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## Chapter 3

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# Effects of Whole-Body Exercise and Inspiratory Muscle Training in People with Asthma

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## Abstract

Asthma is a complex and multi-dimensional disease, both in its pathologic phenotype and its response to treatment. The level of symptom control, a clinical key outcome, results from an interaction of inherent pathological aspects (e.g., airway inflammation, airway hyperresponsiveness and airway remodeling), environmental trigger factors, the patient's perception of disease and response to pharmacological treatment. While a reduction of the exposure to trigger factors and pharmacological treatment are the main interventions to achieve good control of asthma symptoms in most of the patients, physical exercise training as an adjunct to these therapeutic interventions has gained growing interest in the past decades thanks to its unconfined availability, its high cost effectiveness and its contribution to a healthy lifestyle. Despite possible transient negative effects of acute exercise on a variety of asthma-related aspects, unequivocal agreement exists regarding positive effects of exercise training on cardio-pulmonary and muscular adaptations leading to increased physical fitness in stable asthmatics similar to the healthy. These adaptations are mostly accompanied by improvements in asthma symptoms and quality of life and even reduced medication intake although evaluated parameters vary quite substantially between studies. However,

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due to the limited number of studies, evidence is yet missing regarding effects of physical training on asthma-specific pathological mechanisms such as airway inflammation and airway hyperresponsiveness. In summary, while well-controlled studies investigating asthma-specific pathophysiological changes with physical training are urgently needed, regular exercise can and should be recommended to people with stable asthma to increase cardio-respiratory and muscular fitness not only for improving asthma symptoms and quality of life, and possibly reducing asthma medication but also because improved physical fitness is well known to be associated with many other positive health-related effects.

## Introduction

### Definition of Asthma

Asthma is a chronic inflammatory disorder that is characterized by recurrent clinical symptoms such as episodes of wheezing, breathlessness, chest tightness, and coughing (GINA, 2012) that contribute to a reduced quality of life (QoL).

A consistent pathophysiological feature is the presence of an underlying airway inflammation associated with airway hyperresponsiveness related to increased reactivity of airway smooth muscles to allergens and irritants causing recurring airway narrowing and thus airflow limitation. In some asthmatics, a permanent limitation related to structural changes in the airways may develop – referred to as airway remodeling (EPR3, 2007).

Reduction of exposure to relevant allergens and irritants as well as pharmacotherapy are the main asthma treatments (EPR3, 2007; GINA, 2012). However, treatment can be difficult and response unpredictable (Lancet, 2008) and there is still little evidence to suggest that current pharmacological strategies alter the natural history of asthma (Murray, 2008). Also, Lancet (2008) recently stated “Prevention or cure of asthma is still a pipedream and asthma remains a genuine medical mystery”.

### Role of Exercise in Asthma

In the last decades, a growing number studies emerged investigating the effects of exercise training in patients with asthma, followed by narrative reviews (Bundgaard, 1985; Satta, 2000; Welsh, Kemp, & Roberts, 2005), systematic reviews including meta-analyses on randomized-controlled trials (RCT) (Carson; Chandratilleke et al., 2012; Eichenberger, Diener, Kofmehl, & Spengler, 2013; Pakhale, Luks, Burkett, & Turner, 2013; Ram, Robinson, & Black, 2000; Ram, Robinson, Black, & Picot, 2005) as well as on controlled- and non-controlled trials (CT and NCT, respectively) (Eichenberger et al., 2013; Pakhale et al., 2013). Unequivocal consent exists that most stable asthmatics adapt to regular physical exercise in a similar way as their healthy peers, i.e., muscular and cardio-pulmonary adaptations lead to an increase in a variety of measures of physical fitness. However, about 90% of asthmatic subjects suffer from exercise-induced bronchoconstriction (EIB) since high ventilations ( $\dot{V}_E$ ) are associated with airway drying that causes a hyperosmolar environment and subsequent activation of a diversity of pro-inflammatory and bronchoconstricting mediators (Weiler et al., 2010). These exercise-related adverse events might, in fact, keep

asthmatics from exercising although it is currently controversial, whether asthmatics are less fit than their peers, particularly children (Welsh, Roberts, & Kemp, 2004).

However, whether exercise-related improvements in asthmatics are related to changes in asthma-specific pathological features, i.e., a reduction in airway inflammation, airway hyperresponsiveness and airway remodeling, in addition to well-known physiological adaptations, is not yet clear. Thus, up-to-date no asthma-specific recommendations on training type, intensity, duration or frequency can be found in current asthma guidelines (EPR3, 2007; GINA, 2012).

In the recent years, a growing number of experimental studies using animal models of asthma have been conducted to shed light onto potential pathophysiological mechanisms responsible for the observed benefits of regular exercise in asthma.

Evidence is increasing, that physical training has indeed the potential to decrease the expression of a variety of pro-inflammatory markers and to increase several anti-inflammatory markers (Luks, Burkett, Turner, & Pakhale, 2013) and even partly reversing airway remodeling (Hewitt, Estell, Davis, & Schwiebert, 2010; Silva et al., 2010; Vieira et al., 2007; Vieira et al., 2009).

However, some doubt exists regarding the degree to which murine models of asthma effectively reflect airway changes or immunologic responses in human asthma (Luks et al., 2013) since both the method of inducing asthma in animals and the timing of intervention can affect the outcomes. The challenge thus remains to design adequate studies in humans to reproduce the encouraging results found in animal studies.

## Definitions of Physical Activity, Exercise Training and Physical Fitness

In this chapter, various terms related to exercise and physical activity are being used. As these terms are sometimes used interchangeably, we would like to define them beforehand, referring to the definitions presented by Caspersen and coworkers (1985). **1) Physical activity** is defined as any bodily movement produced by skeletal muscles that result in energy expenditure. It encompasses therefore the sum of all energy expended by moving during e.g., leisure time, work and sleep. **2) Exercise training** is a subcategory of physical activity and includes planned, structured, repetitive, and purposive activity in the sense that improvement or maintenance of one or more components of physical fitness is an objective. We will distinguish between whole-body exercise such as running, cycling etc. and exercise of specific muscle groups, e.g., respiratory muscle work without concomitant running, cycling etc. **3) Physical fitness** is a set of attributes that people have or achieve and usually includes components of the cardio-, pulmonary- and muscular system.

The aim of this chapter is to highlight the physiological adaptations of whole-body exercise interventions and specific inspiratory muscle training (IMT) in humans on airway inflammation, airway hyperresponsiveness, pulmonary function and respiratory muscle strength, use of asthma medication, asthma symptoms and QoL and parameters describing aspects of physical fitness.

The effects of whole-body exercise training on major intrinsic and extrinsic factors associated with asthma are summarized in Figure 1.

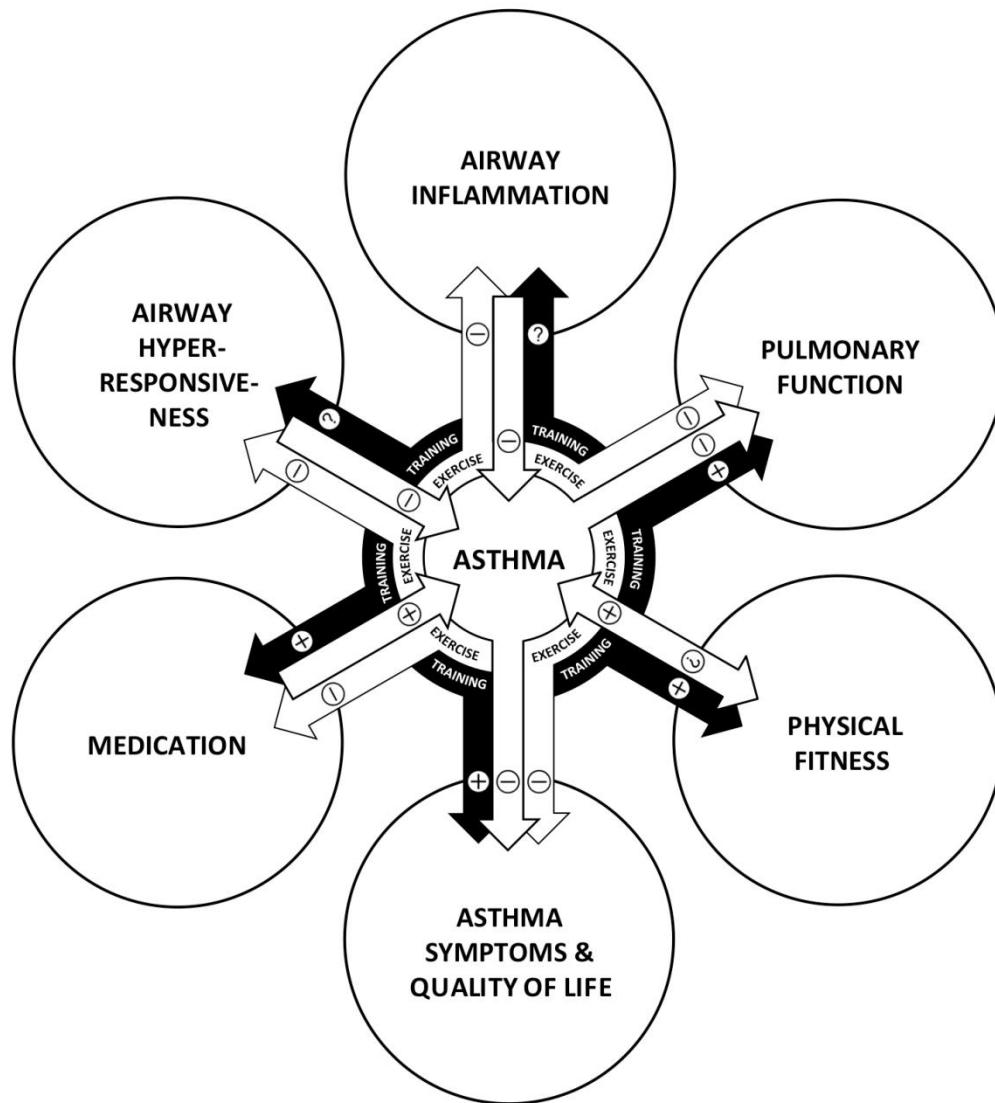


Figure 1. Influence of asthma, acute exercise and chronic exercise training on major intrinsic and extrinsic factors associated with asthma. ⊕: positive influence; ⊖: negative influence; ⊛: conflicting results or lack of good evidence due to missing, well-controlled studies.

## Physiological Adaptations to Whole-Body Exercise Interventions in Asthmatics

This first part will address specific aspects related to physiological adaptations to whole-body exercise training, while training of specific muscle groups such as respiratory muscles will be addressed in the second part of this chapter.

## Effect of Exercise Training on Airway and Systemic Measures of Inflammation in Asthmatics

Despite variable phenotypes of asthma, a central component is the presence of underlying airway inflammation (EPR3, 2007). Several inflammatory cells including lymphocytes, mast cells, macrophages, eosinophils, neutrophils and dendritic cells but also resident cells of the airways and epithelial cells have been identified in playing a distinct role in the development and progression of airway inflammation in asthma. Furthermore, additional key inflammatory mediators including cytokines (e.g., IL-4, IL-5, IL-9, IL-13), eosinophils and mediators released by activated eosinophils (e.g., eosinophil cationic proteins [ECP], cysteinyl-leukotrienes [Cys-LT]), changes in acid-base ratio measured by changes in pH, nitric oxide (NO), immunoglobulins (e.g., IgE), Endothelin-1 (ET-1), C-reactive proteins (CRP), and parameters of oxidative stress are all known to be involved in the highly complex inflammatory processes (Figure 2).

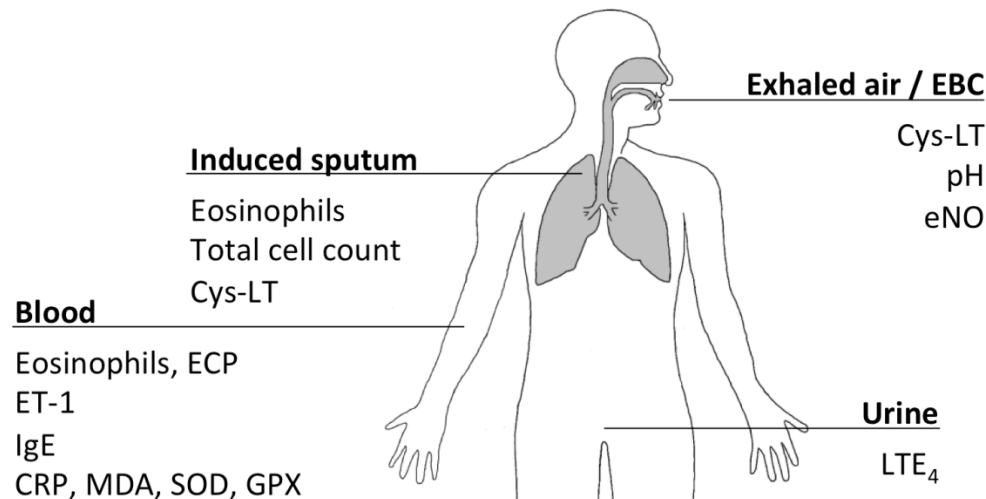


Figure 2. Overview of selected inflammatory parameters reported in interventional studies with asthmatic patients. Cys-LT: cysteinyl-leukotriene; CRP: C-reactive protein; EBC: exhaled breath condensate; ECP: eosinophilic cationic protein; eNO: exhaled nitric oxide; ET-1: endothelin-1; GPX: glutathione peroxidase; IgE: immunoglobulin E; LTE<sub>4</sub>: leukotriene E<sub>4</sub>, MDA: malondialdehyde; pH: acid-base ratio; SOD: superoxide dismutase.

A growing number of exercise training studies in animal models of asthma showed decreased expression of a variety of pro-inflammatory and increased expression of several anti-inflammatory markers and even partial reversal of airway remodeling (Luks et al., 2013). However, only a few very recent studies addressed these mechanisms in humans in response to structured physical whole-body exercise interventions. These studies, however, used different selections of parameters describing only part of the underlying airway and/or systemic inflammation which resulted in rather variable and conflicting outcomes.

In order to facilitate the understanding of the complex inflammation-related changes with exercise training, we will first discuss findings predominantly related to specific airway inflammation with variables measured in induced sputum or exhaled breath condensates

(EBC). Subsequently, we will summarize findings predominantly reflecting aspects of systemic inflammation and oxidative stress. However, we admit that every attempt to fully separate these aspects fails short due to the complex interplay of inflammatory cells and oxidative/antioxidative systems involved in asthma and the heterogeneous asthma phenotypes in the populations studied.

### Local Measures of Airway Inflammation

Mendes and coworkers (2011) assessed parameters of airway inflammation in induced sputum samples after a 12-week running exercise program and found positive changes, i.e., a significantly lower total and eosinophil cell count, while others did not reveal significant changes in eosinophils or ECP in serum after physical training (Boyd et al., 2012; Moreira et al., 2008). The latter is consistent with the fact that serum-derived eosinophil concentrations show a weaker correlation with clinical symptoms, variables of lung function and airway response to methacholine compared to measurements in induced sputum (Pizzichini, Pizzichini, Efthimiadis, Dolovich, & Hargreave, 1997).

Levels of Cys-LT, a mediator released by activated eosinophils, is known to play an important role in the development and severity of EIB (Hallstrand & Henderson, 2009), that is present in up to 90% of asthmatics (Gotshall, 2002). Thus, higher levels of Cys-LT are not only observed in asthmatic compared to healthy subjects (Bikov et al., 2010) but also in EIB-positive asthmatics compared to EIB-negative (Hallstrand, Moody, Aitken, & Henderson, 2005). However, studies that investigated the effect of physical training interventions on basal levels of Cys-LT either in sputum (El-Akkary et al., 2013), in EBC (Bonsignore et al., 2008) or in urine (Gunay et al., 2012) found no significant change but El-Akkary et al. (2013) who exclusively recruited subjects with EIB, reported a significant attenuation in the post-exercise increase in sputum Cys-LT after the intervention period, suggesting a reduced mediator release during acute exercise. In line with this change, the post-exercise decline in forced expiratory volume in 1 s ( $FEV_1$ ) was significantly attenuated and the EIB prevalence dropped from initially 100% to 40% after the training period.

Thus, the present data on changes in eosinophil counts and released mediators in humans do not yet allow to draw firm mechanistic conclusions despite some positive reports on effects of a training intervention on either airway eosinophil counts or changes in Cys-LT after acute exercise.

Exhaled pH was also suggested to be a marker of airway inflammation since asthmatics were shown to have airway acidification, i.e., a lower pH in EBC, compared to healthy subjects, the change being more pronounced with more severe asthma (Tomasiak-Lozowska et al., 2012) and correlating relatively well with changes in other inflammatory parameters, i.e., serum eosinophil count, EPC, IgE and exhaled NO (eNO). Two studies assessed effects of acute or chronic exercise on airway pH in EBC. Acute exercise decreased pH in EIB-positive but not in EIB-negative asthmatics (Bikov et al., 2014) which implies an acute increase in inflammation with exercise and is in line with the acute increase in exhaled Cys-LT (El-Akkary et al., 2013). A 12-week aerobic training intervention (Bonsignore et al., 2008) decreased resting pH in a group of children, however, with no change in resting eNO (see below), thus with conflicting results regarding changes in airway inflammation from different markers while the prevalence of EIB was halved after the training period.

eNO originating in the airway epithelium is reported to be tightly correlated with eosinophilic airway inflammation (Berry et al., 2005), it is elevated in subjects with atopy with/without asthma (Kharitonov et al., 1994; Salome et al., 1999) and decreased with the use of inhaled corticosteroids (ICS) (Kharitonov et al., 1994). Reported effects of exercise on eNO are heterogeneous. While Bonsignore et al. (2008) and Moreira et al. (2008) did not find a significant change in basal eNO after 12-weeks of swimming and aerobic exercise training, respectively, Goncalves et al. (2008) and Mendes et al. (2011) reported significantly lower basal eNO after a 12-week running intervention in subjects with severe asthma. Due to inherent differences between studies, i.e., mild-moderate (Bonsignore et al., 2008; Moreira et al., 2008) versus severe asthma (Goncalves et al., 2008; Mendes et al., 2011), children (Bonsignore et al., 2008; Moreira et al., 2008) versus adults (Goncalves et al., 2008; Mendes et al., 2011) and differences in training protocols/intensities, it is difficult to identify an optimal training regimen for a specific population. Interestingly, Mendes et al. (2011) observed a significant correlation between baseline eNO levels - known to be higher in more severe and less well controlled asthmatics (Kharitonov & Barnes, 2000) - and its reduction after exercise training. Thus, one could speculate that less well controlled patients might benefit the most from exercise training in terms of improving airway inflammation. This hypothesis is further underlined by the fact that a similar correlation exists for baseline eosinophil count and its reduction after exercise training (Mendes et al., 2011). However, it might be questioned whether the observed changes (average reductions from 31 to 27 ppb) are clinically relevant since a clinically significant change should be  $\geq 10$  ppb and/or 20% of baseline when values are in this range (adults: 25 - 50 ppb; children, 20-35 ppb) (Dweik et al., 2011).

## Systemic Measures of Inflammation

To uncover asthma-specific changes of exercise training, investigations also include systemic rather than local assessment of inflammation. However, as briefly noted before, the relation of serum-derived variables with asthma symptoms may be less tight than those assessed locally, e.g., serum eosinophil concentrations correlate less well with the degree of clinical symptoms than sputum concentrations (Pizzichini et al., 1997).

As a further marker, concentrations of endothelins, i.e., pro-inflammatory, pro-fibrotic, broncho- and vasoconstrictive peptides known to play an important role in the development of airway inflammation and remodeling in asthma (Goldie & Henry, 1999), are assessed locally and systemically in asthmatics since ET-1 concentration in plasma, bronchoalveolar lavage or EBC are known to be elevated in asthmatics compared to the healthy (Gawlik, Jastrzebski, Ziora, & Jarzab, 2006; Redington et al., 1997; Trakada, Tsourapis, Marangos, & Spiropoulos, 2000; Zietkowski, Skiepkowski, Tomasiak, & Bodzenta-Lukaszyk, 2008). Also, they are higher in more severe asthmatics (Gawlik et al., 2006; Trakada et al., 2000; Zietkowski et al., 2008) and in asthmatics with EIB (Zietkowski, Skiepkowski, Tomasiak, & Bodzenta-Lukaszyk, 2007). One study therefore assessed changes in serum ET-1 concentrations with physical training. After 8 weeks of a combined exercise plus ICS intervention, in comparison to ICS only (Gunay et al., 2012), ET-1 levels were significantly decreased in children with the combined exercise training + ICS program. Since in-vitro studies showed enhanced synthesis of ET-1 in the presence of pro-inflammatory cytokines (Endo et al., 1992) these post-training

results may implicate that pro-inflammatory cytokines might have been reduced after training, similar to known training-effects in animal models (Luks et al., 2013).

An 8-week interventional study investigated the effects of exercise training on oxidative stress (Onur et al., 2011) because evidence is increasing that chronic airway inflammation leads to an imbalance of oxidants/antioxidants resulting in oxidative stress to the airways. Oxidants are released by activated inflammatory cells such as eosinophils or neutrophils inducing bronchoconstriction, airway hyperresponsiveness, increased permeability of the airways and induce bronchial cell injury, promoting further release of other pro-inflammatory cells and cytokines (Caramori & Papi, 2004). On the other hand, acute aerobic exercise is associated with an increased generation of reactive oxygen species (ROS) (Finaud, Lac, & Filaire, 2006) that is more pronounced with higher exercise intensity (Lovlin, Cottle, Pyke, Kavanagh, & Belcastro, 1987) while aerobic exercise training reduces oxidative stress and enhances antioxidant capacity in healthy subjects (Finaud et al., 2006). In the study with asthmatic patients (Onur et al., 2011), serum biomarkers of oxidative stress (malondialdehyde [MDA]) and of the antioxidant defense system (superoxide dismutase [SOD] and glutathione peroxidase [GPX]) were investigated. While resting MDA serum concentration was significantly lower and SOD concentration significantly higher in both, the combined exercise+ICS and the ICS group, GPX concentration only increased in the exercising asthmatic group with the final level being higher than that of the healthy controls. This data supports above findings and – in face of the tight relationship between airway inflammation and ROS production in asthma (Caramori & Papi, 2004) - suggest that exercise may indeed have a positive effect on airway inflammation, in addition to the effect of ICSs, and thus more well-controlled studies are warranted and needed to confirm these findings.

Lastly, a further marker of systemic inflammation, C-reactive protein (CRP), was investigated since high-sensitive (hs)-CRP in particular was shown to be higher in asthmatics than in healthy, and higher in patients with unstable than with stable asthma (Zietkowski et al., 2009). Also, serum hs-CRP was shown to correlate with eNO levels across all asthma severities (Zietkowski et al., 2009). While 12 weeks of submaximal strengthening and aerobic exercise did not result in a significant change in hs-CRP (Moreira et al., 2008), a small decrease was observed after 6-12 month of military service (Juvonen et al., 2008). However, possibly this decrease not only resulted from increased physical activity, since also smoking habits may have changed with increased physical activity (Tonstad & Cowan, 2009) and/or weight-loss may have contributed since 20% of asthmatics (16% of non-asthmatics) were overweight ( $BMI \geq 25\text{kg/m}^2$ ) and changes in body weight and body composition are associated with changes in CRP (Forsythe, Wallace, & Livingstone, 2008). Thus, the number of studies investigating CRP-changes after exercise training in asthmatics is yet too small to draw firm conclusions on training-induced changes in this variable.

In summary, evidence from human studies is still limited regarding effects of regular physical exercise on underlying airway and systemic inflammation in asthmatics. Clearly, more data is needed addressing dose-response characteristics of type and intensity of exercise and identifying characteristics of asthmatics that benefit most.



## Effects of Exercise Training on Airway Hyperresponsiveness in Asthmatics

Airway hyperresponsiveness is a major feature of asthma. It is defined as an exaggerated narrowing of the airways (bronchoconstriction) to a wide variety of stimuli which would be innocuous in normal persons (GINA, 2012). Hyperresponsiveness can either be measured by so called "direct" or "indirect" challenges, the mode of action on airway smooth muscle contraction depending on the agents used (Sterk et al., 1993), i.e., agents of direct challenges (e.g., histamine, methacholine) act via direct contraction of airway smooth muscles while agents of indirect challenges act via cellular and neurogenic mechanisms indirectly leading to smooth muscle contraction and inflammatory changes in the airways (e.g., exercise, mannitol, adenosine, hyperpnea or allergens) (Sterk et al., 1993). Several mechanisms can contribute to airway hyperresponsiveness whereby airway inflammation appears to be a major factor in determining the degree of airway hyperresponsiveness (Cockcroft & Davis, 2006). Asthma medication, specifically corticosteroids improve both airway inflammation as well as airway hyperresponsiveness to both direct and indirect challenges (Meijer et al., 1999).

### Airway Hyperresponsiveness to Direct Stimuli

Several studies analyzed the effect of exercise training on airway hyperresponsiveness to histamine or methacholine in adults and children with mild to severe asthma but these yielded controversial results. While five studies (two RCTs and three NCTs) reported significant improvements in hyperresponsiveness after 10-24 weeks of swimming, cycling, running and/or aerobic circuit exercise training in mostly mild to moderate asthmatics (Arandelovic, Stankovic, & Nikolic, 2007; Bonsignore et al., 2008; El-Akkary, El-Ghazali, & Younis, 2006; Scichilone et al., 2012; Wicher et al., 2010), another eight studies (three RCTs, three CTs and two NCTs) reported no improvements or improvements in single subjects only after 10-32 weeks of swimming, gymnastics and/or aerobic exercise training in mild to severe asthmatics (Cochrane & Clark, 1990; Emtner, Finne, & Stalenheim, 1998b; Emtner, Herala, & Stalenheim, 1996; Engstrom, Fallstrom, Karlberg, Sten, & Bjure, 1991; Matsumoto et al., 1999; Moreira et al., 2008; Robinson et al., 1992; Schmidt, Ballke, Nuske, Leistikow, & Wiersbitzky, 1997). These diverse findings likely result from differences between subjects' characteristics, exercise protocols and mechanisms involved. A variety of mechanisms have been proposed to explain some of the reported improvements. Some authors (Bonsignore et al., 2008; Scichilone et al., 2012) argued that exercise training possibly exerts an anti-inflammatory effect on the airways, eventually leading to an attenuated hyperresponsiveness as airway inflammation is known to be related to airway hyperresponsiveness as outlined above. However, whether a decrease in airway inflammation translates into lower airway hyperresponsiveness, remains unclear as only very few studies simultaneously assessed parameters of inflammation and airway hyperresponsiveness and results were conflicting so far (Bonsignore et al., 2008; Moreira et al., 2008). One study in a murine asthma model showed normalization of responsiveness to methacholine after 4 weeks of aerobic exercise (Hewitt et al., 2010) but parameters reflecting airway inflammation were not assessed. Instead, the authors attributed their finding, in part, to a reduced abundance of factors that

desensitize  $\beta_2$ -adrenergic receptors on airway smooth muscles and suggested that regular aerobic exercise would lead to an increased sensitivity (compared to sedentary animals) towards bronchodilating substances e.g., catecholamines released during exercise functioning as physiological bronchodilators. These authors also found that exercise-mediated decreases in airways smooth muscle thickness positively correlated with exercise-mediated attenuation of airway hyperresponsiveness. One might thus speculate that possible improvements in direct airway hyperresponsiveness in humans might be secondary to changes in airway remodeling. In fact, two studies in mice showed that parameters of airway remodeling - e.g., airway collagen and elastic fiber deposition, airway smooth muscle and epithelium thickness - were significantly reduced after exercise training (Silva et al., 2010; Vieira et al., 2007) but unfortunately, airway hyperresponsiveness was not assessed in those studies. Indeed, in humans, direct airway hyperresponsiveness, as assessed by methacholine, was shown to be better related to baseline lung function (De Meer, Heederik, & Postma, 2002) than indirect methods (i.e., adenosine), possibly indicating structural remodeling of the airways (De Meer et al., 2002). Clinically, airway remodeling is usually reflected by the magnitude of the irreversible airflow obstruction as measured by the post-bronchodilator FEV<sub>1</sub> (Cockcroft & Davis, 2006) and severe asthmatics with fixed and severe airflow obstruction have indeed been shown to have significantly thicker airway walls than those with reversible airflow limitation (Bumbacea et al., 2004). Thus, despite promising results from a mechanistic point of view provided by animal studies, human studies have not yet rendered similarly convincing data, possibly due to a much more heterogeneous study design compared to animal studies.

### Airway Hyperresponsiveness to Indirect Stimuli

To assess indirect airway hyperresponsiveness, the majority of studies focused on exercise as bronchoconstrictor stimulus. In contrast to direct airway challenges, performance of exercise challenges are less standardized (Crapo et al., 2000) although recommendations for standardization exist for more than 30 years (Anderson, Silverman, Konig, & Godfrey, 1975). Since studies vary in test preparation, environmental conditions, exercise modality (i.e., cycling, treadmill running, free running, swimming), workload profile, and response assessment, comparison between studies is more difficult and mechanistic insights are harder obtained. Improvements in EIB severity after exercise training were often claimed to most likely result from a reduced ventilatory drive associated with improved cardiopulmonary fitness rather than from inherent changes in the clinical picture of EIB itself meaning that  $\dot{V}_E$ , the primary EIB stimulus, was lower in the fit state and thus less EIB was induced. This interpretation is certainly justified in mostly earlier studies that explicitly stated that baseline and post-intervention exercise challenges were performed at the very same absolute workload (Emtner et al., 1998b; Emtner et al., 1996; Fanelli, Cabral, Neder, Martins, & Carvalho, 2007; Freeman, Nute, & Williams, 1989; Henriksen & Nielsen, 1983; Henriksen, Nielsen, & Dahl, 1981; Leisti, Finnila, & Kiuru, 1979; Svenonius, Kautto, & Arborelius Jr, 1983) and/or where post-intervention  $\dot{V}_E$  was measurably lower than at baseline (El-Akkary et al., 2006; Hallstrand, Bates, & Schoene, 2000). Indeed, most of these studies found a significantly attenuated decline in lung function after the exercise challenge (El-Akkary et al., 2006; Fanelli et al., 2007; Freeman et al., 1989; Henriksen & Nielsen, 1983; Henriksen et al., 1981;

Svenonius et al., 1983) or a reduction in the number of subjects with EIB (Emtner et al., 1998b; Emtner et al., 1996). A few studies, however, failed to show improvements in EIB after exercise training. This negative outcome may be related to an inadequate time-point of measurements (Leisti et al., 1979) and inadequate inclusion criteria with, for example, only 2 out of 9 subjects showing EIB at baseline (Leisti et al., 1979) or due to differences in pre- and post-tests (Hallstrand et al., 2000). Similarly, studies using either an absolute or relative level of heart rate or a fixed speed to set and adjust workload during the exercise challenge, mainly reported no significant change in EIB severity (Bundgaard, Ingemann-Hansen, Schmidt, & Halkjaer-Kristensen, 1982; Fitch, Morton, & Blanksby, 1976; King, Noakes, & Weinberg, 1989; Nickerson, Bautista, Namey, Richards, & Keens, 1983; Schnall, Ford; Silva, Torres, Rahal, Terra Filho, & Vianna, 2006; Sly, Harper, & Rosselot, 1972; van Veldhoven et al., 2001) or in the number of subjects with EIB (Bonsignore et al., 2008; Neder, Nery, Silva, Cabral, & Fernandes, 1999; Schmidt et al., 1997) after training. Only three of the studies that used heart-rate controlled EIB-challenges reported significant improvements in EIB (El-Akkary et al., 2013; Sidiropoulou, Fotiadou, Tsimaras, Zakas, & Angelopoulou, 2007; Swann & Hanson, 1983). Some authors set out to shed more light on the role of the intensity used in exercise-challenges. They performed multiple exercise challenges after the training period, i.e., similar absolute workload or similar relative workloads meaning a given percentage of the maximal achievable workload (that is likely larger after a period of physical training). With this design one group (Fitch, Blitvich, & Morton, 1986) found no change in EIB with either method, another (Araki et al., 1991) reported a significant attenuation in EIB only at the same absolute level, while two (Haas et al., 1987; Matsumoto et al., 1999) reported a reduction in EIB after training in tests at the same absolute as well as at the same relative workload (Matsumoto et al., 1999) and when  $\dot{V}_E$  in the exercise challenge was matched before and after the training period (Haas et al., 1987). Although not conclusive either, the latter findings suggest that physical training has the potential to induce intrinsic improvements associated with reduced airway reactivity. Support is given by a previously mentioned study showing a diminished increase in Cys-LT – known to be related to the development and severity of EIB – in the exercise challenge after a period of physical training in 25 children with mild-severe asthma and a history of EIB (El-Akkary et al., 2013). In summary, physical training has the potential to reduce EIB but evidence whether more than a reduced ventilatory drive, i.e., asthma-specific improvements, contributes to reduce EIB, is not yet given. Therefore larger, well-controlled trials, adhering strictly to current guidelines on exercise-challenges are urgently needed.

## **Effects of Exercise Training on Pulmonary Function and Respiratory Muscle Strength in Asthmatics**

### **Pulmonary Function and Maximal Voluntary Ventilation (MVV)**

Measurement of pulmonary function is a fundamental part of diagnosing and monitoring asthma, in particular FEV<sub>1</sub> (EPR3, 2007), providing an objective and highly reproducible estimate of airflow limitation.

In a recent review (Eichenberger et al., 2013) of 24 CTs and RCTs assessing changes in FEV<sub>1</sub> after a physical training intervention, we found a significant overall increase of 3% (adjusted for control-group effects). The meta-analysis of the 11 RCTs revealed a 0.09 L increase in FEV<sub>1</sub> after the exercise intervention period compared to controls. We need to note, however, that this improvement in FEV<sub>1</sub> is smaller than the minimal clinically significant changes of around 10-12% (Reddel et al., 2009). This suggests that exercise training may not have a relevant effect on FEV<sub>1</sub>, a fact also supported by most recent studies that mainly detected increases of only 5-11% in FEV<sub>1</sub> (El-Akkary et al., 2013; El-Akkary et al., 2006; Latorre-Roman, Navarro-Martinez, & Garcia-Pinillos, 2014; Zolaktaf, Ghasemi, & Sadeghi, 2013).

Assessment of MVV, i.e., the maximum volume of air a subject can breathe over a specified period of time, usually 12s, may be useful in those conditions where ventilatory capacity is impaired by mechanisms that are different from those affecting FEV<sub>1</sub> (Miller et al., 2005). MVV is frequently estimated by multiplication of FEV<sub>1</sub> with a constant factor (35 or 37). In asthmatics, however, MVV and the ratio of MVV/FEV<sub>1</sub> (Fairshter, Carilli, Soriano, Lin, & Pai, 1989; Hallstrand et al., 2000) was shown to be lower compared to healthy subjects and lower in those asthmatics with higher responsiveness to methacholine. In fact, the MVV maneuver per se induced a significant decrease in airway conductance in asthmatics while in healthy, airway dilation was observed (Fairshter et al., 1989). Thus, changes in MVV might be of greater relevance to asthmatics than changes in FEV<sub>1</sub>.

Studies investigating the effect of a physical exercise intervention on MVV demonstrated a significant increase (El-Akkary et al., 2006; Farid et al., 2005; Haas et al., 1987; Millman, Grundon, Kasch, Wilkerson, & Headley, 1965; Orenstein, Reed, Grogan, & Crawford, 1985; Shaw & Shaw, 2011a; Shaw & Shaw, 2011b; Wicher et al., 2010), a trend towards improvement (Hallstrand et al., 2000) or no change (Nickerson et al., 1983) while in the majority of studies, MVV did not change significantly in the non-exercising control group. The increase in MVV was accompanied by an increased FEV<sub>1</sub> in some (El-Akkary et al., 2006; Farid et al., 2005; Shaw & Shaw, 2011a; Shaw & Shaw, 2011b; Wicher et al., 2010) but not all of these studies (Haas et al., 1987; Hallstrand et al., 2000; Millman et al., 1965; Nickerson et al., 1983). In one of the latter, reduced airway hyperresponsiveness in response to exercise training may have been responsible for the improved MVV. Indeed, airway hyperresponsiveness is known to affect MVV in asthmatics (Fairshter et al., 1989) and Haas et al. (1987) observed, for example, a significant decrease in EIB severity along with an increase in MVV after exercise training.

## Maximal Inspiratory and Expiratory Pressures

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) represent in- and expiratory muscle strength. To which extent respiratory muscle strength is reduced in asthmatics remains yet unclear. However, respiratory muscle function can be affected in several ways by asthma, including hyperinflation which places the diaphragm in a shortened and flattened position resulting in mechanical disadvantages during inspiration (Perez, Becquart, Stach, Wallaert, & Tonnel, 1996; Weiner, Suo, Fernandez, & Cherniack, 1990), and corticosteroid treatment may lead to a general loss of muscle strength and/or endurance (Decramer, Lacquet, Fagard, & Rogiers, 1994; Perez et al., 1996).

Up to date, only few studies assessed changes in MIP and MEP after an exercise intervention. Significant improvements in MIP were observed in children (El-Akkary et al., 2006; Holzer, Schnall, & Landau, 1984; Wicher et al., 2010) and adults (Foglio et al., 1999) although a potential learning effect (Holzer et al., 1984), or a lack of a control group (El-Akkary et al., 2006; Foglio et al., 1999; Wicher et al., 2010) may compromise a sound conclusion. Furthermore, MIP was not improved in two further studies with asthmatic children (Nickerson et al., 1983; Schnall et al., 1982) possibly related to high baseline MIP values (> 100% predicted) while baseline MIP was below 100% predicted in those studies with training-related improvements. All studies that assessed MEP after an exercise training intervention reported a significant increase (El-Akkary et al., 2006; Foglio et al., 1999; Holzer et al., 1984; Schnall et al., 1982; Wicher et al., 2010).

Also, improvements in respiratory muscle strength in asthmatics are usually seen after specific respiratory muscle training with more consistent improvements in MIP than in MEP (Silva et al., 2013). Although the above exercise training studies did not include specific respiratory muscle training, the chosen exercise modes, i.e., swimming (Schnall et al., 1982; Wicher et al., 2010) or exercises including light abdominal, upper and lower limb muscle strength exercises (Foglio et al., 1999), might explain some of the improvements. Both exercise modalities are, in fact, known to cause respiratory muscle adaptations similar to those with isolated respiratory muscle training alone (DePalo, Parker, Al-Bilbeisi, & McCool, 2004; Mickleborough, Stager, Chatham, Lindley, & Ionescu, 2008). More details on the effect of specific inspiratory muscle training in asthmatics can be found in the following sections.

## **Effects of Exercise Training on Use of Asthma Medication**

Although pharmacotherapy - certainly one of the major modalities of asthma therapy (EPR3, 2007; GINA, 2012) - is usually effective to provide and maintain clinical control in many asthma patients (Bateman et al., 2004), current surveys on asthma-control indicate that asthma remains a serious public health problem with a large proportion of asthmatics still failing to achieve good control (Demoly, Gueron, Annunziata, Adamek, & Walters, 2010). Also, many patients have concerns to take regular medication, particularly ICS. Thus, alternative or adjunct methods to achieve asthma control, e.g., exercise training, are of great importance and reduced asthma medication to attain similar asthma control would reflect an improvement in asthma severity.

While most of the studies that investigated the effect of an exercise intervention on asthma paid attention that subjects kept asthma medication constant during the study period, only few assessed changes in asthma medication as part of the study outcome. However, the type of reporting asthma medication differed widely between studies, rendering the analysis difficult (Eichenberger et al., 2013).

Studies reported either a lower *medication score*, i.e., (1) subjects requiring less medication after the exercise training intervention showing either a significant reduction (Basaran et al., 2006; Emtner, Finne, & Stalenheim, 1998a), a reduction only by tendency (Fitch et al., 1976) or no statistical analysis (Weisgerber, Guill, Weisgerber, & Butler, 2003), or (2) significantly less subjects with high medication score (Neder et al., 1999). In two

studies, improvements seemed to be related to the degree of improvement in physical fitness (Neder et al., 1999), or the amount of exercise training during the observation period (Emtner et al., 1998a). Basaran and coworkers' (2006) and Weisberger and coworkers' (2003) findings may, however, be questioned to some degree as the medication score of the control group was reduced as well.

Two uncontrolled studies reported substantial reductions in the amount of *systemic steroids* per day and number of days requiring systemic steroids (Engstrom et al., 1991; Tanizaki et al., 1984), another study only in those subjects with improved fitness (Neder et al., 1999), a further study found a significant reduction in the number of exacerbations requiring prescription of systemic steroids or antibiotics (Foglio et al., 1999) and another study reported that the majority of subjects in the intervention group reduced the use of inhaler and systemic steroids (King et al., 1989), without providing statistical analyses, however. A more recent RCT (Fanelli et al., 2007) found a tendency ( $p=0.07$ ) towards a larger reduction in ICS dose (-52%) in the intervention group compared to the control group (-23%).

Lastly, two studies assessed *medication intake* without specifying type and dose of medication. While one study (Huang, Veiga, Sila, Reed, & Hines, 1989) observed a significantly larger reduction in days requiring asthma medication in the intervention group (-62%) compared to the control group (-17%), a more recent uncontrolled study (Hildenbrand, Nordio, Freson, & Becker, 2010) found a non-significant decrease (-20%) in medication use per week after the exercise training intervention compared to baseline.

In summary, although clear evidence supporting a significant reduction in asthma medication with exercise training is still lacking, current data suggests the potential for positive effects.

At the least, several mechanisms could explain a reduction in asthma medications, e.g., a decrease in airway hyperresponsiveness (e.g., EIB severity) and a concomitant decrease in exertional dyspnea and asthma symptoms that are all major determinants of asthma control and corticosteroid prescription (GINA, 2012). This mechanism is supported by a study (Fanelli et al., 2007) showing that the shift towards a lower ICS dose was accompanied by a significant reduction in EIB severity and less asthma symptoms. It seems also plausible, that reduced airway hyperresponsiveness (e.g., EIB) after an exercise training intervention leads *per se* to a lower release of inflammatory mediators and therefore to a reduced need for steroids. However, none of the aforementioned studies measured inflammatory parameters. Also, a higher level of self-care and self-confidence towards disease and exercise after an exercise intervention could lead to a more "decided posture in relation to the disease", as suggested by Neder et al. (1999), and consequently to a minimization of the medication required for clinical control. However, more homogeneous and well-controlled studies are needed to provide evidence for mechanisms and outcome.

## **Effects of Exercise Training on Quality of Life and Asthma Symptoms**

QoL is a complex and multidimensional concept that is composed of factors including physical, psychological, emotional as well as social well-being. Patients' perception of

disease burden may differ from objective measures by clinicians and thus may provide complementary information about asthma severity and control (Reddel et al., 2009). Several cross-sectional studies showed that asthma severity and/or perceived asthma symptoms are major factors influencing QoL (Al-kalemji et al., 2013; Laforest et al., 2005; Moy et al., 2001; Pont, van der Molen, Denig, van der Werf, & Haaijer-Ruskamp, 2004). A large scale cross-sectional study with 12,111 participants additionally identified significant associations between QoL and modifiable determinants such as smoking status, physical activity, and body mass index. Physically inactive asthmatics had, in fact, a 2.4 times increased risk of judging their health as 'poor' or 'fair' compared to asthmatics with regular or vigorous physical activity and the risk of being limited in physical activities was 2.8-fold higher in physically inactive versus active asthmatics (Ford). Thus, it is conceivable that reducing asthma symptoms and eliminating behavioral risk factors has the potential to improve QoL in asthmatics.

Studies showed significant improvements after 8-20 weeks of swim or various types of endurance, strength and game-like training in children (Basaran et al., 2006; Fanelli et al., 2007; Fitch et al., 1976; Latorre-Roman et al., 2014; van Veldhoven et al., 2001; Weisgerber et al., 2008) and after 6-12 weeks of various types of endurance training with and without strength training in adults (Cambach, Chadwick-Straver, Wagenaar, van Keimpema, & Kemper, 1997; Fesharaki, Paknejad, & Kordi, 2010; Foglio et al., 1999; Goncalves et al., 2008; Mendes et al., 2010; Turner, Eastwood, Cook, & Jenkins, 2011).

In two studies (Dogra, Jamnik, & Baker, 2010; Moreira et al., 2008), improvements in asthma-related QoL did not differ significantly in the exercise training group from that in the control group while another two studies did not find any significant improvements (Hildenbrand et al., 2010; Miyamoto et al., 2014). In Moreira and coworkers' study (2008), however, the exercise-group showed improvements in all subunits (symptoms, physical activity, emotion) while the control-group improved in the physical activity domain only. In Dogra and coworkers' study (2010), on the other hand, clinically significant improvements were observed in 7 out of 12 subjects in the exercise group but in only 1 out of 12 controls. Asthmatics in three of these studies were already well-controlled, possibly leaving little room for further improvement as suggested by two further studies (Foglio et al., 1999; Mendes et al., 2010) where larger or clinically relevant improvements were associated with worse baseline levels of QoL compared to the non-improvers.

A few studies systematically assessed the presence of asthma symptoms apart from QoL. Most of these reported improvements in days without asthma symptoms (Goncalves et al., 2008; Mendes et al., 2011; Mendes et al., 2010) and in frequency (Dogra et al., 2010) or amount (Emtner et al., 1996) or quality of asthma symptoms (Basaran et al., 2006; Emtner et al., 1998b). Mendes et al., (2011) also observed significantly less asthma exacerbations and hospital visits compared to subjects in the control group.

The mechanisms, however, responsible for a reduced perception of asthma-symptoms and increased QoL are complex and not well established. A large, longitudinal cohort-study on women with asthma showed that the number of total exacerbations and urgent office visits was inversely related to the level of physical activity which suggests that the higher the level of physical activity, the lower the risk of exacerbation (Garcia-Aymerich, Varraso, Anto, & Camargo, 2009). Interestingly, this association was independent of asthma severity. One might therefore speculate that a reduction in asthma-symptoms might be more directly linked to physical exercise. However, the correlation between changes in asthma symptoms and

parameters of exercise tolerance is rather poor. For instance Mendes et al. (2010) observed only a weak correlation ( $r=0.47$ ) between changes in days without asthma symptoms and maximal oxygen consumption ( $\dot{V}O_{2,max}$ ), whereas others reported no significant correlation between QoL and exercise tolerance (i.e., 6-minute walking test and  $\dot{V}O_{2,max}$ ) (Basaran et al., 2006; Cambach et al., 1997; Fanelli et al., 2007; Foglio et al., 1999). Authors argue that changes in symptoms and/or QoL-scores were mostly independent of changes in physiological parameters which probably reflects the complex nature of pulmonary rehabilitation and the fact that QoL depends on more than exercise alone. This is to some extent underlined by Cochrane and Clark (1990) who demonstrated that asthma symptoms contribute to but are not the sole predictors of training-related improvements. Apart from a direct relationship, the effect of physical exercise training on improvements in QoL and asthma symptoms might also be partly mediated by the effect on airway hyperresponsiveness (Eichenberger et al., 2013) and/or on airway inflammation (Goncalves et al., 2008; Mendes et al., 2011).

One important factor that needs consideration is that asthma treatment according to pharmacotherapy guidelines is associated with higher QoL, especially in terms of symptoms and environmental exposure (Pont et al., 2004). Therefore, change in medical treatment during the intervention period is a potential bias when evaluating changes in QoL. Even though most of the recent studies investigating the effects of exercise interventions in asthma did not change controller medication throughout the study period, some studies report both, reductions in controller medication as well as improvements in measures of QoL (Basaran et al., 2006; Fanelli et al., 2007). The first thereby reported a decrease in ICS intake and a concomitant, significant increase in QoL in the exercise group. The latter study observed a more pronounced increase in QoL in the exercise training compared to the control group which points towards changes in medication explaining only part of the observed improvements in QoL. Clearly, more studies are needed to clarify the exact nature and mechanism of improvements in QoL and asthma symptoms as well as the role of exercise therein.

In conclusion, despite large heterogeneity in terms of QoL assessment, there is evidence to suggest that regular aerobic exercise improves parameters of QoL and reduces asthma symptoms.

## **Effects of Exercise Training on Physical Fitness in Asthmatics**

### **Oxygen Consumption and Performance**

First, we would like to state that the assumption asthmatics would have lower aerobic fitness in general compared to their healthy counterparts is lacking evidence (Freeman et al., 1989; Hallstrand et al., 2000; Robinson et al., 1992; Welsh et al., 2004).

Following exercise training interventions, the vast majority of studies observed significant increases in  $\dot{V}O_{2,max}$  (Afzelius-Frisk, Grimby, & Lindholm, 1977; Ahmaidi, Varray, Savy-Pacaux, & Prefant, 1993; Araki et al., 1991; Boyd et al., 2012; Bundgaard et al., 1982; Cochrane & Clark, 1990; Counil et al., 2003; Fanelli et al., 2007; Foglio et al., 1999;



Freeman et al., 1989; Goncalves et al., 2008; Hallstrand et al., 2000; Hildenbrand et al., 2010; King et al., 1989; Mendes et al., 2011; Mendes et al., 2010; Neder et al., 1999; Orenstein et al., 1985; Robinson et al., 1992; van Veldhoven et al., 2001; Varray, Mercier, & Prefaut, 1995; Varray, Mercier, Terral, & Prefaut, 1991; Zolaktaf et al., 2013) with similar maximal effort as judged by similar maximal heart rate achieved prior to and after the exercise training intervention (Afzelius-Frisk et al., 1977; Ahmaidi et al., 1993; Boyd et al., 2012; Cochrane & Clark, 1990; Fitch et al., 1986; Freeman et al., 1989; Graff-Lonnevig, Bevegard, Eriksson, Kraepelien, & Saltin, 1980; Holzer et al., 1984; King et al., 1989; Nickerson et al., 1983; Orenstein et al., 1985; Robinson et al., 1992).

Not surprisingly, subjects with the lowest fitness level at baseline were those that improved their  $\dot{V}O_{2,max}$  the most (Bonsignore et al., 2008; Mendes et al., 2010; Neder et al., 1999; van Veldhoven et al., 2001). In fact, Cochrane and Clark (1990) could demonstrate that approximately 88% of the variation observed in relative improvements in  $\dot{V}O_{2,max}$  could be explained by (1) the initial  $\dot{V}O_{2,max}$ -level, (2) the symptoms on training days and (3) the initial level of motivation. Interestingly, however, factors such as number of exercise sessions, pre-study lung function or daily variation in peak expiratory flow (PEF) did not significantly contribute to the prediction of the degree of improvement. In contrast, symptoms on training days could affect training progress since training intensity might need to be reduced or an entire training might be missed. A reduction in training intensity seems, in fact, to be more relevant, since the number of training sessions did not contribute to their model. In studies that did not find a significant increase in  $\dot{V}O_{2,max}$ , poor compliance to unsupervised exercise and poor adherence to training intensity was raised as an issue (Dogra et al., 2010; Fitch et al., 1986), also a low training intensity associated with the fun aspect of the training (Graff-Lonnevig et al., 1980) or relative to the level of subjects' fitness (Bonsignore et al., 2008), unspecific  $\dot{V}O_{2,max}$ -test modalities (cycling) compared to training (running) (Nickerson et al., 1983) or invalid estimations of  $\dot{V}O_{2,max}$  (Weisgerber et al., 2008) were raised as possible reasons for a lack in improvement in  $\dot{V}O_{2,max}$ .

At submaximal levels of exercise, most studies reported a significant increases in  $\dot{V}O_2$  when comparing at the anaerobic threshold (Bonsignore et al., 2008; Counil et al., 2003; Fanelli et al., 2007; Goncalves et al., 2008; Hallstrand et al., 2000; Schmidt et al., 1997), at the ventilatory threshold (Ahmaidi et al., 1993; Varray et al., 1995; Varray et al., 1991), at the respiratory compensation point (Goncalves et al., 2008), at the workload of the anaerobic threshold (Fanelli et al., 2007; King et al., 1989; Matsumoto et al., 1999; Schmidt et al., 1997) and at a heart rate of  $170 \text{ min}^{-1}$  (Basaran et al., 2006; Fitch et al., 1976). This is likely explained by concomitant increases of the workloads associated with these thresholds after training. Only one study (van Veldhoven et al., 2001) reported an increase in  $\dot{V}O_{2,max}$  without an increase in the anaerobic threshold, possibly due to methodological inadequacies, as stated by the authors.

Improved submaximal physiological changes are also seen in the generally reduced submaximal heart rate observed either at fixed workloads (Afzelius-Frisk et al., 1977; Orenstein et al., 1985; van Veldhoven et al., 2001), at 60% of maximal initial workload (Cambach et al., 1997), at various submaximal running velocities (Freeman et al., 1989) or during constant-load tests to assess EIB (Emtner et al., 1996; King et al., 1989). Accordingly, oxygen pulse, i.e., oxygen consumption per heartbeat, was significantly increased in all studies that assessed this parameter (Ahmaidi et al., 1993; Cochrane & Clark, 1990; Counil et

al., 2003; Fanelli et al., 2007; Goncalves et al., 2008; Neder et al., 1999; Orenstein et al., 1985; van Veldhoven et al., 2001; Varray et al., 1991).

Thus, measures of submaximal exercise performance such as distance walked in 6 min (Basaran et al., 2006; Cambach et al., 1997; Foglio et al., 1999; Latorre-Roman et al., 2014; Turner, Eastwood, et al., 2011), in 12 min (Emtner et al., 1998b; Emtner et al., 1996) or during a shuttle walk test (Miyamoto et al., 2014), distance run in 6 min (Schmidt et al., 1997; Scichilone et al., 2012), in 9 min (Silva et al., 2006) or in 12 min (Nickerson et al., 1983; Weisgerber et al., 2008), distance swum in 9 min (Fitch et al., 1976), time needed to run 3.2 km (Freeman et al., 1989), or to row 1000 and 2000 m (Scichilone et al., 2012) as well as time to exhaustion in a constant-load test when cycling at 75% of predetermined maximal workload (Cambach et al., 1997) or running at a given submaximal heart rate (van Veldhoven et al., 2001) all showed significant improvements with one exception only (Weisgerber et al., 2008).

## Ventilation and Breathing Pattern

During maximal exercise tests, an equal number of studies found a significantly increased (Afzelius-Frisk et al., 1977; Bonsignore et al., 2008; Cochrane & Clark, 1990; Graff-Lonnevig et al., 1980; van Veldhoven et al., 2001; Varray et al., 1991) or an unchanged (Afzelius-Frisk et al., 1977; Counil et al., 2003; Freeman et al., 1989; Hallstrand et al., 2000; Holzer et al., 1984; King et al., 1989; Nickerson et al., 1983)  $\dot{V}_{E,max}$  after the exercise training intervention. Of these, a subset of studies investigated concomitant changes in breathing pattern, i.e., changes in tidal volume ( $V_T$ ) and breathing frequency ( $f_B$ ) at maximal exercise. A significant increase in  $\dot{V}_{E,max}$  was mostly accompanied by an increase in  $V_{T,max}$  while  $f_{B,max}$  remained unchanged (Cochrane & Clark, 1990; Hallstrand et al., 2000; Varray et al., 1991) with only one exception (Afzelius-Frisk et al., 1977).

Considering the increase in  $\dot{V}O_{2,max}$ , an increased  $\dot{V}_{E,max}$  is expected unless  $\dot{V}_E$  becomes more efficient as seems to be the case in those studies that reported unchanged  $\dot{V}_{E,max}$  despite a higher workload. More efficient  $\dot{V}_E$  is also suggested by submaximal comparisons that report a lower ventilatory response at identical  $\dot{V}O_2$  (Cochrane & Clark, 1990; Hallstrand et al., 2000; Varray et al., 1995) or identical workload (Afzelius-Frisk et al., 1977) after training compared to before. This is consistent with the reported reduced slope of  $\dot{V}_E$  vs. workload (Robinson et al., 1992) after the exercise intervention with a larger change being associated with greater improvements in  $\dot{V}O_{2,max}$  and larger reductions in  $\dot{V}_E$  at higher workloads (Varray et al., 1995), suggesting an improved aerobic metabolism after training.

Changes in  $\dot{V}_E$  were likely related to a more efficient breathing pattern, i.e., one study (Hallstrand et al., 2000) reported the lower ventilatory response being related to a reduced  $f_B$  at unchanged  $V_T$  and a lower ventilatory equivalent for oxygen after the exercise intervention period while another (Varray et al., 1995) observed a higher  $V_T$  for a given ventilatory level, both suggesting an overall enhanced ventilatory efficiency due to improved alveolar ventilation and reduced air turbulences.

## Levels of Perceived Breathlessness / Dyspnea

Only a few studies assessed the level of perceived breathlessness (Borg score) (Afzelius-Frisk et al., 1977) or dyspnea (Borg scale) (Fanelli et al., 2007) or the level of a calculated dyspnea index (Cochrane & Clark, 1990; Hallstrand et al., 2000; Varray et al., 1995) at maximal exercise. Interestingly, despite significantly higher  $\dot{V}O_{2,max}$  and/or maximal workload, the scores achieved either remained unchanged after training (Afzelius-Frisk et al., 1977; Cochrane & Clark, 1990) or they were even lower (Fanelli et al., 2007; Hallstrand et al., 2000; Varray et al., 1995).

Accordingly, at submaximal exercise levels all but one study reported significantly decreased levels of perceived breathlessness (Borg scale) at various submaximal  $\dot{V}O_2$ -levels (Cochrane & Clark, 1990) or similar exercise intensity (Afzelius-Frisk et al., 1977; Foglio et al., 1999), significantly lower levels in the calculated dyspnea index at 75%  $\dot{V}O_{2,max}$  (Hallstrand et al., 2000) and at various submaximal  $\dot{V}O_2$ -levels (Varray et al., 1995). As the  $\dot{V}_E$ -level during incremental exercise was shown to be the best predictor of perceived dyspnea in asthmatics (Laveneziana et al., 2006), one potential mechanism for this reduction in dyspnea is, of course, the reduced ventilatory requirement at a given submaximal exercise intensity as present in most of these studies.

In conclusion, asthmatics respond and adapt to physical exercise training similar to healthy subjects as long as the underlying asthma is adequately controlled and stable.

## Physiological Adaptations to Inspiratory Muscle Training (IMT) in Asthmatics

IMT in asthmatics has mostly been performed by the use of an external device offering inspiratory pressure threshold loading (Lima et al., 2008; McConnell, Caine, Donovan, Toogood, & Miller, 1998; Sampaio, Jamami, Pires, Silva, & Costa, 2002; Turner, Mickleborough, et al., 2011; Weiner, Azgad, Ganam, & Weiner, 1992; Weiner, Berar-Yanay, Davidovich, Magadle, & Weiner, 2000; Weiner, Magadle, Beckerman, & Berar-Yanay, 2002; Weiner, Magadle, Massarwa, Beckerman, & Berar-Yanay, 2002). This requires individuals to produce a negative intrathoracic pressure sufficient to overcome a threshold load and to thereby initiate inspiration (McConnell & Romer, 2004). This threshold was usually set in relation to MIP (range 15-80% MIP) and re-evaluated during the intervention period to ensure a proper progression in training intensity. Only one study using an external device specifically mentioned the exact procedure of inspiration, namely, that the inspiratory maneuver was initiated from residual volume to total lung capacity with breaks in between to minimize hyperventilation-induced hypocapnia (Turner, Mickleborough, et al., 2011). Apart from inspiratory threshold loading a resistive breathing method was used. This included inspiring and expiring maximally through a tube 10 cm in length and 1 cm in diameter while - at the same time - stabilizing weight on the abdominal cavity (Shaw & Shaw, 2011a; Shaw & Shaw, 2011b; Shaw, Shaw, & Brown, 2010). Progression of training intensity was ensured by increasing this weight (weeks 1-4: 2.5 kg; weeks 5-8: 5 kg). A substantial limitation of this latter training regimen is that the inspiratory training load is not only a function of the

diameter of the orifice in the tube but also of flow (McConnell & Romer, 2004) which is not monitored if breathing pattern is not reinforced.

## **Effects of IMT on Pulmonary Function and Respiratory Muscle Strength in Asthmatics**

IMT was consistently shown to increase MIP (Lima et al., 2008; McConnell et al., 1998; Sampaio et al., 2002; Turner, Mickleborough, et al., 2011; Weiner et al., 1992; Weiner et al., 2000; Weiner, Magadle, Beckerman, et al., 2002; Weiner, Magadle, Massarwa, et al., 2002) and possibly MEP can also be increased although only few studies investigated this variable (Lima et al., 2008; Sampaio et al., 2002). However, whether IMT improves parameters of lung function is still controversial. While several studies reported significant increases in FEV<sub>1</sub> and FVC after threshold loading (Weiner et al., 1992) and resistive breathing (Shaw & Shaw, 2011a; Shaw & Shaw, 2011b; Shaw et al., 2010), several others did not (McConnell et al., 1998; Turner, Mickleborough, et al., 2011; Weiner, Magadle, Beckerman, et al., 2002) or did not report post-training data (Weiner et al., 2000). The same applies to PEF which significantly increased according to some reports using threshold loading (Lima et al., 2008; McConnell et al., 1998) or resistive breathing (Shaw & Shaw, 2011a; Shaw & Shaw, 2011b) but not according to others (Turner, Mickleborough, et al., 2011). The discrepancies between studies might be explained by differences in IMT training duration and/or, more importantly, by the inclusion of individuals with different asthma severity (uncontrolled or moderate-severe asthma versus mild-moderate asthma). The increase in pulmonary function was thought to be secondary to increases in inspiratory muscle strength (evident by increases in MIP). Stronger inspiratory muscles work more efficient against elastic recoil forces of the chest wall and the lung, and thus more air volume can be inhaled (Weiner et al., 1992).

Two studies reported MVV before and after 8 weeks of resistive breathing (Shaw & Shaw, 2011a; Shaw & Shaw, 2011b) and found no significant change. This is in accordance with training-specificity of respiratory muscle training, shown by Leith and Bradley (1976).

## **Effects of IMT on Asthma Symptoms and Use of Asthma Medication**

One study (Weiner et al., 1992) showed fewer asthma symptoms including nighttime asthma, morning tightness, daytime asthma, cough, number of hospital days and sick-leave days due to asthma following IMT training, changes that were not evident in the control group. Another study in children with uncontrolled asthma (Lima et al., 2008) found fewer diurnal and nocturnal symptoms, blunted impairment in performing activities of daily living and fewer asthma attacks. However hospitalization and emergency room treatment were not significantly different compared to the control group. In both of these studies as well as in others (Weiner et al., 2000; Weiner, Magadle, Beckerman, et al., 2002; Weiner, Magadle, Massarwa, et al., 2002), the amount of mean daily puffs of  $\beta_2$ -agonists decreased over the course of the IMT intervention period, a change also not evident in the control group.

Interestingly, one study showed a highly significant positive correlation between improvements in MIP and decreases in need for reliever medication (Weiner, Magadle, Beckerman, et al., 2002) possibly mediated by reduced perception of dyspnea. These authors had also reported (Weiner et al., 1992) that 5 out of 6 patients were able to stop oral steroid intake without any clinical deterioration after IMT while only 1 of 7 could do so in the control group. Both findings are in accordance with reports of the same research group showing that subjects with high  $\beta_2$ -agonists consumption (i.e., >1 puff/d) perceive a distinctly higher level of dyspnea at any given imposed airway resistance compared to low consumers (i.e.,  $\leq 1$  puff/d) (Weiner, Magadle, Beckerman, et al., 2002).

## Effects of IMT on Physical Performance in Asthmatics

Only little data is available on changes in physical performance after IMT in asthmatics. In fact, only one study assessed time to exhaustion during a cycling test at 70% of pre-determined maximal power output (Turner, Mickleborough, et al., 2011) and found a significant 22%-increase in asthmatics with no change observed in the control group. In these subjects,  $\dot{V}O_2$  was significantly (6-12%) lower after IMT at various time points as well as at exhaustion compared to baseline while ventilation and breathing pattern remained unchanged and end-expiratory lung volume (EELV) only decreased slightly. The authors argue that the decrease in EELV might point towards a reduction in hyperinflation, which is seen in some asthmatics and can significantly contribute to improved exercise capacity (Kosmas et al., 2004). A reduction in hyperinflation may be associated with a lower level of inspiratory muscle work and thus might explain, in part, the reduced  $\dot{V}O_2$  during exercise. In this study, the lower exercise-induced decrease in MIP after IMT (suggesting reduced development of respiratory muscle fatigue after training) may indeed indicate that inspiratory muscle work during exercise was lower after training. The consistently reported reduction in the perception of dyspnea after IMT during incremental inspiratory threshold loading (Weiner et al., 1992; Weiner et al., 2000; Weiner, Magadle, Beckerman, et al., 2002; Weiner, Magadle, Massarwa, et al., 2002), during maximal incremental cycling exercise (McConnell et al., 1998) as well as during constant-load cycling exercise to exhaustion (Turner, Mickleborough, et al., 2011) is also likely to contribute to increased performance. In summary, IMT may be a promising therapy option or adjunct to exercise training to improve subjective and objective limitations in physical performance in asthmatic subjects.

## Conclusion

The effects of whole-body exercise training on major intrinsic and extrinsic factors associated with asthma are summarized in Figure 1.

Despite transient negative aspects of acute whole-body exercise in susceptible subjects, e.g., release of pro-inflammatory mediators, decline in pulmonary function eventually leading to exercise-induced bronchoconstriction, dyspnea and need for prophylactic and/or reliever medication, there is a high degree of agreement that most stable and well-controlled

asthmatics show cardio-pulmonary and muscular adaptations and a concomitant increase in parameters of physical fitness similar to the healthy after regular physical exercise training.

Similarly, pulmonary function, medication intake and subjective parameters such as asthma symptoms and quality of life show - despite a high degree of heterogeneity of the evaluated parameters - slight improvements. Due to the lack of robust and well-controlled studies, doubt still exists on the effects exercise training on intrinsic pathological changes such as improvements in airway inflammation and airway hyperresponsiveness.

In summary, while well-controlled studies investigating asthma-specific pathophysiological changes with physical training are still urgently needed, people with stable asthma should be encouraged to exercise on a regular basis to increase cardio-respiratory and muscular fitness not only for improving asthma symptoms and quality of life, and possibly reducing asthma medication but also since improved physical fitness is well known to be associated with many other, positive health-related effects.

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