Asthma

4

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Abstract

Extensive evidence exists on the beneficial effect of training and rehabilitation programs in asthma. On the other hand, intense and repeated physical exercise may trigger transient airway narrowing, defined exercise-induced bronchoconstriction (EIB). The prevalence of EIB has been reported to be up to 90% in asthmatic patients, reflecting the level of disease control. However, EIB may develop even in subjects without clinical asthma, particularly in athletes, children and subjects with atopy or rhinitis and following respiratory infections. The occurrence of EIB, however, can be optimally managed and should not prevent from an adequate practice of physical activity.

4.1 Introduction

Regular physical activity is strongly recommended by worldwide healthcare systems and evidence-based guidelines as one of the most effective tools to prevent chronic diseases and maintain good health [1]. Indeed, extensive evidence exists on the beneficial effect of training and rehabilitation programs in respiratory diseases, particularly in asthma [2]. It has been in fact shown that physical activity improves symptoms, quality of life, exercise capacity and pulmonary function, as well as reduces airway inflammation and responsiveness in asthmatic subjects [3–5].

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On the other hand, intense physical exercise may trigger airway narrowing by imposing high demands on the respiratory system, requiring subjects to ventilate primarily through the mouth and bypass the nasal filter, with a subsequent increased pulmonary exposure to inhalant allergens, pollutants, irritants and adverse (i.e. cold, dry) environmental conditions [6]. Furthermore, intense physical training may induce a transient status of immune downregulation, clinically associated with an increased prevalence of atopy and viral upper respiratory tract infections (URTI)—see Chap. 9—both representing relevant risk factors for the onset and worsening of asthma [7, 8].

The transient airway narrowing that occurs as a result of exercise is defined exercise-induced bronchoconstriction (EIB) [6]. Already in the first century A.D., Aretaeus the Cappadocian described respiratory symptoms induced by physical exercise: "if from running, gymnastics, or any other work, breathing becomes difficult, it is called asthma" [9]. However, a scientific objective interest for this phenomenon can be dated back to 1960, when Jones and co-workers focused on the physiologic response to exercise in asthmatic children and named the airway obstruction after an exercise challenge "exercise-induced asthma" (EIA) [10]. Subsequent studies defined the different patterns of response to exercise in asthmatic patients, as well as the influence of antiasthmatic drugs on EIA [11, 12]. Although exercise may trigger bronchial obstruction and respiratory symptoms in almost all asthmatic patients, independently from the underlying causes and mechanisms of asthma [13], some authors consider EIA a distinct phenotype of asthma [14]. However, the concept that exercise may induce bronchial obstruction only in asthmatic patients is at present under debate [15]. In fact, despite the physiologic response to exercise usually results in slight bronchodilation, EIB may develop even in subjects without clinical asthma [9]. To bring some clarity to this controversial issue, a practice parameter, jointly developed by the American Academy/College of Allergy Asthma and Immunology (AAAAI/ACAAI) [16], recommended to abandon the term EIA, and more recently an American Thoracic Society Clinical Practice Guideline [6] suggested to name EIB with asthma (EIBa), the occurrence of bronchial obstruction after exercise in asthmatic patients, and EIB without asthma (EIBwa), the occurrence of exercise-induced bronchoconstriction in subjects without other symptoms and signs of clinical asthma.

4.2 Clinical Features

EIB typically develops within 15 min following at least 5–8 min of high-intensity aerobic training (>85% of maximal voluntary ventilation), although it can also occur during exercise, and spontaneously resolves within 60 min [17]. After an episode of EIB, there is often a refractory period of about 1–3 h during which, if exercise is repeated, the bronchoconstriction is less accentuated [12]. Most common symptoms include cough, dyspnoea, breathlessness, wheezing and chest tightness [6].

4.3 Prevalence

The prevalence of EIB varies from 5 to 20% in the general population and has been reported to be up to 90% in asthmatic subjects, reflecting the level of disease control, with EIBa occurring more frequently in more severe and uncontrolled asthmatic patients [13]. EIBwa is also particularly frequent in athletes [18], children [19, 20] and subjects with rhinitis [21] and following respiratory infections [22].

In particular, several studies called attention to an increased occurrence of asthma and EIB in athletes, with prevalence rates widely ranging from 3.7 to 54.8% (Table 4.1) depending on the study population and the criteria used for diagnosis (i.e. questionnaires, anti-doping records, baseline spirometry, bronchial provocation challenges). Independently from these potential confounders, studies performed in comparable samples and with similar diagnostic methodologies seem to indicate that the asthma incidence is on the increase: from 9.7% in 1976 to 11.2% in 1984, 16.7% in 1996 and 21.0% in 2000 in the US Olympic delegation [23–25]. More recently, a 12-year study including four cross-sectional surveys performed between 2000 and 2012, before Summer and Winter Olympics, showed that the prevalence of asthma in 659 Italian Olympic athletes was 14.7%, with a significant increase from 2000 (11.3%) to 2008 (17.2%) [26].

With regard to a gender effect [27], a study recently performed in 187 elite athletes (101 swimmers and 86 tennis players) showed a higher prevalence of asthma symptoms in females, although there was no significant difference in the prevalence of EIB when measured through a mannitol and a sport-specific challenge [28]. Norqvist et al. also reported that, compared to males, elite female athletes had a higher prevalence of asthma, respiratory symptoms, use of medications and healthcare services [29].

It has been also extensively reported that asthma and allergic rhinitis frequently coexist, with symptoms of rhinitis being reported in 80–90% of asthma patients and asthma symptoms reported in 20–40% of patients with allergic rhinitis [21]. Prospective studies also suggest that rhinitis frequently precedes the development of asthma [30] and that many patients with rhinitis alone show non-specific bronchial hyperresponsiveness after exercise or methacholine, this being a risk factor for developing asthma [31]. Furthermore, it has been proven that the severity of allergic rhinitis and asthma are related and that proper management of allergic rhinitis improves asthma control [21]. Additionally, exercise can be a trigger for rhinitis, especially in outdoor sports and even greater with cold dry air exposure in winter sports, e.g. the “skier’s nose” [32]. On the basis of all the above, the ARIA recommendation [21] to screen every subject with rhinitis for asthma should be also extended to athletes [33].

Despite extensive epidemiological data, EIB progression in athletes has not been yet fully studied. However, in a 5-year prospective study, subjects who stopped training experienced an attenuation or in some circumstances disappearance of

Table 4.1 Prevalence of asthma and EIB among athletes

Study population (n)	Prevalence	Methodology for diagnosis	Reference
US College athletes (80)	42.5%	Questionnaire, exercise challenge	Burnett DM, 2016
US 1998 Olympic team (170)	23.0%	Spirometry, exercise challenge	Wilber RL, 2000
US 1998 Olympic team (196)	21.9%	Questionnaire	Weiler JM, 2000
Summer athletes (162)	22.8%	Questionnaire, spirometry, histamine challenge	Helenius IJ, 1998
Australian 2000 Olympic team (214)	21.0%	Questionnaire	Katelaris CH, 2000
US 1996 Olympic team (699)	16.7%	Questionnaire	Weiler JM, 1998
Italian Olympicathletes (659)	14.7%	Questionnaires, lung function tests	Bonini M, 2015
Polish 2008 Olympic team (222)	11.3%	Questionnaire, spirometry, methacholine challenge	Kurowski M, 2016
Italian 2000 pre-Olympic team (265)	10.9%	Questionnaire, spirometry	Lapucci G, 2003
Australian 1976 Olympic team (185)	9.7%	Physical examination	Fitch KD, 1984
Australian 1980 Olympic team (106)	8.5%	Physical examination	Fitch KD, 1984
Spanish 1982 Olympic team (495)	4.4%	Questionnaire	Drobnic F, 1994
US 1984 Olympic team (597)	4.3%	Questionnaire, exercise challenge	Voy RO, 1984
Swiss athletes (2060)	3.7%	Questionnaire	Helbling A, 1990
Cross-country skiers (42)	54.8%	Questionnaire, spirometry, methacholine challenge	Larsson K, 1993
Swedish and Norwegian cross-country skiers (171)	42.0%/12.0%	Questionnaire, spirometry, methacholine challenge	Sue-Chu M, 1996
Ice hockey players (88)	21.5%	Questionnaire, spirometry, histamine challenge	Lumme A, 2003
Ice hockey players (50)	11.5%	Questionnaire, spirometry, methacholine and exercise challenge	Leuppi JD, 1998
Crosscountry skiers (20)	10.0%	Exercise challenge	Pohjantähti H, 2005
Swimmers (90)	39.0%	EVH challenge	Bougault V, 2010
US swimmers (738)	13.4%	Questionnaire	Potts J, 1996
Marathon runners (208)	32.0%	Questionnaire	Robson-Ansley P, 2012
Finnish runners (103)	15.5%	Questionnaire	Tikkanen H, 1994
US track and field (73)	15.1%	Exercise challenge	Schoene RB, 1997
Figure skaters (124)	35.0%	Exercise challenge	Mannix ET, 1996
US football players (156)	11.5%	Questionnaire, methacholine challenge	Weiler JM, 1986

Blue = various sports; green = winter sports; purple = swimming; orange = track and field; yellow = others

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EIB, whereas bronchial responsiveness, exercise-induced respiratory symptoms and eosinophilic airway inflammation increased among those who continued strenuous physical exercise, regardless of the pharmacological treatment strategies [34]. Put into context, ongoing intense training therefore appears to be a causative, and not just a concomitant, factor of airway inflammation and narrowing.

4.4 Pathogenesis

The increase in airways osmolarity due to respiratory water loss and the vasodilation associated with airways rewarming have been commonly reported to be the major determinants of EIB (osmotic and thermal theories) [35, 36]. However, as with the current approach in asthma phenotypes, different endotypes (i.e. disease subtypes specifically defined by functional or pathological molecular mechanisms and/or treatment response) of EIB have been recently reported (Fig. 4.1) [37]. Intense physical training may induce a transient status of immune downregulation with a shift towards a relatively prevalent T2-high response, clinically associated with an increased prevalence of atopy [8, 26]. However, despite in a large proportion of EIB subjects the occurrence of bronchial obstruction following exercise is associated with allergic diseases [26] and markers of a T2-high response [38], EIB is also present in subjects with no evidence of atopic sensitisation. In such non-T2-high variants of EIB, the bronchial epithelial damage directly caused by physical activity has been suggested as a relevant pathogenic mechanism [37]. A direct injury of the bronchial epithelium might also be caused by viral upper respiratory tract infections, which are reported to occur more frequently in athletes [39]. Inflammatory mediators released by the damaged epithelium have been found both in sputum (i.e. interleukin-8) [40] and in serum (i.e. nerve growth factor) [41] and seem to be associated with a neutrophilic or mixed neutrophilic/eosinophilic inflammatory response. Furthermore, the evidence that CC16 proteins, secreted by club cells in the distal bronchioles to protect the respiratory tract against oxidative stress and inflammation, are increased in urine and serum following an exercise challenge

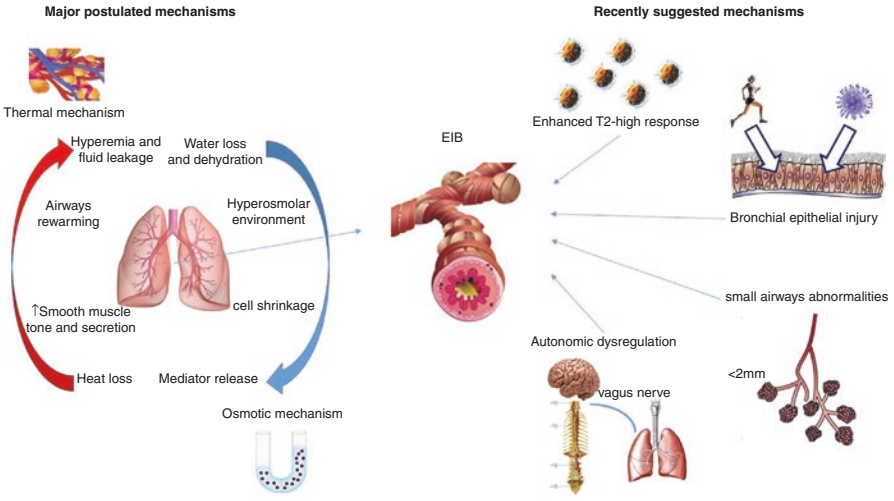

Fig. 4.1 Pathophysiological mechanisms of exercise-induced bronchoconstriction (EIB). Reproduced with permission of the © ERS 2018. ERJ Open Research Jan 2018, 4 (1) 00010–2018. https://doi.org/10.1183/23120541.00010-2018

[42] has prompted renewed and increasing interest in the role of small airways in EIB. Notably, small-airway abnormalities have been related to the onset and severity of asthma and may occur even in the absence of a response in the large airways [43]. In addition, an alternative noninflammatory mechanism, autonomic dysregulation with an enhanced parasympathetic response, measured by both pupillometry and heart rate variability, has been shown to significantly relate to EIB [44].

4.5 Diagnosis

A careful history taking and physical examination is always recommended. The use of questionnaires specifically developed and validated for screening atopy and allergic diseases in athletes may represent an additional useful and easy-to-use diagnostic tool [45]. However, research performed over the past years has consistently revealed a poor relationship between the presence of "asthma-like" symptoms and objective evidence of EIB [46].

Furthermore, baseline spirometry appears to be poorly predictive of EIB in athletes, often being within the normal ranges even in the presence of disease [47]. The assessment of small airways, whose involvement has been reported in EIB [48], through ad hoc diagnostic investigations such as impulse oscillometry, multibreath nitrogen washout and fraction exhaled nitric oxide (FeNO) at multi-flows, might provide further useful information, particularly in the early and mild forms [43]. However, in order to establish a secure diagnosis of EIB, it is strongly recommended to perform objective bronchoprovocative tests (BPTs) to document dynamic changes in airway function.

Measuring the change in the forced expiratory volume in 1 s (FEV1) before and after a standardized exercise challenge test (ECT), in the laboratory or in the field, represents the most intuitive and commonly adopted approach to diagnose EIB [49]. An ECT should be performed in subjects with EIBa only when their baseline FEV1 is ≥70% of normal. A ≥ 10% fall in FEV1 at any two consecutive time points (1, 3, 5, 10, 15, 20, 25, 30, 60, 90 min.) after 6 to 8 min of treadmill or cycloergometer exercise in laboratory-specific ambient conditions (20–25 °C; relative humidity <50%) is considered diagnostic of EIB. The intensity of exercise should be enough to reach in the first 2–3 min. 40–60% of the predicted maximum voluntary ventilation (estimated as baseline FEV1 × 35) or 80–90% of the predicted maximal heart rate (calculated by 220—age). Indeed, it has been reported that the mean fall in FEV1 after an exercise challenge is more than doubled after achieving 95% of HR max, compared to 85% [50]. Sports-specific challenges in the field may be also used, although these are more difficult to standardize, limiting their application.

Moreover, other BPTs can be adopted as surrogate diagnostic tools for EIB. Direct BPTs (i.e. methacholine provocation) are accurate to document bronchial hyperreactivity in EIBa, while indirect tests, such as eucapnic voluntary hyperpnea (EVH), mannitol and saline hyperosmolar challenges, better reproduce the effects of exercise on the airways and are therefore more accurate to diagnose EIBwa. EVH is often preferred in highly trained athletes, where standard criteria for ECT may fail to

Table 4.2 Thresholds set by the International Olympic Committee (IOC) to document EIB through the different bronchial provocation tests (BPTs)

Diagnostic procedure	Diagnostic criteria
Exercise challenge	↓ FEV1 ≥ 10%
Methacholine challenge	↓ FEV1 ≥ 20% with a: PC20 ≤ 4 mg/mL (for subjects not taking ICS) or PC20 ≤ 16 mg/mL (for subjects taking ICS for at least 1 month)
Eucapnic voluntary hyperpnea (EVH)	↓ FEV1 ≥ 10%
Hyperosmolar tests (mannitol, saline)	↓FEV1 ≥ 15%

reproduce the bronchoprovocative stimulus experienced while practising their own sport disciplines [51]. However, correlations between ECT and other indirect BPTs are at present arguable. Thresholds set by the International Olympic Committee (IOC) for a positive response to the different BPTs are reported in Table 4.2.

The differential diagnosis of EIB should take into account physiologic limitations; anxiety; exercise-induced laryngeal dysfunctions, hyperventilation and hypoxemia; dyspnoea on exertion in obese or poorly fit individuals; shortness of breath with exercise due to lung diseases other than asthma and cardiac diseases; anaemia; and myopathies [6]. In particular, vocal cord dysfunction (VCD) is increasingly recognized as a condition that may mimic EIB. However, in VCD, the inspiratory stridor during exercise usually resolves within 5 min representing the major differential sign, associated with negative BPT result and poor response to antiasthmatic drugs. Vocal cord dysfunction may also coexist with EIB. If pruritus, urticaria or systemic reactions are associated with symptoms of EIB, the diagnosis of exercise-induced urticaria or anaphylaxis should be at last considered [52].

4.6 Management

Treatment of both EIBa and EIBwa is essentially based on reversing bronchial obstruction by using short-acting beta-2 agonists [13].

4.6.1 Non-pharmacological Prevention

Similar measures can be adopted in both EIBa and EIBwa. These include, whenever possible, avoiding exercise in an at-risk air environment because of temperature, humidity, pollutants and specific allergens in sensitized subjects [16]. Education about self-management is essential and should include advice about environmental measures, inhaler technique and the use of an action plans, in addition to regular follow-up [13]. Progressive warming-up and cooling-down periods are constantly

suggested [53]. Some athletes may also take advantage of the refractory period following bronchial obstruction deliberately induced by hyperventilation or by an intense exercise challenge. The use of face masks to warm and humidify the air has been reported to provide benefits, especially in winter athletes [54]. There is at last some evidence that weight loss and dietary factors, such as vitamin D supplementation, may be helpful in reducing the risk and severity of EIB [55, 56]. The potential occurrence of EIB should not prevent subjects from an adequate practice of physical exercise, which has been proven not to be associated with an increased risk of asthma developing or worsening [4], and should instead represent part of their treatment.

4.6.2 Pharmacological Prevention

Because EIBa is a sign of poor asthma control, prevention essentially consists of following international guidelines to avoid symptoms and reduce the risk of exacerbations [13]. Multiple therapeutic options seem also appropriate to prevent EIBwa, although usually they do not completely avoid the occurrence of bronchoconstriction, but rather attenuate it or shift the dose-response relationship, so that some submaximal efforts become tolerated.

Regular use of inhaled corticosteroid (ICS) represents a key strategy for controlling asthma and therefore is a recommended treatment to prevent EIBa [57]. The prophylactic administration of ICS has been also suggested in EIBwa, particularly if physical activity is performed regularly (>3 times per week), representing a repetitive stimulus for the onset of bronchoconstriction [16]. However, the use of ICS in the prevention of EIBwa may be controversial. In fact this pharmacological strategy is at present not supported by ad hoc designed clinical trials, and response to treatment may be impaired in subjects with underlying non-eosinophilic inflammatory pattern.

Beta-2 adrenergic drugs, both short- and long-acting (SABA and LABA), when given in a single inhaled dose or with intermittent administration before exercise, are the most effective drugs to prevent both EIBa and EIBwa [58], providing complete protection against exercise (FEV1 fall <10%) in approx. 70% of subjects [59]. The effect usually lasts 2 to 4 h for SABA and up to 12 h for LABA. Heterogeneity observed in the efficacy of beta-2 adrenergic agents to prevent EIB is not dependent on the type of molecule used, but rather on the population sample studied, with more variable effects reported in children [59]. However, the chronic use of SABA and LABA often results in a reduction of the duration and/or magnitude of protection against EIB with cross-reacting tolerance to other beta-2 agonists [59, 60]. This impaired efficacy has been shown to be predicted by baseline levels of FeNO [61]. Salpeter and co-authors reported that tolerance to beta-2 agonists is only partially prevented by concomitant use of ICS [61]. Furthermore, daily use of SABA and LABA may result even in a worsening of EIB [62] and expose subjects to an increased risk of cardiovascular side effects and death [63, 64]. Therefore, SABA and LABA should be used with caution on a regular basis to prevent EIB. LABA

administration should be also always avoided without concomitant use of ICS according to the US Food and Drug Administration (FDA) warning.

Mast cell stabilizers, disodium cromoglycate and nedocromil sodium, attenuate both EIBa and EIBwa when inhaled shortly before exercise but have a short duration of action [65].

Leukotriene antagonists (i.e. montelukast) have been reported to be effective in preventing EIBa. However, protection occurs in approximately 50% of subjects and may not be complete [66].

Ipratropium bromide prevents EIBa, although this effect is not consistent among patients and may be variable in the same patient [67]. Whether subjects with EIBwa or with a prevalent autonomic imbalance represent an EIB phenotype more responsive to anticholinergic agents represents an interesting hypothesis, still waiting for further experimental testing [68].

Calcium channel blockers, beta-adrenergic receptor antagonists, inhaled furosemide, heparin and hyaluronic acid have been studied to prevent EIB with inconsistent results.

Special precautions must be taken, at last, with respect to the World Anti-Doping Agency (WADA) rules on the use of EIB medications in competitive athletes—see Chap. 13.

4.7 Tips and Pitfalls

The intensity, duration and type of training have been associated with the occurrence of bronchial symptoms, airway hyperresponsiveness and asthma in elite athletes (Table 4.3).

Asthma is most commonly found in athletes performing endurance activities, such as long-distance running, cycling, triathlon and pentathlon. The high prevalence of EIB among endurance athletes has been mainly attributed to an increased minute ventilation through the mouth (bypassing the nasal filter) and exposure to allergens and pollutants. In major national and international competitions, local pollen counts (i.e. www.polleninfo.org) and air quality forecasts should be therefore always made available in advance to athletes, their coaches and medical teams.

Environmental factors (i.e. cold and dry air) also play a relevant role for athletes practising winter sports.

Swimming has been long considered a safe and recommended sport activity for subjects with asthma due to the inhalation of humid air; however, despite conflicting data, an increased risk of EIB with swimming and pool attendance has been reported [34, 69]. These findings are thought to be the result of repeated hyperventilation challenges together with the exposure to chlorine-based derivatives, commonly used to disinfect swimming pools, such as trichloramine. This hypothesis is further supported by studies on occupational asthma in swimming pool workers and lifeguards and by studies comparing exposures to non-chlorinated pools (copper-silver pools) vs. chlorinated pools.

Table 4.3 Sport disciplines and risk of exercise-induced bronchoconstriction (EIB)

Low-risk sports	Medium-risk sports	High-risk sports
All sports where the exercise lasts <5–8 min	Team sports where continuous exercise rarely lasts more than 5–8 min	All sports where the exercise lasts >5–8 min and/or is performed in special environments (i.e. dry/cold air, chlorinated pools)
Track and field: • Sprint (100, 200, and 400 m) • Middle distance (800 and 1500 m) • Hurdles (100, 110, 400 m) • Jumps • Throws	Soccer Rugby American football Basketball Volleyball Handball Baseball Cricket Field hockey	Track and field: • Long distance (5000 and 10,000 m) • 3000 m steeplechase • Walks (20 and 50 km) • Marathon
		Cycling
Tennis		Cross-country skiing
Fencing		Downhill skiing
Gymnastics		Ice hockey
Boxing		Ice skating
Golf		High-altitude sports
Weightlifting		Triathlon
Body building		Pentathlon
Martial arts		Swimming
		Water polo

It is of interest to report that when the risk factors "type of sport" and "atopy" are combined in a logistic regression model, the relative risk of asthma is considerably high: 25-fold in atopic speed and power athletes, 42-fold in atopic long-distance runners and 97-fold in atopic swimmers compared with non-atopic control subjects [70].

No clear classification of EIB endotypes has yet been adopted in clinical practice, and the distinction between T2-high and non-T2-high variants is currently made only by exclusion of a T2-high signature. Therefore, the lack of specific functional and inflammatory biomarkers to classify T2-low EIB subjects currently prevents clear identification of these endotypes and, therefore, an adequate design of clinical research trials. Proper endotyping of EIB would also have extremely relevant clinical translational impact, by significantly contributing to improved disease assessment and management. In fact, although prevention and treatment of EIB is mainly based on the effective use of short- and long-acting β2-agonists, high heterogeneity in individual therapeutic responses and the occurrence of tolerance and side effects have been observed, suggesting the existence of subpopulations requiring an endotype-driven approach to optimize therapy. Moreover, while several targeted therapies are available or under development for a "precision medicine" in T2-high asthma, no tailored strategies are currently available for the non-T2-high forms, in which corticosteroids have shown to be poorly effective. This could be also of relevance in professional athletes in view of the WADA regulations.

4.8 Conclusions

Although regular physical activity is strongly recommended for a proper prevention and management of asthma, evidence has been accumulating that intense and repeated exercise is associated with a higher prevalence of both EIBa and EIBwa. This is particularly true for endurance, winter sports and swimming. Furthermore, in athletes, EIB seems to be only partly reversible, representing exercise itself a causative factor of airway inflammation and symptoms. However, it is reassuring that, when properly diagnosed and optimally treated, athletes with EIB are able to participate on the highest level with their peers [71] with even more chances to succeed and win medals than others in the Olympic Games and other major international competitions [72]. Further research is at last desirable in order to fully address the unmet needs outlined above and to allow the vast population of subjects undertaking physical activity to fully profit from the very beneficial effects of exercise, without incurring health risks or affecting their performance and quality of life.

Key Points

- Exercise-induced bronchoconstriction (EIB) is defined as the transient airway narrowing that occurs as a result of exercise.
- Current guidelines recommend to distinguish EIB with underlying clinical asthma (EIBa) from the occurrence of exercise-induced bronchial obstruction in subjects without other symptoms and signs of asthma (EIBwa).
- The intensity, duration and type of training have been associated with the occurrence of EIB with higher prevalence rates in endurance disciplines, winter sports and swimming.
- When properly managed, EIB does not restrict exercise performance and does not prevent competition at elite level.

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