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Non Pharmacological Strategies to Manage Exercise Induced Bronchoconstriction

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SYNOPSIS (100 words)

Pharmacological management of exercise induced bronchoconstriction (EIB) is the mainstay of preventative therapy. However, there are some non-pharmacological interventions that may assist the management of EIB. In this review we will discuss these non-pharmacological interventions and how they may be applied to patients and athletes with EIB.

KEY WORDS (4-8):

Warm-Up, Face Mask, Asthma, Pollution, Avoidance, Athletes, Nutrition, Training

KEY POINTS:

- There is emerging evidence that non-pharmacological strategies can be used to supplement traditional therapy to reduce exercise-induced bronchoconstriction (EIB) severity and lessen respiratory symptoms associated with exercise
- Most investigations into non-pharmacological have included non-athletes, extrapolating towards athletes should be done with caution and studies in athletes with EIB are encouraged.
- There is currently insufficient evidence to support the use of any non-pharmacological EIB treatment strategy in the absence of regular pharmaceutical therapy for EIB.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is an asthma-related condition, which occurs during or following exercise as a result of large volumes of 'unconditioned air' entering the lower airways to meet the increased ventilatory demands of exercise[1,2]. In susceptible individuals, EIB arises via multiple mechanisms that may involve dehydration of airway surface liquid, mucosal cooling and epithelial damage (ref to pathophysiology paper in series), which induces an airway inflammatory response (involving histamine, neuropeptides, leukotrienes and prostaglandins) with resultant airway smooth muscle constriction[3]. Management of EIB in athletes is almost exclusively based around pharmacological therapies (ref to pharmacological paper in series), such as glucocorticoids and β_2-Agonists[1,2]. Although clinical data on non-pharmacological therapies has been equivocal, there is emerging evidence that non-pharmacological strategies could be used to supplement traditional therapy to reduce EIB severity and lessen exercise respiratory symptoms (table 1). This paper reviews the evidence and provides recommendations for the use of non-pharmacological strategies in the management of EIB.

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Table 1. Non-pharmacological strategies to manage EIB

Strategy	Intervention	Potential effect	Evidence level	Pitfalls	References
Pre-exercise warm up	Repetitive 30-s bouts close to VO_{2max}/HR_{max}	Reduces post-exercise fall in FEV1	Good	May accumulate peripheral fatigue prior to exertion	5
Face masks	HME face masks	Reduces post-exercise fall in FEV1	Insufficient	May affect ventilation and be associated with discomfort	9-12
Omega-3 fatty acid supplementation	3 g/d EPA and 2 g/d DHA	Reduces systemic inflammation	Medium	Side effects: Acid reflux, bloating, diarrhea and nausea	34-37,40
		Reduces airway inflammation	Insufficient		
		Reduces post-exercise fall in FEV1	Insufficient		
Caffeine	5-10 mg/kgbw	Induces bronchodilation	Good	Slow absorption Side effects: Muscle tremors, tachycardia	47-52, 55-56
		Reduces post-exercise fall in FEV1	Medium		
		Improves respiratory muscle fatigue resilience	Medium		
		Counteracts exercise-induced hypoxemia	Insufficient		
Vitamins and anti-oxidants	1500 mg/d vitamin C	Reduces systemic inflammation	Medium	Side effects: Diarrhea, vomiting, headache, insomnia, nausea, kidney stones	57-68
	64 mg/d β-carotene	Scavenge ROS	Medium		
		Reduces post-exercise fall in FEV1	Insufficient		
Breathing control	See table 2	Reduces perception of respiratory symptoms	Insufficient		69-72
Respiratory muscle training	30 breaths x 2/d at 50% of MIP	Improves respiratory muscle fatigue resilience	Good	Time-consuming	73-88
		Reduces asthma severity	Insufficient		

52 FEV1: forced expired volume in 1 s, HME: heat and moisture exchange, HR_{max}: maximal heart rate, MIP: maximal

53 inspiratory pressure, ROS: reactive oxygen species, VO_{2max}: maximal oxygen consumption

PRE-EXERCISE WARM UP

In approximately half of those who suffer from EIB, high intensity pre-exercise warm up effectively protects against subsequent bronchoconstriction[3]. A recent systematic review[4] reported that intermittent high intensity pre-exercise warm up (repetitive sprints of ~30 s close to peak oxygen consumption or maximal HR) provides about 10% reduction in the fall in FEV_1 post exercise, whereas neither low intensity nor continues high intensity pre exercise warm up provides significant protection in individuals with EIB.

The refractory period or refractory effect, that is induced after a first exercise bout, has frequency been proposed to explain why high intensity warm-ups protect against EIB. It has been proposed that the first exercise induces a variable period (called the refractory period) during which (2-4 hours) subsequent exercise will not result in EIB or will result in decreased fall in FEV_1. As discussed by XXXX (ref to refractory paper in this series), preceding exercise may deplete constrictive mediators, induce secretion of protective mediators (particularly prostaglandins) and cause desensitization of smooth muscle to bronchoconstrictive mediators[3]. Regardless of the mechanism, there is good evidence to suggest a clinical benefit of warm ups in protecting against EIB.

While high intensity exercise warm-ups may attenuate EIB[3-4], the exercise intensity that is required for the warm-up, may potentially cause perturbations in the exercising musculature and compromise subsequent exercise performance[5]. However, emerging evidence suggests that isolated respiratory warm-ups can provide similar bronchoprotective effects as whole-body warm up[6]. Instead of using whole-body warm up, a recent study[6] evaluated the effect of a respiratory-only warm up on subsequent decline in FEV_1 induced by exhaustive cycling (≈ 14 min). In that study, subjects performed normocapnic hyperpnoea at different intensities (30-

80% of maximal voluntary ventilation). Notably, all hyperpnoea sessions attenuated post-exercise decline in FEV_1 regardless of the intensity of the hyperpnoea session conducted and without compromising cycling performance[6]. Perception of respiratory dyspnoea was also reduced by preceding normocapnic hyperpnoea. Consequently, both pre-exercise whole body and respiratory warm ups may be used to protect against EIB.

AVOIDANCE OF TRIGGERS

Heat and Moisture Exchange Face Masks

Exercise in dry and cold environments can be a significant trigger of bronchoconstriction (ref to paper in series). The bronchoconstriction is thought to be caused by dehydration of the airway surface liquid, which causes cell shrinkage, release of inflammatory mediators precipitating airway smooth muscle constriction[7]. Repeated exposure of the airways to cold dry air may also lead to airway epithelial cell damage, microvascular leakage and airway remodelling, which may worsen asthma severity[8]. Given the increased risk of bronchoconstriction in dry and cold environments, individuals with asthma may be advised to avoid exercise outside. This places obvious constraints on athletes with asthma-related conditions who have to train and complete in dry and cold environment and also the proportion of individuals with asthma who engage in physical activity as part of their daily routines during the winter months.

Face masks that incorporate a heat and moisture exchanger (HME) are a novel non-pharmacological tool to counteract EIB in dry and cold environments. Although few studies have investigated the efficacy of HME face masks in counteracting EIB, some studies have demonstrated a protective effect as measured by an attenuation in post-exercise decline in FEV_1[9-12]. This suggests that individuals with asthma may use HME face masks to protect

against EIB when they engage in moderate to vigorous exercise in cold dry environments. Currently, it is unknown whether the HME face masks reduce airway inflammation over acute and multiple bouts of exercise. Nor is it known whether HME face masks reduce respiratory symptoms and β_2-Agonists usage over several weeks of engaging in exercise in dry cold environments. If HME face masks are to be considered as part of a non-pharmaceutical therapy plan, the design of the masks need to be considered, as individuals with asthma-related conditions are unlikely to wear the masks if they find the masks large and cumbersome. However, athletes may not see HME face masks as a viable strategy to prevent EIB as the masks may not be practical wear to achieve optimal sporting performance or permitted by the rules of the sport.

Air pollution

Air pollution has been shown to increase asthma severity and may have significant effects on athletes due to the high ventilation rates they achieve and sustain during intense exercise[13]. Air quality is inversely correlated with exercise-induced respiratory symptoms[14]. The risk is also greater in those athletes who train on a regular basis in environments with poor air quality[15]. Small particles, particularly ultra-fine ones (<100 nm diameter) like those from combustion engines, have high lung deposition and may cause epithelial damage. These particles include ozone (O_3), sulfur dioxide (SO_2), nitrogen oxides (NOx) and particulate matter (PM2.5, particles smaller than 2.5 mic diameter). Ice skaters are particularly exposed to combination of cold dry air as well as PM1 (PM < 1 mic diameter) in confined space of indoor ice arenas and multiple ice-resurfacing by gas- or propane-powered machines. Particle inhalations have been shown to induce oxidative stress, airway inflammation and airway remodelling. All these result in higher prevalence of asthma symptoms, and great degree of small airway dysfunction[16-19].

With regard to management, mechanical barriers, such as face masks, may help reduce the effects of polluted particles[9]. Avoidance of training in low humidity conditions or during times of high levels of atmospheric pollutants is advisable, yet its practical usage and scientific benefit is still questionable. Similarly, whenever possible, it may be recommended to avoid training close to busy major roadways or during rush hours or other times of elevated vehicular congestion[20].

Swimming

The pathogenic mechanisms of EIB classically involve both osmolar and vascular changes in the airways in addition to cooling of the airways[2,7]. Increased minute ventilation during exercise, requires significant warming and humidification of the inspired air. The resulting respiratory heat and water loss from the airway mucosa into the inspired air may release bronchoconstrictive mediators. In that respect, sports in warm humid environments, such as indoor pools, are encouraged. Swimming has often been recommended as a less asthmogenic trigger compared to other sports, because of the humid environment. Yet, a recent Cochrane review concluded that there is insufficient evidence to suggest that aquatic-based exercise is superior to comparative nonaquatic exercise in asthmatics[21].

Chlorination is the most commonly used method for ensuring water hygiene in swimming pools. Chlorine gas and its aerosol byproducts, (eg, trichloramine, hypochlorous acid, and mono- and dichloramine), which float just above the water surface, may affect the nose, pharynx, larynx trachea and bronchi with chronic exposure leading to structural epithelial changes. During exercise, nasal breathing at rest shifts to oro-nasal breathing, thereby significantly reducing the filtering effect of the nose. Aerosol particles travel and deposit further into the lung. Trichloramine gas formed in chlorinated pools was suggested as a cause

for EIB in competitive swimmers and increased airway hyperreactivity (as measured by methacholine or EVH challenge) has been demonstrated in swimmers where 43-68% of them showed it[22-24]. Increasing evidence supports the notion that chronic repetitive swimming in indoor pools may induce airway epithelial damage, inflammation, and remodelling[23-25], and increase the risk for atopy and asthma[26,27]. A recent study found increased levels of 8-isoprostane (8-IsoP) (as a marker of airway oxidative stress) in the exhale breath condensate of competitive swimmers after a swimming session[27]. Whenever possible, swimmers should train in pools cleaned with non-chlorine water disinfection methods (such as copper/silver and ozone) as well as in well ventilated pool environments. Yet, apart for some case reports[29], the scientific evidence to support or refute many of these recommendations is lacking.

DIETARY STRATEGIES

Omega-3 fatty acid supplementation

It has been noted that populations who consume large quantities of oily fish have a lower prevalence of asthma[30]. Oily fish are rich in omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are precursors to powerful agents involved in the resolution of inflammation. Two mechanisms of action underpinning the anti-inflammatory bio-actions include the ability of EPA to compete with arachidonic acid as a substrate for cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO) enzymes and be converted to less inflammatory leukotrienes and prostanoids[31], and to generate the potent anti-inflammatory E-series resolvins[31]. DHA may also alter gene transcription and translation via direct or indirect actions on intracellular signalling pathways[33].

The anti-inflammatory properties of EPA and DHA make a diet high in oily fish an attractive addition to the therapy of an individual with EIB. Initial investigations demonstrated 10 weeks

dietary supplementation of 3.2 g/d EPA and 2.2 g/d DHA reduced leukotriene production by 50%, but not reduction in post-exercise decline in FEV_1 in asthmatics[34]. However, using the same EPA and DHA dietary supplementation over a three week period, Mickleborough and co-workers reported significant reductions in airway inflammation, which was accompanied by 64-80% reductions in FEV_1 fall post exercise in individuals with EIB[35,36]. Notably, post-exercise decline in FEV_1, whilst on EPA and DHA supplementation, was similar to those of the non-EIB control group. In addition, 3.2 g/d EPA and 2 g/d DHA were observed to be as favourably as 10 mg/d montelukast in reducing airway inflammation and hyperpnoea-induced bronchoconstriction in participants with mild to moderate persistent asthma37. However, there appears to be no additional benefit of combining EPA and DHA supplementation with 10 mg montelukast[37]. Furthermore, a recent pilot study found no beneficial effect of vitamin D and fish oil supplementation for 3 weeks on reduction in FEV_1 induced by EVH in recreational athletes with EIB[38].

Recently, the marine lipid fraction of the New Zealand green-lipped mussel (Perna canaliculus) PCSO-524, which is rich in omega-3 fatty acids, has been shown to produce similar reductions in inflammation and bronchoconstriction (57% reduction of FEV_1 fall) following a eucapnic voluntary hyperpnoea challenge[39]. In this investigation the attenuation of airway inflammation and bronchoconstriction cannot be explained entirely by the EPA and DHA content of PCSO-524, since the amount of EPA and DHA consumed daily was only 72 mg and 48 mg respectively. Therefore, it may be that the additional constituents of PCSO-524 act synergistically with EPA and DHA to bring about the anti-inflammatory effect and reduction in bronchoconstriction.

While a low intake of EPA and DHA does not appear to be a safety issue a few side effects can occur, such as a fishy aftertaste, flatulence, acid reflux, bloating, diarrhoea, nausea and possibly an increased risk of bleeding and immunosuppression with a high intake of omega-3 fatty acids[40].The initial investigations provide promise for EPA and DHA dietary supplementation to protect against EIB and associated airway inflammation. However, large-scale clinical studies in individuals with EIB are required to determine the minimum effective dose, duration required to observe the beneficial effect and compare the effect of combining omega-3 fatty acid supplementation with prevention inhaler therapy (e.g. inhaled glucocorticoids).

Caffeine

Caffeine (1,3,7-trimethylxanthine) is among the most commonly used supplements by athletes[41]. While formerly being subjected to anti-doping regulations, the restrictions towards caffeine were lifted by the World Anti-Doping Agency (WADA) in 2004 and can as such be used freely in and out of competition. Caffeine works as a non-selective competitive adenosine receptor antagonist for all subtypes of the adenosine receptor[42,43], but may also act as a phosphodiesterase inhibitor[44]. Accordingly, caffeine induces intracellular cAMP-dependent/protein kinase A signalling, which like β_2-Agonists, causes smooth muscle relaxation[45]. Indeed, studies have shown dose-related bronchodilator effects of caffeine on basal airway function[46]. The interest in caffeine as a bronchoprotective agent started some 30 years ago when Becker and co-workers (1984) observed that 10 mg/kg_{bw} of orally ingested caffeine had a similar bronchodilating effect as 5 mg/kg_{bw} oral theophylline in children with asthma[47]. Comparable bronchodilating effect was later shown in adult asthma patients after ingestion of 5 mg/kg_{bw} caffeine[47] or 3 cups of coffee[49].

Although caffeine shows promise as a bronchodilator, only a few studies have investigated its potential to counteract EIB of which none have been performed in athletes. In non-athletes, ingestion of caffeine was shown to have a post-exercise bronchoprotective effect compared to placebo in individuals with EIB[50]. While post-exercise decline in FEV_1 was 24% for placebo, it was less than 1% after ingestion of 7 mg/kg_{bw} caffeine and 8% after 3 mg/kg_{bw} caffeine. In accordance with this observation, Duffy & Phillips (1991) observed that ingestion of 10 mg/kg_{bw} caffeine reduced bronchoconstrictor response to EVH-provocation compared to placebo in EVH-positive individuals[51]. When compared to inhalation of β_2-Agonist salbutamol (180 mg albuterol), ingestion of 9 mg/kg_{bw} caffeine was shown to be as effective as salbutamol in attenuating post-exercise reduction in FEV1 in asthmatics with EIB[52].

Aside from its bronchoprotective effect, caffeine has a variety of other effects of relevance for airway function during exercise. During submaximal exercise, as little as 3 mg/kg_{bw} oral caffeine has been shown to modulate ventilatory dynamics by reducing the physiological dead space ventilation/tidal volume ratio and breathing frequency, while concurrently increasing tidal volume[53,54]. In addition, caffeine may counteract exercise-induced hypoxemia (desaturation) in elite athletes at submaximal intensities[55] and improve respiratory muscle fatigue resilience[56].

Despite the small number of studies undertaken, there is some evidence to suggest that caffeine has the potential to reduce EIB severity and improve ventilatory dynamics and respiratory muscle fatigue resilience during exercise. The amount of orally ingested caffeine needed for bronchoprotection is approximately 5-10 mg/kg_{bw}, which would be equivalent to 2-4 cups of coffee. However, it appears that the bronchoprotective effect of caffeine is highly individual. A limitation of caffeine is the slow absorption rate when ingested, giving rise to a

bronchodilator response 2 hours after ingestion. Future studies should investigate more thoroughly the therapeutic efficacy of caffeine as a bronchoprotective substance during exercise in athletes with EIB.

Vitamins and anti-oxidants

Supplementation with various vitamins and anti-oxidants has attracted some attention as means to counteract EIB because of their ability to suppress proinflammatory signalling[57], to lower levels of histamine[58,59] and prostaglandin F2α[60], and to scavenge reactive oxygen species (ROS)[61,62]. In practical terms, however, interpretation of the therapeutic efficacy of each individual vitamin and anti-oxidant as bronchoprotective substances in EIB is limited by the small number of studies that have been undertaken in individuals with EIB, especially in athletes. Most convincing is the bronchoprotective effect of acute and chronic supplementation with vitamin C on post-exercise decline in FEV_1 in individuals with EIB[60,63-65]. In addition, one week supplementation with β-carotene (64 mg), a provitamin A carotenoid, has been shown to reduce post-exercise reduction in FEV_1[66]. Conflicting results have been observed after one week supplementation with the carotenoid lycopene (30 mg), in which a post-exercise bronchoprotective effect was found in asthmatic individuals with EIB, whereas adolescent athletes with EIB had no effect[67,68].

STRATEGIES TO REDUCE PERCEPTION OF EXERTIONAL DYSPNOEA

Above we have discussed strategies that may help control EIB. In addition, there may also be a role for utilising breathing control and inspiratory muscle training in order enable athletes with EIB to reduce perceptions of exertional dyspnoea.

Breathing control

A significant symptom of EIB is dyspnoea during and after exercise. There are a variety of breathing exercises that may benefit individuals who experience asthma/EIB exacerbations that include yogic breathing[69-71] and physiotherapist-supervised breathing training[72]. Although these forms of breathing control exercises may not be able to reduce asthma severity they may be able to reduce the perception of respiratory symptoms and increase perception of asthma control[69]. Moreover, breathing exercises have been shown to improve quality of life[70], reduce use of relief medication[70], reduce the levels of anxiety and depression[72] and airway hyperresponsiveness[71]. Future research is required to understand the mechanisms behind these observations in asthmatic individuals.

It is currently unknown how these forms of breathing control exercises may be beneficial for athletes with EIB, whose main symptoms are experienced during exercise. However, the use of breathing training incorporating, inspiratory muscle training and breathing technique training (table 2), has been shown to be helpful in reducing the perception of breathing in an athlete with non-asthmatic exercise respiratory conditions[73]. Future research is required to investigate how athletes with EIB respond to using breathing exercises. Furthermore, the current breathing control methods may need to be adapted to replicate respiratory control during exercise rather than focusing on breathing control at rest.

301 Table 2: Summary of breathing training for athletes

Breathing Control Methods	Overview
Breathing Technique	Encourage initiation of inspiration from the lower rib cage. Inspiratory manoeuvre should be smooth with little tension through the shoulders and neck. Aids such as elastic strap or hands placed on sides of torso over lower ribs can be used to help athletes. Athlete can begin to attempt to practice this technique in functional sport specific positions
Inspiratory Muscle Training (IMT)	Ensure breathing technique is addressed before initiating IMT. Athletes with poor breathing technique, who proceed directly to IMT, may experience exacerbation of their symptoms. IMT should incorporate forceful inspiratory manoeuvres through a hand-held device providing resistance to the inspired airflow. Focus during the IMT should be on good breathing technique (as described above). An IMT session should comprise of 30 continuous forced inspiratory efforts at the equivalent of 30 breath repetition maximum, with relaxed expiration.

302 Adapted from Dickinson, J. McConnell A. Ross E. Brown, P. Hull, J. Assessment and
303 Management of Non-Asthma Related Breathing Problems in Athletes. The Sport and Exercise
304 Scientist. 2015; 45: 8-9

305

306 **Respiratory Muscle Training**

307 Respiratory muscle training is an easy and cheap way to enhance both inspiratory and
308 expiratory muscle strength[74], and has also been associated with improvements in exercise

performance during various exercise protocols in healthy individuals[75,76]. However, despite decades of research into the applications of respiratory muscle training, the area is still controversial and subject to scientific debate[77-79]. Respiratory muscle training has shown some promise in the management of chronic obstructive pulmonary disease[80], inspiratory stridor[73] and exercise-induced vocal cord dysfunction[81,82]. However, although studies also have shown that respiratory muscle training may have beneficial effects on asthma severity and $beta_2$-agonist usage[83-85], a recent cochrane review, based on 113 asthmatics, concluded that there is no conclusive evidence to support or refute the therapeutic efficacy of inspiratory muscle training in asthma[86]. Nevertheless, given individuals with EIB may experience airway obstruction and airflow limitation during intense exercise[87], which potentially puts a larger work load on respiratory muscles[3,88], it could be speculated that respiratory muscle training may be beneficial for athletes with EIB. However, to our knowledge, no studies have investigated the effectiveness of respiratory muscle training on EIB severity[89].

SUMMARY AND FUTURE CONSIDERATIONS

There are numerous non-pharmacological strategies that can be utilised to support the treatment of EIB, however the evidence is inconclusive and future studies are encouraged before any recommendations are implemented. There is currently insufficient evidence to support the use of any non-pharmacological EIB treatment strategy in the absence of regular pharmaceutical therapy for EIB. While there is some encouraging findings with regards to nutritional supplementation and respiratory muscle training, future studies are encouraged, especially in athletes. Most studies have included non-athletes and extrapolation towards athletes should therefore be done with caution. Furthermore, data on other commonly used supplements by athletes, such as beta-alanine and creatine are lacking in relation to EIB. For instance, beta-

alanine supplementation increases intracellular content of carnosine, which among other factors[90], may affect nitric oxide production and modulate inflammation[91,92], both of which could affect EIB severity. In addition, creatine supplementation has been shown to exacerbate airway inflammation, increase airway hyperresponsiveness and induce smooth muscle thickening in mice[93]. However, no studies, have to our knowledge, investigated the effect of creatine supplementation on EIB severity in athletes. Consequently, there are numerous non-pharmacological strategies yet to be studied in athletes with EIB.

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