and animal models. It will also discuss the changing paradigm regarding the impact of physical activity in patients with bronchial asthma, and the new perspectives of exercise-based rehabilitation in patients with respiratory diseases such as chronic obstructive pulmonary disease (COPD).

2. Exercise-induced bronchoconstriction

In patients with bronchial asthma, occurrence of bronchoconstriction and symptoms after exercise is common and has been known for a long time (Lee & Anderson, 1985; Cabral et al., 1999). Exercise-induced bronchoconstriction (EIB) is characterized by respiratory symptoms, such as wheezing and chest tightness, secondary to an acute, transient airway narrowing that typically occurs in the first 15-20 min after cessation of exercise. In some instances, a late-phase response also occurs 3 to 13 h after completing exercise (Freed, 1995; Speelberg et al., 1989). In asthmatic patients, exercise-induced symptoms are considered as clinically important indicators of insufficient asthma control, and suggest the opportunity to increase or change the medication regimen.

In the laboratory, EIB is defined as a decrease in forced expiratory volume of 1s (FEV_1) ≥ 10% from the baseline value after appropriate exercise provocation (Kyle et al., 1992). Exercise is the most common trigger of bronchospasm in those who are known to be asthmatic, and 50% to 90% of asthmatic individuals have airways that are hyperreactive to exercise (Rundell et al., 2002).

EIB also occurs in up to 10% of subjects who are not known to be atopic or asthmatic (Gotshall et al., 2002). Prevalence of EIB or exercise-induced symptoms in elite athletes is high (Parsons & Mastronarde, 2005; Turcotte et al., 2003), and asthma in athletes may develop according to different phenotypes, likely influenced by environmental exposures during exercise (Haahtela et al., 2008). Prevalence of asthma is high in athletes of winter sports and endurance sports such as swimming or running (Helenius & Haahtela, 2000; Karjalainen et al., 2000; Lumme et al., 2003; Langdeau et al., 2004; Durand et al., 2005; Vergès et al., 2005, Lund et al., 2009), even in subjects who do not report symptoms during childhood, atopy or a family history of asthma (Langdeau et al., 2004). On the other hand, exercise-induced symptoms are poor predictors of EIB (Parsons, 2009) since they are variably associated with objectively documented bronchial hyperreactivity to exercise (Sue-Chu et al., 1996; Rundell et al., 2001; Langdeau et al., 2000, 2004; Bougault et al., 2010). Finally, a gender effect has been recently underlined, with female athletes reporting more exercise-associated symptoms and showing a higher prevalence of bronchial hyperreactivity at rest compared to male athletes (Langdeau et al., 2009). Unfortunately, data on prevalence of EIB according to gender are not available, and more studies are necessary to ascertain whether exercise-associated bronchoconstriction is more common in women than in men, and the mechanism(s) responsible for such an effect.

2.1 Pathophysiology of EIB: Main theories

While bronchial asthma is known to be associated with a complex inflammatory picture at the airway level usually triggered by exposure to allergens or exercise, EIB in otherwise healthy subjects is difficult to explain. To this aim, two theories have been proposed, based

on the possibility of post-exercise engorgement of bronchial vessels with decreased bronchial luminal area (the vasomotor hypothesis) and the hypothesis of insufficient conditioning of inspired air (the hyperosmolar theory).

The vasomotor hypothesis proposed that cooling of the airways followed by rapid re-warming may cause vasocostriction followed by reactive hyperemia of the bronchial microcirculation, together with edema of the airway wall (McFadden, 1990). Nevertheless, neither airway cooling or re-warming appear necessary for EIB to occur (Lee & Anderson, 1985; Anderson & Daviskas, 1992; Anderson & Daviskas, 2000; Anderson & Kippelen, 2008).

The main theory on EIB pathophysiology is that exercise hyperventilation causes drying of the airways, thus increasing osmolarity of the airway surface lining fluid (Anderson et al., 1989; Boulet & Turcotte, 1991; Anderson & Daviskas, 1992, 2000; Freed, 1995; Anderson & Kippelen, 2008). As water evaporates, the airway surface liquid becomes hyperosmolar and provides an osmotic stimulus for water to move from any cell nearby, resulting in cell volume loss. Therefore, the change in regulatory volume after cell shrinkage is believed to be the key event, which results in release of inflammatory mediators that cause airway smooth muscle to contract and the airways to narrow (Anderson & Daviskas, 2000). It has been calculated that severe hyperosmolarity can occur in the airways during intense exercise (Anderson & Daviskas, 1992), and clinical tests based on hyperosmolar stimulation, such as eucapnic voluntary hyperventilation (EVH) (Anderson et al., 2001) or mannitol inhalation (Holzer et al., 2003; Anderson et al., 2009), are widely used, instead of exercise provocation tests, to assess the predisposition to develop EIB in the laboratory.

Both hyperosmolarity and vasomotor changes might be involved in the pathogenesis of EIB in asthmatic patients (Kanazawa et al., 2002). Bronchial epithelial cells *in vitro* release IL-8 upon stimulation with either hyperosmolar solutions or cooling-rewarming, indicating that the proposed mechanisms are capable of activating the bronchial epithelium (Hashimoto et al., 1999). In addition, corticosteroids have been shown to inhibit the activation of bronchial epithelial cells caused by hyperosmolar exposure (Hashimoto et al., 2000).

2.2 EIB in athletes of different sports

In athletes involved in winter sports, EIB is especially frequent (Durand et al, 1995; Provost-Craig et al., 1996, Lumme et al., 2003) and a specific clinical picture has been described in cross-country skiers ("ski asthma"). Similar to other athletes, elite cross-country skiers show a high prevalence of exercise-induced respiratory symptoms, which however resulted poorly correlated with the degree of bronchial hyperresponsiveness (Durand et al., 2005; Stenfors, 2010). Ski asthma shows some peculiar features, such as evidence of airway remodelling and inflammation (Sue-Chu et al., 1999; Karjalainen et al, 2000), lymphoid aggregates in endobronchial biopsies (Sue-Chu et al., 1998), and lack of clinically significant response to corticosteroids (Sue-Chu et al., 2000).

Summer sports can also be associated with asthma and EIB, possibly because of increased allergen exposure during outdoor activities (Helenius & Haahtela, 2000). Asthma and EIB show the highest frequency among adult elite swimmers, possibly due to the prolonged exposure to the irritant effects of chlorine in indoor swimming pools (Helenius et al, 1998a; Langdeau et al, 2000). A role of swimming on bronchial reactivity and airway inflammation

is confirmed by reversibility of such changes upon cessation of intense training in adult athletes (Helenius et al., 2002; Bougault et al., 2011). In young swimmers, the relevance of exposure to chlorine-derived products in causing pathological airway changes has been recently questioned (Pedersen et al., 2008; Font-Ribera et al., 2011; Piacentini et al., 2011). Nevertheless, the increasing popularity of swimming suggests the opportunity to further assess the potential detrimental effect of exposure to chlorine associated with swimming, especially at young age (Bernard et al., 2008, 2009, 2011; Voisin et al., 2010).

2.3 Do acute exercise and training decrease bronchial reactivity?

Exercise is a very powerful bronchodilator stimulus, in both normal subjects and asthmatic patients. Even symptomatic patients with insufficiently controlled mild or moderate asthma showed bronchodilatation during acute incremental exercise, with preserved maximal ventilation and oxygen consumption (Crimi et al., 2002). The effects of acute incremental exercise were about 60% of the maximal bronchodilatation obtained after inhalation of albuterol (Milanese et al., 2009). The response to bronchoconstrictor agents in asthmatic patients was also lower during submaximal exercise compared to resting conditions (Stirling et al., 1983; Inman et al., 1990). The effects of constant-load submaximal exercise are somewhat controversial, since some studies reported persistent bronchodilatation in asthmatics (Mansfield et al., 1979; Inman et al, 1990), while others found that initial bronchodilation was followed by progressive bronchoconstriction during exercise in adult asthmatic patients (Milanese et al., 2009). Finally, eucapnic voluntary hyperventilation, mimicking the ventilation profile observed during exercise in asthmatic patients, was associated with bronchodilatation (Stirling et al., 1983; Gelb et al., 1985), while sympathoadrenal activation did not appear to play a major role (Gilbert et al., 1988; Hulks et al, 1991). Therefore, during acute exercise, the behaviour of airways appears quite similar in asthmatic patients and normal subjects.

Recent data indicate that intensive physical training may profoundly affect the airways and could decrease airways responsiveness (Scichilone et al., 2005). The intricate mechanisms underlying the pathophysiology of increased airway responses to inhaled broncoconstrictors, and the impact of physical activity on the occurrence and/or worsening of bronchial hyperreactivity, imply that research should first focus on interventions in healthy, non-asthmatic subjects. Therefore, we tested whether bronchial reactivity at rest differed between trained non-asthmatic amateur athletes and sedentary non-asthmatic controls, and found that the airway response to a spasmogen was lower in amateur runners than in sedentary individuals (Scichilone et al., 2005). Moreover, the "airway hyporesponsiveness" state of the athletes became more pronounced immediately after a competitive marathon.

This phenomenon can be explained by airway smooth muscle alterations induced by habitual heavy exercise. We speculated that the increased frequency of airway stretch that occurs with exercise hyperpnea could change the plasticity of airway smooth muscle cytoskeleton (Gunst & Tang, 2000; Gunst & Wu, 2001) or the myosin-actin interactions (Fredberg et al., 1996; Fredberg et al., 1997), enabling the smooth muscle fibers to become more resistant to spasmogens. Reorganization of the contractile apparatus of the airway smooth muscle may take place with habitual endurance exercise, thus enabling the smooth muscle fibers to adapt to changes in cell shape. Although we favour the mechanical explanation, other mechanisms, such as changes in the neural and/or biochemical control of the airways induced by physical training, may also contribute (Moreira et al., 2011a).

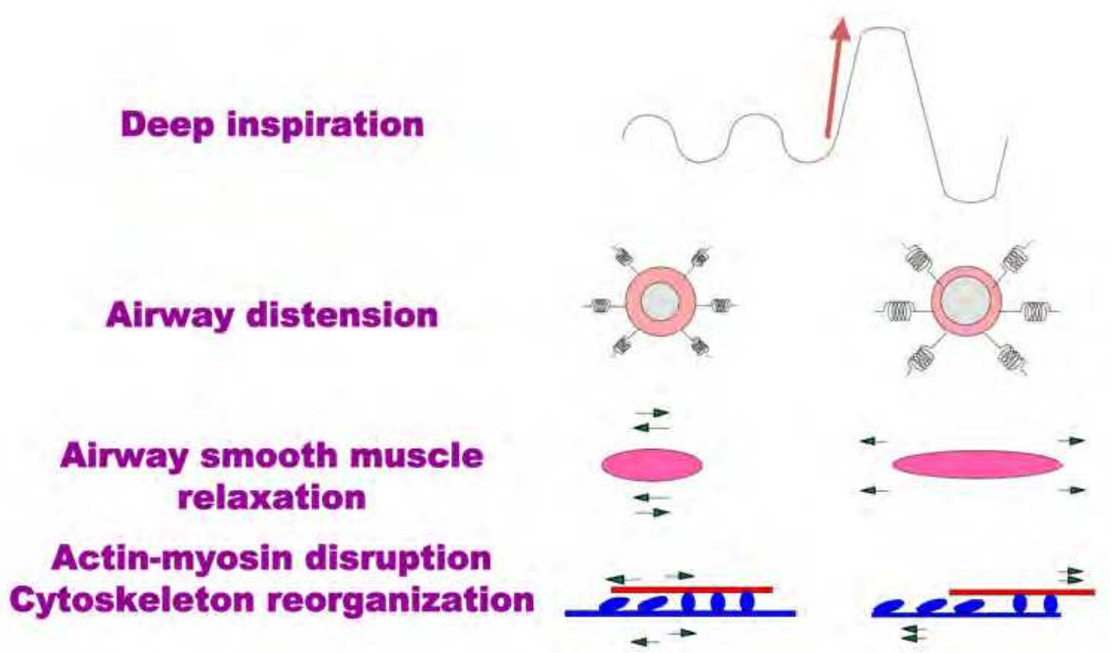

Fig. 1. Cascade of events that likely contribute to reduce airway smooth muscle contractility during lung inflation

In this scenario, development of asthma in atopic individuals could be in part secondary to lack of exercise and a sedentary lifestyle. In the European Community Respiratory Health Survey (ECRHS) II study, both frequency and duration of physical activity, as assessed by questionnaires, were inversely related to bronchial reactivity in a large population cohort independent of other variables (Shaaban et al., 2007). In a cohort of 411 Danish children born to mothers with asthma and closely monitored for occurrence of symptoms suggestive of asthma, the amount of habitual physical activity correlated inversely with occurrence of bronchial reactivity (Brasholt et al., 2010). These epidemiological data suggest that increased prevalence of asthma could be a consequence of changes in lifestyle related to physical activity and dietary habits, as confirmed by the increased prevalence of obesity worldwide, also at young age. In addition, a large longitudinal study recently found a decreased risk of asthma exacerbations associated with regular physical activity in older women (Garcia-Aymerich et al., 2009), suggesting that exercise may positively affect asthma control.

2.3.1 Results of methacholine tests in the absence of deep breaths in sedentary subjects and nonasthmatic athletes

Altered airway responsiveness in asthmatics has been primarily attributed to enhanced shortening ability of the airway smooth muscle. However, a wealth of evidence has accumulated to support the concept that factors other than smooth muscle reactivity are implicated in the overall response to a spasmogen. Indeed, changes in breathing pattern can modulate the response to bronchoconstrictor stimulation in healthy subjects, since the response to methacholine becomes almost indistinguishable from that of asthmatics when only shallow breaths are allowed (Skloot et al., 1995). Thus, excessive airway narrowing

likely results from an imbalance of opposing factors: on one hand, the forces generated by airway smooth muscle contraction; on the other hand, the effects of increased lung volumes, which may mechanically counteract smooth muscle shortening (Macklem, 1989).

Deep inspirations have been demonstrated to play a central role in opposing to airway narrowing, in that they are able to prevent bronchoconstriction in nonasthmatic subjects (Kapsali et al., 2000). Interestingly, such physiological function of lung inflation fails to occur in subjects who have airways hyperresponsiveness. In addition, deep inspirations can also reverse bronchoconstriction in both healthy subjects and patients with mild asthma (Scichilone et al., 2001); this phenomenon tends to decrease with increasing severity of asthma (Scichilone et al., 2007). Taken together, these observations imply that at least three factors are involved in the hyperreactive phenotype: the smooth muscle contractile properties and the bronchoprotective and bronchodilatory effects of deep inspirations.

We reasoned that by avoiding any effect of deep inspiratory maneuver thoroughout a bronchoprovocation protocol, the "true" smooth muscle reactivity could be assessed. Our group applied a single dose methacholine bronchoprovocation test to specifically study the response to spasmogen in the absence of large lung inflations (Scichilone et al., 2001). This modified bronchoprovocation challenge is more sensitive than the conventional challenge with incremental methacholine doses, as it causes substantial bronchoconstriction even in healthy individuals. In such protocol, the response to methacholine can be evaluated based on the dose of spasmogen inhaled, and the degree of bronchoconstriction obtained.

Nonasthmatic amateur runners responded less to methacholine in the absence of deep inspirations (higher amount of methacholine and lower degree of bronchial obstruction) than age-matched sedentary subjects (Scichilone et al., 2005). These findings suggest that smooth muscle of the athletes underwent exercise-induced structural changes, thus becoming more resistant to the effect of a bronchial spasmogen (bronchoprotective effect). The decreased reactivity in the athletes did not appear to depend on higher lung volumes at baseline compared to sedentary subjects (Scichilone et al., 2005). Deep inspiration may also exert a stronger bronchodilatory effect in athletes compared to the sedentary controls, but this hypothesis has not been tested yet.

Following this cross-sectional study, we longitudinally tested the effects of training in a group of healthy sedentary subjects undergoing intensive rowing training for 3 months. A significant reduction in the degree of bronchial reactivity in the absence of deep breaths was recorded during and at the end of the study (Scichilone et al., 2010). This observation shed new light in the field of bronchial hyperreactivity, since it indicates a significant effect of regular intensive exercise. Interestingly, Hewitt and colleagues recently reported that repeated bouts of moderate-intensity aerobic exercise (Hewitt et al., 2010), but not acute exercise (Hewitt et al., 2009), improved bronchial reactivity in OVA-treated mice. In amateur endurance athletes training in the Mediterranean area, no evidence was found for increased prevalence of EIB, suggesting that moderate intensity training does not worsen respiratory health (Kippelen et al., 2004). Therefore, moderate physical training could become a new, still relatively unexplored, management tool in asthma. In addition, given the potential to affect the progression of asymptomatic bronchial reactivity to asthma, we could conclude as stated in the editorial from Chapman and colleagues in 2010: "*the next time a physician hands an asthmatic patient a prescription and exclaims "take two at a time", the response may be – "do you mean pills or stairs?*" (Chapman et al., 2010).

2.3.2 Experimental data on the effects of deep inspirations on airway smooth muscle

Airway smooth muscle is subjected to mechanical strain associated with tidal breathing, and more so when deep inspirations take place. In 1995, it was shown that the active force generated by the airway smooth muscle decreases with increasing the amplitude of stretch (Pratusevich et al., 1995). In another *in vitro* study (Gump et al., 2001), a 3% increase of muscle length reduced force generation by 50%, which was comparable to the effect of isoproterenol treatment. *In vitro* experiments also showed that the magnitude of force generation of the airway smooth muscle decreases in parallel with increasing amplitude and duration of length oscillations applied to the relaxed muscle.

After a deep inspiration, the smooth muscle is believed to increase its length by 12% from its baseline value, and greater values can be reached during exercise (Fredberg et al., 1997). Bridge dynamic disruption (Fredberg et al., 1996, Fredberg et al., 1997) and plastic reorganization of the cytoskeleton (Gunst & Wu, 2001) both of which can lead to a state of lower airway smooth muscle contractility, have been advocated to explain the effect of lung inflation on airways. Kuo and colleagues showed that the density of thick myosin filaments decreases with varying the length of the airway smooth muscle (Kuo et al., 2001).

Prolonged changes in the contractile function of airway smooth muscle have been shown after long-term alterations in smooth muscle resting length. Chest strapping to maintain low end-expiratory lung volume in sheep increased airway smooth muscle contractility (McClean et al., 2003), while prolonged application of continuous positive airway pressure, which increased end-expiratory volume, decreased airway smooth muscle contractility in ferrets (Xue et al., 2008).

In summary, there is growing evidence indicating a major effect of deep inspiration in modulating airway smooth muscle cell reactivity. Habitual exercise training, with repeated intense hyperpnea, may be an important factor in regulation of bronchial reactivity in healthy and asthmatic subjects. More studies, however, are needed to extend the available results and identify optimal frequency and intensity of training to evoke positive changes in bronchial reactivity in humans.

3. Exercise-induced changes in airway cells

Exercise–induced changes in airways cells were initially studied in relation to occurrence of EIB. It was hypothesized that, similar to bronchial asthma, subjects developing EIB after intense exercise might also show a background of inflammatory activation in their airways.

In asthmatic patients, occurrence of EIB was found to be associated with intense eosinophilic inflammation (Yoshikawa et al., 1998). Asthmatic patients with EIB showed increased bronchial epithelial cells and eosinophil counts, as well as increased histamine, cysteinyl-leukotrienes and tryptase, and decreased prostaglandin E2 (PGE2) and thromboxane B2 in induced sputum after exercise challenge (Hallstrand et al., 2005a, 2005b). Leukotrienes are believed to be major players in EIB and asthma (Hallstrand et al., 2010), and increased leukotriene concentrations have been reported in exhaled breath condensate in asthmatic children with EIB (Carraro et al., 2005). A role for oxidative stress was also suggested by increased 8-isoprostane levels in exhaled breath condensate collected in asthmatic children developing EIB (Barreto et al., 2009). For further information, the reader is referred to a comprehensive review on EIB in asthmatic patients (Brannan & Turton, 2010). Finally, recent data suggest a relationship between neutrophilic inflammation and airway dehydration in asthmatics (Loughlin et al., 2010), indicating that asthma and EIB may share the common

pathophysiological mechanism of airway drying and hyperosmolarity. However, more studies are needed to confirm this hypothesis.

Studies in athletes found that changes in airways cells are common and occur independent of exercise-associated symptoms or spirometric changes. Increasing evidence suggest that habitual training is associated with airway inflammation in athletes of different endurance sports performed in cold or temperate environments (Bonsignore et al 2001, 2003b; Karjalainen et al., 2000; Sue-Chu et al., 1999; Lumme et al. 2003; Morici et al., 2004). However, the degree and type of airway inflammation under resting conditions is variable in athletes who perform different sports, and the role of inflammatory cells in the airways is currently unclear. Furthermore, airway inflammation in endurance athletes shows some peculiarities, since it may not be associated with bronchial hyperreactivity, post-exercise respiratory symptoms (Karjalainen et al., 2000; Bonsignore et al., 2001) or clear evidence of cell activation after acute exercise in humans or mice (Bonsignore 2001, 2003b; Morici et al., 2004; Hewitt et al., 2008) or after training in animal models (Chimenti et al. 2007, 2009; Silva et al., 2010; Vieira et al., 2007, 2011).

3.1 Studies in human athletes

Airway inflammation has been well characterized in athletes who exercise in a very cold environment (e.g skaters, ice hockey players, cross-country skiers) (Provost-Craig et al., 1996 ; Karjalainen et al., 2000, Lumme et al., 2003; Bougault et al., 2009). In cross-country skiers studied at rest, lymphocytes were increased in bronchoalveolar lavage fluid (Karjalainen et al., 2000), and endobronchial biopsies of proximal airways showed increased lymphocytes, but also neutrophils and eosinophils and evidence of airway remodelling, i.e. increased tenascin expression in the basement membrane (Sue-Chu et al., 1999). Skiers showed neutrophil infiltration, and relatively mild infiltration with eosinophils, mast cells, and macrophages. These results suggested that the inflammatory process in these athletes is different from classic asthma. Moreover, bronchial biopsy findings did not correlate with bronchial reactivity, atopy, or symptoms of asthma (Sue-Chu et al., 1999). Ice hockey players also showed increased neutrophil and eosinophil counts in induced sputum (Lumme et al., 2003). All these data were obtained in athletes under resting conditions, and the effects of acute exercise on airway cells in skiers have not been assessed, at least in part because of the objective environmental difficulties in collecting samples in these athletes.

Airway inflammation has been found in endurance athletes who perform sports in a temperate climate. In non-asthmatic amateur runners, neutrophil counts in induced sputum were increased after a marathon race compared to baseline level (Bonsignore et al, 2001); under resting conditions, the percentage of neutrophils in induced sputum of runners was higher than in sedentary controls, suggesting a chronic increase in neutrophils in the airways possibly related to habitual training (Bonsignore et al, 2001; Kippelen et al., 2004; Denguezli et al., 2008; Bougault et al., 2009). More recently, increased bronchial epithelial cell counts and interleukin-8 concentration, and apoptosis of bronchial epithelial cells, were found in induced sputum collected in nonasthmatic runners shortly after a half-marathon race, while neutrophil absolute counts were unchanged (Chimenti et al., 2010). Induced sputum samples collected the morning after a half-marathon race showed a slight increase in neutrophils compared to resting conditions (Chimenti et al., 2009). Increased bronchial

epithelial cell counts were also reported in induced sputum of elite swimmers collected at rest (Bougault et al. 2009).

These data suggest that neutrophil influx into the airways might be secondary to mild bronchial epithelial damage caused by intense exercise, but requires some time to occur. Similar to runners, well-trained young competitive rowers with normal bronchial reactivity to methacholine showed predominance of neutrophils in induced sputum both at rest and after exercise, and increased bronchial epithelial cell counts in induced sputum collected after a short bout of very intense exercise (Morici et al., 2004; Bonsignore et al, unpublished observations). Therefore, studies on the effects of exercise should take into account both the duration and the intensity of exercise; in addition, the time course of airway cell changes is likely to be complex, explaining some discrepancies between results of different studies.

The inflammatory pattern found in swimmers is very complex, as recently underlined (Haahtela et al., 2008), and different phenotypes of asthma in swimmers likely exist. On one hand, swimming is traditionally considered as a good type of physical activity for asthmatic patients, since it is associated with low allergen exposure. On the other hand, data in elite swimmers do suggest an important pro-inflammatory role played by environmental exposure to chlorine-derived compounds. Some time, however, might be required for airway cell changes to develop, as suggested by the negative results recently found in adolescent elite swimmers (Pedersen et al., 2008). Adult elite swimmers at rest, about half of them hyperreactive to methacholine, showed more eosinophils and neutrophils in induced sputum than sedentary subjects, with some evidence of inflammatory activation (Helenius et al., 1998a). Airway inflammation increased at 5-year follow-up in swimmers who continued training, but decreased in swimmers who had stopped competitive activity (Helenius et al., 2002). In adult non-asthmatic swimmers habitually training in an outdoor pool, airway neutrophil differential counts at baseline were higher than in sedentary controls but cell counts did not change significantly after a 5-km trial (Bonsignore et al., 2003b). After a 5-km competition in the sea, a condition of potential hypertonic airway exposure during exercise, the same swimmers showed slightly increased eosinophil and lymphocyte differential counts in induced sputum (Bonsignore et al., 2003b). These results suggested that the effects of chlorine exposure might be limited in athletes training in outdoor swimming pools; however, a study in adolescents swimmers attending outdoor pools confirmed an elevated risk of asthma also in this population (Bernard et al., 2008). More recently, asthmatic and nonasthmatic swimmers showed increased neutrophil counts in induced sputum, which correlated with increased airway vascular permeability assessed as the ratio of albumin in sputum and serum (Moreira et al., 2011b). Conversely, other studies found increased airway neutrophils only in swimmers who were hyperreactive to methacholine (Boulet et al., 2005; Belda et al., 2008, Bougault et al., 2009). Finally, a mixed type of inflammation, with increased eosinophil and neutrophil counts in induced sputum at rest, was reported in elite swimmers who showed hyperreactivity to methacholine (Moreira et al., 2008).

To our knowledge, only one study assessed airway cells in non-asthmatic athletes experiencing EIB (Parsons et al., 2008). The study shows some methodological limitations, such as EIB assessment only as response to eucapnic voluntary hyperventilation, and lack of baseline induced sputum samples. This study reported increased inflammatory mediators in

EIB+ athletes. However, airway cell counts were similar in EIB+ and EIB- athletes and did not correlate with concentration of mediators in sputum supernatants (Parsons et al., 2008). Our study on the effects of training in non-asthmatic subjects found that changes in airway cells and in the response to methacholine in the absence of deep inhalations showed different time courses (Scichilone et al., 2010). The picture can be further complicated by interactions between airway epithelial cells and smooth muscle cells, as suggested by a study showing that hyperosmotic stimuli induce epithelial dependent relaxation in the guinea pig trachea *in vitro* (Munakata et al., 1988). Therefore, further studies are needed to better characterize the role of airway epithelium in airway inflammation and its relationship with occurrence of EIB.

3.2 Studies in animal models and cultured bronchial epithelial cells

The functional and cellular events triggered by exercise hyperventilation have been studied in animal models, confirming that bronchial epithelial cells likely play an important role in exercise-induced airway changes. Besides functioning as a barrier against environmental toxins and injury, bronchial epithelial cells may modulate the immune response. In addition, in the long term, epithelial damage may favour sensitization to allergens, at least partly explaining the high prevalence of asthma in elite athletes (Helenius et al, 1998b).

In anesthetized dogs challenged with high flows of air into a lung segment during bronchoscopy, hyperventilation with dry air caused hyperosmolarity of airway surface lining (Freed & Davis, 1999) and bronchoconstriction (Freed et al., 1985). Repeated dry air challenges (DACs) in the same model, mimicking chronic exposure such as during training, caused epithelial damage with eosinophil and neutrophil influx, and increased peptidoleukotriene concentrations in bronchoalveolar lavage fluid (BALF) (Davis et al., 2001). Bronchial epithelial damage also occurred in horses after exercise while breathing cold air (Davis et al., 2002). In cultured human bronchial epithelial cells, exposure to a hyperosmolar medium or cooling-rewarming increased the expression of IL-8 and RANTES partly through the activation of p38 MAP Kinase (Hashimoto et al., 1999, 2000). Therefore, both hyperventilation and airway hyperosmolarity appear capable to cause bronchoconstriction and inflammatory response.

Data obtained in a normal mouse model of endurance training support the interpretation that exercise causes limited inflammation in small airways but may damage bronchial epithelium. Increased leukocyte infiltrate was observed in bronchiolar walls and lumen of endurance-trained mice undergoing mild-intensity training for 45 days (Chimenti et al., 2007). Bronchiolar epithelium showed progressive changes during training. In mice trained for 45 days, the number of ciliated epithelial cells was significantly lower compared to sedentary mice, and apoptosis of bronchiolar epithelial cells increased. Epithelial thickness was increased in trained compared to sedentary mice. Bronchiolar epithelium of trained mice showed an increased number of proliferating cells, suggesting that habitual exercise may increase epithelial turnover in the airways (Chimenti et al., 2007).

Bronchial epithelial cells play a crucial role in the asthma pathophysiology. A number of studies have demonstrated the beneficial effects of aerobic exercise in chronic allergic airway inflammation (Table 1).

Author, yr	Animal model	Aerobic training intensity	duration	Airway inflammation	BHR	Other post-training data
Pastva et al., 2004	OVA-sensitized mice	Moderate	4 wk	Trained mice showed ↓ inflammation when OVA-tested	Not tested	↓ NFkB expression
Davis et al., 2003	Sled dogs	High	2-4 mo	Not tested	=, but increased pre-training compared to control dogs	-
Chimenti et al., 2007	Normal mice	Low-moderate	45 d	↑inflammatory cells, ↓ NFkB expression in small airways	Not tested	-
Vieira et al, 2007	OVA-sensitized mice	Low-moderate	30 d	Trained OVA+ mice showed ↓ inflammation	Not tested	↓ remodeling
Vieira et al, 2008	OVA-sensitized mice	Low-moderate	30 d	Trained OVA+ mice showed ↓ vascular and parenchymal inflammation	Not tested	
Hewitt et al, 2009	OVA-sensitized mice	Moderate	4 wk	Not tested	↓	B2AR involved in BHR response
Silva et al., 2010	OVA-sensitized mice	Moderate	4 wk	Trained OVA+ mice showed ↓ inflammation		↓ remodeling
Lowder et al., 2010	OVA-sensitized mice	Moderate	4 wk	trained OVA+ mice showed ↓ inflammation associated with ↑ Treg cell response	Not tested	-
Vieira et al., 2011	OVA-sensitized mice	Moderate	4 wk	Trained OVA+ mice showed ↓ inflammation	Not tested	↓ remodeling; ↑ IL-10 in bronchial epithelium in OVA+ and OVA- trained mice

Table 1. Effects of training on airway inflammation and bronchial reactivity in animal models. Abbreviations: BHR: bronchial hyperreactivity; OVA: ovalbumin; B2AR: beta2-adrenergic receptor; NFkB: nuclear factor k B; = unchanged; ↑: increased; ↓ decreased; IL-10: interleukin-10

Regular aerobic exercise performed at low or moderate intensity decreased eosinophilic and lymphocytic inflammation and Th-2 immune response in a murine model of allergic asthma (Pastva et al., 2004; Vieira et al., 2007, 2008, 2011; Hewitt et al., 2009, 2010; Lowder et al., 2010). These studies showed that the effects of exercise training were mediated by reduced activation and expression of NF-kB, insulin like growth factor 1 (IGF-1), RANTES (CCL2) and glucocorticoid receptors. Exercise training increased the expression of interleukin 10 (IL-10) and of the receptor antagonist of IL-1 (IL-1ra) suggesting an immune-regulatory role of habitual exercise on airway epithelium.

3.2.1 Markers of airway inflammation

To assess whether the increased inflammatory cells in the airways were activated, markers of inflammation were analysed in endurance athletes or animal models. According to some studies, the increased number of airway inflammatory cells was not associated with major signs of inflammatory activation in BALF or induced sputum in cross-country skiers at rest (Sue-Chu et al., 2000), or in induced sputum of runners studied at rest and after a marathon race (Bonsignore at al., 2001). In amateur swimmers who trained outdoor throughout the year, there was no evidence of inflammatory cell activation at rest or after exercise in outdoor pool or sea as suggested by low levels of neutrophil elastase and decreased expression of L-selectin by airway cells (Bonsignore et al., 2003b). However, in runners IL-8 concentration in induced sputum supernatants doubled after a half-marathon and was positively correlated with absolute bronchial epithelial cell counts (Chimenti et al., 2010). We speculate that the increase in neutrophils found in large airways of athletes after prolonged exercise (Bonsignore et al., 2001) or the morning post-race (Chimenti et al., 2009) might be at least partly secondary to release of chemotactic factors, such as IL-8, by bronchial epithelial cells during exercise. On the other hand, IL-8 concentration in sputum supernatants collected on the morning after a half-marathon race was low (Chimenti et al., 2009), suggesting that exercise-induced inflammatory activation is transient. In runners, increased IL-8 in induced sputum at rest was found during a competitive period, but did not correlate with sputum cells counts (Denguezli et al., 2008).

Data on lung-derived proteins measured in serum or urine, suggest that pulmonary epithelial permeability may increase after intense exercise (Hermans et al., 1999; Chimenti et al., 2010, Romberg et al., 2011) or after eucapnic hyperventilation, independent of training status or occurrence of EIB (Bolger et al., 2011). In amateur runners, CC-16 levels did not correlate with air pollutants levels, and were normal in samples collected the morning after a half-marathon race (Chimenti et al., 2009). Thus, intense exercise appears to transiently increase epithelial permeability.

Data obtained in a murine model of allergic asthma suggest that inflammatory activation in the airways may actually be inhibited by exercise training (Table 1). In ovalbumin-sensitized mice, nuclear translocation of nuclear-factor-κB (NF-κB) in airway cells was lower in trained compared to sedentary animals (Pastva et al., 2004). More recently, exercise training in ovalbumin-sensitized mice decreased epithelial expression of IL-4, IL-5, IL-13, CCL11, CCL5, adhesion molecules ICAM-1 and VCAM-1, iNOS and NF-kB, while the expression of the anti-inflammatory cytokine IL-10 increased, suggesting a positive effect of training on control of inflammation in asthmatic airways (Vieira et al., 2011). In small airways of endurance-trained nonasthmatic mice, NF-κB translocation and inhibitor-alpha of NF-κB (IκBα) phosphorylation were not affected, and goblet cells in bronchioles were negative at

Alcian-PAS staining, indicating that training did not cause excess mucus production (Chimenti et al., 2007).
Other studies found increased airway inflammatory markers in athletes. Increased concentrations of eosinophil peroxidase and neutrophil lipocalin in induced sputum were observed in elite swimmers of the Finnish National team (Helenius et al., 1998). In young athletes, concentration of cysteinil-leukotrienes, prostaglandin E2 (PGE-2), histamine, thromboxane B2 (TXB2), and leukotriene B4 (LTB4) in induced sputum after a eucapnic voluntary hyperventilation challenge were higher in subjects with than without EIB (Parsons et al., 2008).
In summary, data from athletes or animal models are somewhat controversial, as some studies did not show any clear evidence of significant inflammatory activation in the airways, while others reported increased inflammatory mediators. These studies did not assess exercise-induced changes but only examined airway cells and mediators under resting conditions. The few data available on the effects of acute exercise suggest that changes in inflammatory markers, if any, might be transient. The relationship between EIB and inflammation is still unclear, and its assessment is often complicated by the concomitant occurrence of asthma and bronchial hyperreactivity in athletes.

4. Could exercise training be useful in patients with respiratory disease?

The possibility that habitual exercise may affect inflammatory processes in the airways opens the way to a new perspective regarding exercise-based rehabilitation. Until recently, exercise training in patients with respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD), was based on the assumption that the main effect of rehabilitation was to improve muscle function and decrease ventilatory requirements. While this holds true, especially in physically deconditioned patients, the possibility that exercise training may also modulate airway cell biology is being increasingly considered. The following paragraphs report a summary of recent findings suggesting that this could well be the case in patients with asthma or COPD, respectively.

4.1 Asthma

In subjects with asthma, the level of activity is restricted mainly because bronchoconstriction occurs after exercise. On the other hand, physical training increases the capacity for physical work (Freedman, 1992; Arborelius & Svenonius, 1984), and the anaerobic threshold (i.e., the level at which lactic acid production, and the associated increase in ventilation, occur). Consequently, hyperpnea, one of the major stimuli for EIB, is delayed and exercise tolerance improves after aerobic training. Ventilatory muscle training might also improve the capacity for sustaining physical activity, or, at least, minimize muscle fatigue (Leith & Bradley, 1976).
In asthmatic patients, an exercise-based training program improved asthma symptoms (Arborelius & Svenonius, 1984; Haas et al., 1987), even though baseline lung function remained unchanged. None of these studies tested whether airway responsiveness was affected by exercise training.
Table 2 summarizes the studies on the effects of physical training in normal subjects and patients with asthma. Some studies examined the effects of training on inflammation, other studies tested bronchial reactivity before and after training, and some did analyze other aspects such as quality of life and asthma control.

Author, yr	n	Training type	duration	Airway inflammation	BHR	Other post-training data
Matsumoto et al., 1999	8 children with mild-moderate asthma	swimming	6 wk	Not tested	=	Lac Thr ↑
Neder et al., 1999	42 children with mild-moderate asthma	aerobic	2 mo	Not tested	=	↓ use of B2A
Hallstrand et al., 2000	5 pts with mild asthma, 5 controls	aerobic	10 wk	Not tested	Not tested	Less HV during exercise
Kippelen et al., 2005	13 healthy subjects	aerobic	1 yr	Not tested	Not tested	Lung function=
Fanelli et al, 2007	Moderate-severe persistent asthma (21 T, 17 C children)	mixed	16 wk	Not tested	↓ EIB in trained group	↑ QoL
Bonsignore et al., 2008	Mild asthma (25 placebo, 25 montelukast, M, children)	aerobic	12 wk	=	↓ Mch PC20 in both groups	↓ FEV1 slope and exacerbations in M group
Moreira et al., 2008	34 asthmatic children (17 T, 17 C)	aerobic	12 wk	Not worsened by training, possible ↓ in IgE	Not tested	-
Dengzueli et al., 2008	10 endurance runners	aerobic	1 yr	↑ in precompetitive period	Not tested	Lung function =
Mendes et al., 2010	Moderate-severe persistent asthma (51 C, 50 T)	aerobic	3 mo	Not tested	Not tested	↑ asthma control and QoL
Scichilone et al., 2010	10 sedentary healthy subjects	rowing	10 wk	↑IL-8 in induced sputum supernatants at 10 wk	↓ response to Mch in the absence of deep inspiration at wk 5 and 10	-
Dogra et al., 2011	Incompletely controlled asthma (15 C, 21 T adults)	Mostly aerobic	24 wks	Not tested	Not tested	↑ asthma control and QoL
Mendes et al., 2011	Moderate-severe persistent asthma (24 C, 27 T adults)	Aerobic	3 mo	↓ only in trained group	Not tested	↑ asthma control

Table 2. Effects of training on airway inflammation and reactivity in normal and asthmatic subjects. Abbreviations: BHR: bronchial hyperreactivity; Lac Thr: lactate threshold; T: trained; C: control; B2A: beta2-agonist; FEV1: forced expiratory volume in 1 second; HV: hyperventilation; Mch: methacholine; PC20: provocative concentration causing 20% fall in FEV1; QoL: quality of life; NFkB: nuclear factor k B; = unchanged; ↑: increased; ↓ decreased; IL-8: interleukin-8.

Overall, the data in humans show no worsening or improvement of asthma after exercise training. The studies in animal models (Table 1) are much more refined in term of assessment of mediators and potential mechanisms involved. Therefore, additional work is required to improve our understanding of the effects of exercise training in human patients with asthma. The asthmatic athlete, on the other hand, might be considered a "special case", given the high intensity/frequency of training and the role of environmental exposures.

4.2 Chronic obstructive pulmonary disease

The literature on the physiological effects of pulmonary rehabilitation in COPD is large, but the majority of studies have examined the effects of training on skeletal muscles and markers of systemic inflammation, while changes in airway cells occurring during exercise or physical training in COPD patients remain largely unknown. The most recent studies have focused their attention on the amount, intensity, and pattern of daily physical activity in COPD patients, rather than the degree of physical fitness examined by traditional exercise stress tests, since the former is a better indicator of the impact of the disease on the quality of life of the patients. These studies are made easier today by the availability of accelerometers, which are very useful tools to objectively assess daily physical activity in and elderly population such as COPD patients. At least two meta-analyses have shown that daily physical activity in COPD patients is lower than in controls (Bossenbroek et al., 2011; Vorrink et al., 2011), but the involved mechanism are far from being clarified.

Interestingly, similar to studies on asthmatic patients, some epidemiological studies highlighted the prognostic importance of maintaining a good level of daily physical activity in COPD. Patients maintaining a regular level of physical activity underwent less hospital admission for COPD exacerbations (Garcia-Aymerich et al., 2006; Benzo et al. 2010). Moreover, in a population-based cohort the decline in lung function and the risk to develop COPD were found to be lower in smokers with an active lifestyle compared to smokers with a sedentary lifestyle (Garcia-Aymerich et al., 2007). Finally, an active lifestyle was associated with a more favorable clinical and functional status in a large sample of COPD patients (Garcia-Aymerich et al., 2009). An inverse association between life-long physical activity and the risk of COPD has also been recently reported by a case-control study conducted in Japan (Hirayama et al., 2010). Therefore, increasing evidence suggests a protective effect of an active life against the development of COPD and disease severity.

No study is available yet in humans on training-associated changes in airway responses in COPD patients. In a mouse model of COPD, favourable effects of 24-week exercise training in animals chronically exposed to cigarette smoke compared to the sedentary group have been reported (Toledo et al., 2011). Regular aerobic physical training of moderate intensity reduced oxidative stress and the development of emphysema in mice (Toledo et al., 2011). Therefore, it can be expected that studies in the near future will increasingly examine the protective effects of exercise training in the lung of COPD patients.

5. Conclusions

The effects of acute exercise and training on bronchial reactivity and airway inflammation are still a puzzle with many missing elements, but the general picture is appearing with an increasing number of details. In elite athletes, the combination of high exercise intensity,

environmental exposure and genetic background is likely responsible for the varying airway involvement described for different sports. However, it is likely that the levels of exercise commonly observed in the active population are associated with positive effects on bronchial reactivity and tight control of airway inflammation.

The majority of studies in patients with asthma similarly suggest a beneficial effect of training on the control of airway inflammation, although little evidence is currently available on the potentially beneficial effects of habitual exercise on bronchial reactivity. Instead, the only evidence in favour of physical activity in COPD patients comes from epidemiological observations and limited experimental results. A better understanding of the pathophysiology of exercise training in patients with asthma and COPD will be the first step towards a rational, evidence-based development of specific recommendations targeted to improve the quality of life and possibly the prognosis of these patients.

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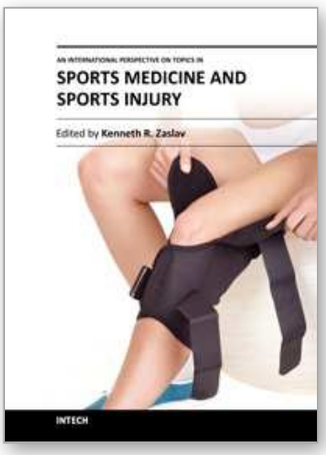

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