

# Management of exercise-induced bronchoconstriction

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Exercise-induced bronchoconstriction (EIB) is a common clinical manifestation of asthma, occurring in 70% to 80% of asthmatics. Evidence suggests that exercise and the ensuing bronchoconstriction do not contribute to a worsening of asthmatic inflammation. Asthmatics should not be discouraged from exercising, and, with adequate management, most patients should be able to exercise regularly with only minor symptoms. The first step in the management of patients with EIB should be to obtain optimum control of the underlying asthma, often requiring regular treatment with inhaled steroids. Regular treatment with inhaled corticosteroids usually reduces the extent of EIB by 50% or more. Frequently, despite optimal management of the underlying asthma, patients develop EIB symptoms requiring additional treatment. Short and long acting inhaled beta<sub>2</sub>-agonists are highly effective at reducing the magnitude of EIB, although there are concerns that the extent of protection diminishes during periods of regular use of these agents. Inhaled cromolyn and nedocromyl are effective at reducing the extent of EIB in some patients, although this protection does not extend beyond 2 to 3 h after treatment. The recently developed leukotriene receptor antagonists are effective at reducing the extent of EIB by 40% to 70%, and have the advantage that this protection lasts throughout the day and does not appear to diminish with regular use. Other agents, including anticholinergics and antihistamines, have been shown to offer partial protection against EIB, suggesting the possibility of using a combination treatment to manage some patients' symptoms. Finally, there is encouraging evidence suggesting that modifications of the pattern of exercise can markedly reduce the extent of EIB.

**Key Words:** *Asthma; Exercise; Inflammation; Therapy*

## Traitement de la bronchoconstriction d'effort

**RÉSUMÉ :** La bronchoconstriction d'effort (BE) est une manifestation clinique courante de l'asthme chez 70 à 80 % des patients. Selon des études, les exercices physiques et la bronchoconstriction qui s'ensuit n'aggravent pas l'inflammation des voies respiratoires. Il ne faudrait donc empêcher les asthmatiques de bouger et, avec un traitement approprié, la plupart des patients devraient être en mesure de faire régulièrement des exercices avec un minimum de symptômes. La première étape du traitement de la BE consiste à stabiliser l'asthme, généralement par la prescription de corticostéroïdes en aérosol, ce qui permet dans la plupart des cas une diminution de 50 % et plus de l'intensité de la BE. Malgré le traitement optimal de l'asthme, il arrive souvent que les patients présentent des symptômes de BE, qui exigent, à leur tour, un traitement. Les agonistes  $\beta_2$  en aérosol à action brève et prolongée s'avèrent très efficaces pour diminuer l'intensité de la BE, mais il est possible que leur degré de protection diminue avec les périodes d'utilisation prolongée. Le cromolyn sodique et le nédocromyl en aérosol diminuent également l'intensité de la BE chez certains patients; toutefois, leur protection ne dépasse pas deux ou trois heures. Par ailleurs, les antagonistes des récepteurs des leucotriènes, conçus depuis peu, permettent une diminution de 40 à 70 % de l'intensité de la BE, en plus de présenter l'avantage d'offrir une protection qui dure toute la journée et qui ne semble pas diminuer avec l'emploi prolongé. D'autres agents, dont les anticholinergiques et les antihistaminiques, protègent jusqu'à un certain point les patients contre la BE, ce qui laisse entrevoir la possibilité d'associer différents médicaments pour traiter certains symptômes. Enfin, des données encourageantes semblent indiquer que le fait de modifier le type d'exercices peut réduire sensiblement l'intensité de la BE.

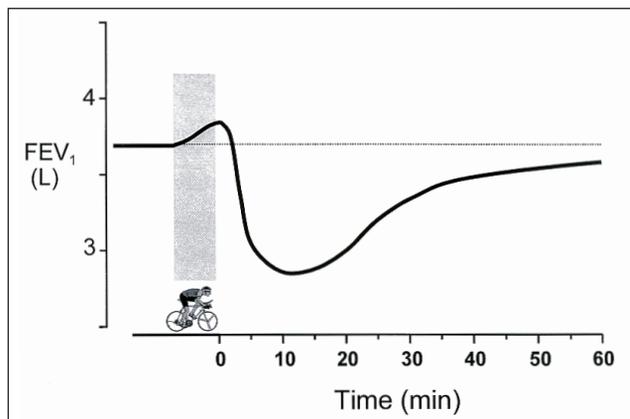
Exercise-induced bronchoconstriction (EIB) is a common clinical manifestation of asthma, occurring in 70% to 80% of patients with asthma. Bronchoconstriction associated with exercise is often referred to as 'exercise-induced asthma'; however, this is a misnomer, because exercise, unlike allergen inhalation, does not cause asthma, but rather causes bronchoconstriction in some patients with asthma. Evidence suggests that small, if any, inflammatory changes in the asthmatic airway occur as a result of exercise (1-3). Thus, the term exercise-induced asthma should be avoided, if only to reduce the belief, often held by parents of children with asthma, that exercise will worsen their child's asthma. Moreover, with correct management, EIB can be prevented or markedly reduced in almost all cases; there are no reasons to recommend that patients with asthma should avoid exercise.

### MECHANISMS OF EIB

Ideally, appropriate management of a disease should be based on an understanding of the basic mechanisms underlying that disease, rather than a simple appreciation of the effectiveness and efficacy of the available management options. While it is not the intent of this paper to provide a detailed description of the current understanding of the mechanisms of EIB, a brief overview is attempted.

While bronchoconstriction may occur during exercise, it is more common to see bronchodilation during exercise, with bronchoconstriction beginning shortly after exercise and resolving within an hour if left untreated (Figure 1). Two theories have been proposed to explain how the airway is protected from bronchoconstriction during exercise but susceptible to bronchoconstriction after exercise (4,5). The two theories are similar, in that both identify the evaporation of water lining the airway due to the increased level of ventilation, as being the primary stimulus for bronchoconstriction. Gilbert and colleagues (6) have suggested that airway cooling during exercise and subsequent warming, with reactive hyperemia of airway tissue after exercise, is responsible for the major component of the postexercise bronchoconstriction. Anderson (7) has suggested in an alternative hypothesis that the evaporation during exercise produces increased osmolarity in the airway tissue, promoting the degranulation of mast cells and release of bronchoconstrictor mediators.

Support for the rewarming and reactive hyperemia theory is that breathing warmed air following exercise can augment the degree of bronchoconstriction (8). However, this theory does not explain why lengthening the duration of exercise beyond 2 mins can worsen the degree of bronchoconstriction, despite observations that no further airway cooling occurs after 2 mins (6). Compelling support for the hyperosmolarity theory is that the degree of bronchoconstriction is more closely related to respiratory water loss than to respiratory heat loss (7,9,10). Further support can be found in observations that plasma histamine levels are elevated in association with EIB (11), and that both EIB and the associated rise in plasma histamine can be attenuated by prior treatment with terbutaline (12) or cromolyn sodium (13).



**Figure 1** An illustration of the typical response of forced expiratory volume in 1 s ( $FEV_1$ ) during and following a short bout of moderately intense exercise

Protection against bronchoconstriction throughout the exercise period has been attributed to the bronchodilating effect of circulating catecholamines (14). However, this explanation does not account for observations that bronchoconstriction associated with isocapnic hyperventilation is also often delayed until ventilation has returned to normal. An alternative explanation is that the increased tidal volume during exercise exerts a protective effect on the airway (15,16), likely in a similar manner to the bronchodilating effects of a single deep inspiration (17).

**Relationship between EIB and underlying inflammation or airway hyperresponsiveness:** Because bronchoconstriction following exercise appears to be in part due to mast cell degranulation and release of bronchoconstrictor mediators, one would expect that the degree of bronchoconstriction should be related to underlying airway inflammation and nonspecific airway responsiveness. In a recent study, eosinophil numbers and eosinophil cationic protein (ECP) levels in induced sputum were both predictors of EIB severity ( $r=0.59$  and  $r=0.47$ , respectively) in a group of subjects with asthma (18). Several studies have shown a significant relationship between EIB and airway responsiveness to inhaled histamine and AMP (19-23). The likely relationship between the degree of inflammation and EIB has been further demonstrated in studies in which allergen avoidance decreased EIB (19), allergen exposure increased EIB (24) and prolonged treatment with inhaled corticosteroids decreased EIB (25-29).

**Mediators of bronchoconstriction in EIB:** The current state of understanding suggests that several mediators are involved in EIB. This understanding is based on studies where mediators known to be bronchoconstrictors by nature are detected in increased levels at the time of EIB and studies where specific mediator blockade has attenuated the magnitude of EIB.

**Histamine:** It is widely recognized that histamine is a bronchoconstrictor, particularly in patients with asthma (30-32). Plasma histamine levels are elevated in association with EIB (11). Treatment with the histamine-blocking agent, terfenadine, has been shown to partially reduce the severity of EIB

(33,34). However, in both of these studies, the degree of protection afforded by terfenadine was less than 40%, suggesting that other mediators are involved.

**Acetylcholine:** Inhalation of cholinergic agents results in bronchoconstriction, which is more pronounced in patients with asthma (35,36). Treatment with the anticholinergic agent, ipratropium, attenuates the magnitude of EIB by approximately 35% (33).

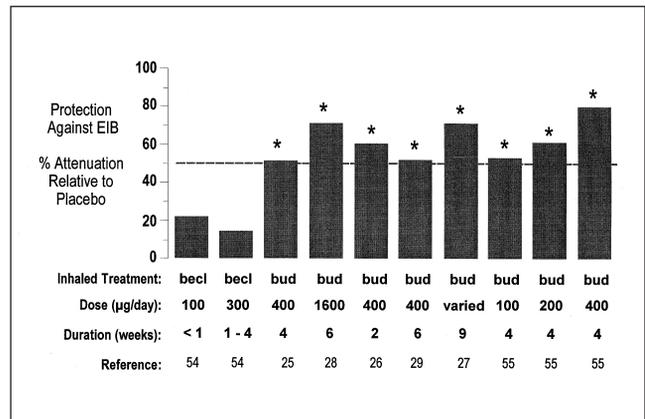
**Leukotrienes:** The cysteinyl leukotrienes (LTs) C<sub>4</sub> and D<sub>4</sub> have been shown to be more potent bronchoconstrictors than histamine and methacholine (37-39). Urine levels of LT E<sub>4</sub> are elevated in association with EIB (40,41). Treatment with inhibitors of LT synthesis (42,43), as well as LT receptor antagonists (44,45), has been shown to reduce significantly the severity of EIB. Moreover, the degree of protection afforded by these agents is approximately 50%, suggesting that LT release accounts for a large component of the bronchoconstriction following exercise.

### TREATMENT OPTIONS TO MANAGE OF EIB

As is reflected in most treatment guidelines (46-49), management of asthma should be aimed at reducing the degree of airway inflammation, with resulting decreases in the morbidity associated with the disease. This recommendation should also apply to the management of EIB. However, it is quite common for EIB to persist despite otherwise good control of asthma symptoms in patients treated with anti-inflammatory agents. For this reason, the use of bronchodilating or bronchoprotecting agents is common in asthmatic patients with EIB. Discussion in the following sections focuses on the effects of inhaled corticosteroids, which can substantially attenuate EIB when used appropriately to control asthma, and examines the additional benefit that can be obtained from other agents including inhaled beta<sub>2</sub>-agonists, anti-LTs, inhaled cromones, anticholinergic compounds and antihistamines, and the benefits that can be achieved with nonpharmacological intervention.

**Corticosteroids:** When treating patients with EIB, the primary concern should be the appropriate management of the underlying asthma, rather than simply relief from the symptoms of EIB. Because EIB is associated with airway hyperresponsiveness and eosinophilic inflammation (18,50), it is not surprising that inhaled corticosteroids, which attenuate both of these features of asthma (51-53), reduces, but does not usually eliminate, symptoms associated with exercise.

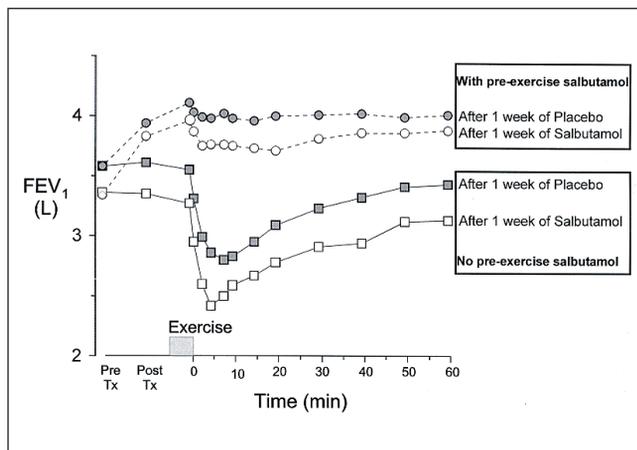
The first investigation of the effects of inhaled steroids on the magnitude of EIB did not report any benefit from this treatment (54). However, in this study, 11 subjects were treated with single inhalations of beclomethasone (100 µg) only 20 mins before exercise. A further study was performed with six subjects after treatment with beclomethasone for periods ranging from one to four weeks with no difference detected between placebo and treatment arms (54). Since these initial studies, it has been demonstrated that, to have an effect on airway inflammation or airway hyperresponsiveness, treatment with inhaled steroids must persist over a period of weeks to months. Studies, with longer treatment periods,



**Figure 2** The degree of protection afforded against exercise-induced bronchoconstriction (EIB) in a number of trials of inhaled corticosteroids. becl Beclomethasone; bud Budesonide

have shown that the severity of EIB can be reduced by corticosteroid therapy. Henriksen and Dahl (25) treated 14 children with inhaled budesonide (400 µg/day) for four weeks and attenuated the exercise-induced fall in the forced expired volume in 1 s (FEV<sub>1</sub>) by 51%. Vathenen et al (28) treated 40 adults with inhaled budesonide (800 µg twice daily) for six weeks and attenuated the postexercise fall in FEV<sub>1</sub> by 71%. In this study, the attenuation of EIB correlated significantly with reductions in histamine airway responsiveness. Henriksen (26) subsequently treated 14 children with budesonide (200 µg twice daily) for two weeks and attenuated the postexercise fall in FEV<sub>1</sub> by 62%. This need for prolonged treatment with inhaled corticosteroids was highlighted by Molema et al (29), who treated 22 young adults with inhaled budesonide (100 µg four times daily) for a total of six weeks, performing exercise challenges during an initial placebo treatment period, and at three and six weeks of active treatment. Budesonide resulted in significant attenuation of the postexercise fall in FEV<sub>1</sub> after three weeks' treatment (33% attenuation), with further reduction after six weeks' treatment (52% attenuation). Farrero et al (27) have recently treated 20 children and young adults with inhaled budesonide for two months and observed a 75% reduction in the postexercise fall in FEV<sub>1</sub>. Perhaps the most compelling support for using inhaled steroids to manage EIB was that shown by Pedersen et al (55) who observed a dose response effect with a range of doses of budesonide delivered to children with asthma for four weeks before exercise. The greatest attenuation relative to placebo in this study was 83%, following four weeks of 400 µg/day treatment. The observation that greater protection was found at the highest budesonide dose supports trials of increased corticosteroid dose in patients currently treated with low dose inhaled steroid but with persistent exercise symptoms. It is possible that increased protection against exercise symptoms will be obtained using a corticosteroid dose greater than that required to control other features of asthma.

Thus, while single or short course treatments with inhaled or oral steroids are not effective in the management of EIB, these studies clearly indicate that long term management of



**Figure 3** Effects of salbutamol treatment on the response of forced expiratory volume in 1 s ( $FEV_1$ ) following exercise. Regular treatment was with inhaled salbutamol (200 mg four times daily) or placebo for the week before the exercise challenge. Pre-exercise treatment was with inhaled salbutamol (200 mg) or placebo, inhaled 5 mins before exercise.  $FEV_1$  responses were with or without pre-exercise salbutamol were significantly lower when regular salbutamol had been taken during the previous week. Reproduced with permission from reference 77. Tx Treatment

patients with asthma of all ages with inhaled corticosteroids produces significant and substantial reductions in the magnitude of EIB. In all of these studies, where a range of steroid doses were employed, the attenuation of the postexercise fall in  $FEV_1$  exceeded 50% (Figure 2). Clearly, this evidence points to the early introduction of low doses of inhaled steroids in the management of patients with asthma affected by symptoms of EIB. However, these studies also demonstrate that, in many patients, a component of EIB persists despite inhaled corticosteroid treatment. This incomplete protection is in agreement with observations that treatment with oral or inhaled corticosteroids does not block the increased LT production associated with asthma (56,57). Depending on the magnitude of persistent EIB, patients may require treatment with one or more of the following agents.

**Nonspecific bronchodilator therapy – Inhaled beta<sub>2</sub>-agonists:** Inhaled beta<sub>2</sub>-agonists remain the most widely used treatment for the prevention of or relief from EIB. Rather than acting on specific mediators, these agents act directly on airway smooth muscle, either protecting against bronchoconstriction or reversing existing bronchoconstriction. Recently, the use of the newer long acting beta<sub>2</sub>-agonists has been recommended for the treatment of EIB. While both short and long acting agents provide excellent protection against EIB, there is controversy regarding their use on a regular basis.

**Short acting beta<sub>2</sub>-agonists:** When inhaled in the hour before exercise, beta<sub>2</sub>-agonists produce both bronchodilation before exercise as well as marked attenuation of EIB. In numerous clinical trials with both adult and pediatric populations, the degree of attenuation of the postexercise fall in  $FEV_1$  has ranged from 50% to 100% for inhaled salbutamol (200 µg) (58-60), terbutaline (500 to 1000 µg) (61,62) and fenoterol (50 to 800 µg) (63-65). Another important feature of

inhaled beta<sub>2</sub>-agonist treatment is its ability to reverse EIB when administered after exercise. When eight adults in each of three parallel treatment groups were treated with either inhaled placebo, salbutamol (200 µg on two occasions separated by 5 mins) or terbutaline (500 µg twice) 10 mins after exercise, there was 100% reversal of the postexercise fall in peak expiratory flow within 5 mins of treatment, which did not occur with placebo treatment (66).

While oral delivery of beta<sub>2</sub>-agonists is frequently employed in the management of pediatric asthma, this delivery route provides questionable protection against EIB. In doses sufficient to provide significant bronchodilation, oral salbutamol has been shown to provide protection against EIB in some studies (67) but was ineffective in others (59,68). While an early study of oral terbutaline (5 mg) demonstrated effectiveness compared with placebo for up to 6 h in the prevention of EIB in five adults with asthma (69), a subsequent study found no effect relative to placebo at doses ranging from 4 to 12 mg in 17 children with asthma (70). Thus, oral beta<sub>2</sub>-agonists do not provide reliable protection against EIB, but may be useful in some patients.

The duration of action of short acting beta<sub>2</sub>-agonists is an important concern for the patient, especially in the pediatric population. While the protection from inhaled salbutamol (200 µg) (71,72), terbutaline (500 µg) (62) and fenoterol (400 to 800 µg) (64) persists for at least 2 h, this protection is completely lost compared with placebo as early as 3 h after dosing (62,64,72-76). Thus, although short acting inhaled beta<sub>2</sub>-agonists provide excellent relief from EIB, this protection cannot be expected to last for more than 2 to 3 h. Clearly, multiple dosing throughout the day would be required by children or individuals who expect to exercise frequently during a single day. However, this type of multiple daily dosing with inhaled beta<sub>2</sub>-agonists cannot be recommended for management of EIB. Two studies have observed the effect of regular short acting beta<sub>2</sub>-agonists on EIB. Gibson et al (67) demonstrated that regular treatment of six adults with oral salbutamol for four to 20 weeks resulted in significant loss of the protective effect from inhaled salbutamol (200 µg) against EIB. However, in this same study, six adolescents were treated for similar periods with regular inhaled salbutamol (800 µg/day) with no observed loss of protection. The author's laboratory have subsequently demonstrated a significant loss of protection against EIB at the end of only one-week regular treatment with inhaled salbutamol (200 µg taken four times daily). In this study, the postexercise  $FEV_1$  both with and without pre-exercise salbutamol was significantly lower following a week of regular inhaled salbutamol (77) (Figure 3). Thus, while inhaled beta<sub>2</sub>-agonists provide excellent protection against EIB, the degree of protection may be attenuated following a period of regular or frequent use. If patients who are treated with inhaled corticosteroids still require frequent beta<sub>2</sub>-agonist use to protect against EIB, a trial with another agent should be considered.

**Long acting beta<sub>2</sub>-agonists:** As discussed above, protection against EIB can be expected to last only for 2 to 3 h after treatment with inhaled short acting beta<sub>2</sub>-agonists. In re-

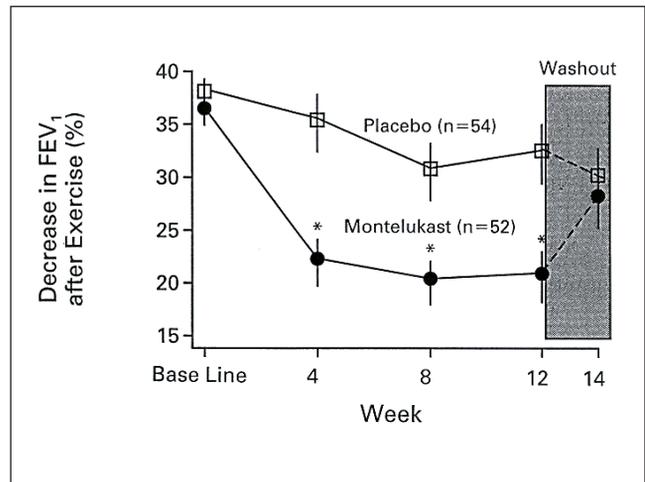
**TABLE 1**  
**Summary of the protective effects against exercise-induced bronchoconstriction (EIB) from antileukotriene agents**

Reference	Agent	% attenuation of EIB
44	MK-571 (receptor antagonist)	70
120	ICI 204219 (receptor antagonist)	40
121	SK&F 104353 (receptor antagonist)	31
122	ICI 204219 (receptor antagonist)	52
43	Zileuton (5-LO inhibitor)	45
42	ABT-761 (5-LO inhibitor)	61
45	Cinalukast (receptor antagonist)	44
86	Montelukast (receptor antagonist)	47
87	Montelukast (receptor antagonist)	59

LO Lipoxigenase

sponse to this short effective duration, new classes of longer acting inhaled beta<sub>2</sub>-agonists are currently available. Treatment with the inhaled long acting beta<sub>2</sub>-agonist salmeterol (50 µg) provides almost complete attenuation of EIB, when taken 30 mins before exercise (78,79). Moreover, the degree of attenuation of the postexercise fall in FEV<sub>1</sub> at this dose remains greater than 50% compared with placebo or short acting beta<sub>2</sub>-agonists for at least 12 h (74,75,78-80). Also, inhaled formoterol has been shown to almost completely prevent EIB when taken 30 mins before exercise (73) and to attenuate at least 50% of the postexercise fall in FEV<sub>1</sub> compared with placebo or short acting beta<sub>2</sub>-agonists 4 to 12 h following treatment (71,72,76,81). Clearly, these longer acting agents solve the problem of the short duration of protection afforded by single doses of salbutamol, terbutaline or fenoterol.

However, there is strong evidence that regular treatment with long acting beta<sub>2</sub>-agonists results in a loss of protection. Ramage et al (82) observed the protective effects of a single dose of salmeterol (500 µg inhaled) on exercise challenges 6 and 12 h later, both before and after a four-week period of regular treatment with salmeterol (500 µg twice daily) in 12 adults with asthma. Before the period of regular treatment, salmeterol attenuated 65% of the postexercise fall in FEV<sub>1</sub> 6 h after treatment and 40% 12 h after treatment, both significantly different than placebo. When the same treatment and challenges were performed following four weeks of regular treatment, attenuation of both challenges was less than 30% and not significantly different than placebo treatment. In a similar study, 14 children with asthma were treated for four weeks with once daily salmeterol (500 µg inhaled) (83). In this study, following four weeks' treatment, the protective effect of salmeterol was reduced from 67% to 33% and was no longer different from placebo. Furthermore, it has recently been shown that the decline in protection against EIB with time from salmeterol inhalation is faster at the end of a period of chronic treatment than after a single dose (84). While no studies have reported a loss of protective effect against EIB following regular formoterol treatment, diminished protection against methacholine-induced bronchoconstriction has been reported (85).



**Figure 4** The effects of 12 weeks' treatment with placebo or montelukast (10 mg, once daily, 20 to 24 h pre-exercise) on the maximum fall in forced expiratory volume in 1 s (FEV<sub>1</sub>). Values are mean ± SEM. \*Significant difference between groups. Note that approximately 50% protection was afforded by montelukast, there was no loss of protection throughout the treatment period and no rebound worsening of exercise-induced bronchoconstriction during washout. Reproduced with permission from reference 92

Thus, while long acting beta<sub>2</sub>-agonists provide excellent and lasting protection against EIB, this effect may be reduced following periods of regular treatment. Care must be taken therefore, when using these agents frequently for the prevention of symptoms, particularly given that the dose, frequency and treatment duration required for a loss of protection is not known.

**Treatment specifically directed at known bronchoconstricting mediators:** Although inhaled beta<sub>2</sub>-agonists are extremely effective at attenuating EIB, the potential loss of the protective effect with regular or frequent use means that there is a need for protective agents that can be used regularly.

**Anti-LT agents:** The first demonstration that treatment with specific LT receptor (cysLT<sub>1</sub> receptor) antagonists are effective in attenuating EIB was by Manning et al (44). In this study, a single treatment with MK-571 (160 mg intravenously 20 mins before exercise) was effective in attenuating the postexercise fall in FEV<sub>1</sub> by 69%. Several other LT receptor antagonists have been evaluated in exercise challenge studies (42,43,45,86,87). In all of these studies, summarized in Table 1, the agents afforded significant attenuation of EIB.

Adelroth et al (45) addressed the issue of the duration of effectiveness of one LT receptor antagonist in protection against EIB. In this study, subjects were given either placebo or one of three doses of the long acting cysLT<sub>1</sub> receptor antagonist, cinalukast (10, 50 or 200 mg orally). Exercise challenges were performed 2 h and 8 h following treatment. All three doses were effective in attenuating the postexercise fall in FEV<sub>1</sub>, and this protection was still present, to the same extent, 8 h following treatment. Interestingly, in this same study, the protective effect afforded by the 10 mg dose was lost after one week regular treatment (10 mg orally three

times daily). However, this loss of protection did not occur following the same treatment regimen at either of the higher doses. It was concluded from this study that the LT receptor blockade may provide protection against EIB for periods greater than 8 h, but that loss of protection, possibly through receptor upregulation may occur with regular treatment at lower doses. In a subsequent study, exercise challenges were performed after four, eight and 12 weeks of once daily treatment with montelukast (10 mg orally, once daily) (87). In this study, where exercise challenges were performed 20 to 24 h after treatment, the extent of EIB was reduced by approximately 50%, and there was no loss of protection observed with time (Figure 4). These findings are supported by the preliminary report that loss of protection against EIB occurred following eight weeks' treatment with salmeterol, while the protective effect of montelukast was maintained (88).

While the degree of protection afforded with anti-LT treatment does not appear to match that with short acting inhaled beta<sub>2</sub>-agonists, the duration of effectiveness and sustained protection with regular use suggests a useful role in the management of EIB. This is particularly true for children and athletes, who often exercise frequently throughout the day. In one study, the treatment of children age six to 14 years, with the LT receptor antagonist montelukast, reduced the extent of EIB by 59% when exercise challenges were performed 20 to 24 h after treatment (86). In this group, for whom regular treatment with inhaled beta<sub>2</sub>-agonists may have diminishing effectiveness (77,82), anti-LT treatment may prove to be valuable.

**Anticholinergics:** Treatment with the inhaled anticholinergic agent, ipratropium bromide, has been effective in reducing EIB in some studies but not in others. Poppius et al (89) found no protective effect against EIB following inhalation of ipratropium (0.2 to 2 mg) 1 h before exercise. Boulet et al (60), and Finnerty and Holgate (33) have reported protective effects of 54% and 34%, respectively. While it appears that anticholinergic treatment may offer only modest protection and not be effective in all patients, it may be useful in some patients, particularly when used in combination with other agents (33).

**Antihistamines:** Pretreatment with the oral antihistamine terfenadine has been shown to offer some protection against EIB. In two separate studies, Finnerty and Holgate (33,90) have demonstrated that terfenadine treatment (180 mg) attenuates the postexercise fall in FEV<sub>1</sub> by 18% to 36%. MacFarlane and Heaf (34) have shown that terfenadine treatment attenuates the postexercise fall in FEV<sub>1</sub> by 32% in 20 children with asthma. This degree of protection is modest compared with other agents. However, the combination of terfenadine with other treatments may provide additive effects. For example, it has been shown that the combination of terfenadine and ipratropium bromide treatment results in attenuation of the postexercise fall in FEV<sub>1</sub> by 55%, significantly greater than the protection afforded by either agent alone (33). With growing concern over the use of frequent or regular treatment with inhaled beta<sub>2</sub>-agonists, treatment with drug combinations such as this may become more common in the management of EIB.

### **Cromones – Cromolyn sodium and nedocromil sodium**

**Cromolyn sodium:** It has been known since 1972 that cromolyn sodium inhaled before exercise substantially attenuates the degree of bronchoconstriction in patients with asthma (91,92). Silverman and Turner-Warwick (92), in the first randomized, placebo controlled trial, showed that cromolyn (20 mg, inhaled 10 to 15 mins before exercise) attenuated the postexercise fall in FEV<sub>1</sub> by 62%. Since these first studies, the effects of cromolyn, inhaled in various forms, have been studied extensively. In a dose response study of 11 young adults, it was shown that the maximum degree of protection achieved was a 70% attenuation of the postexercise fall in FEV<sub>1</sub> (93). This protection was achieved with a dose of 20 mg (aerosolized metered dose inhaler), while less protection (55% attenuation) was achieved at the lower dose of 10 mg. The duration of protection afforded by different doses of cromolyn has also been studied (94). In this study, the maximum protection, a 75% attenuation of the postexercise fall in FEV<sub>1</sub> was afforded by 20 mg (metered dose aerosol) inhaled 15 mins before exercise. In this same study, there was still 64% attenuation of the postexercise fall in FEV<sub>1</sub> when 20 mg of cromolyn was inhaled 4 h before exercise, while smaller degrees and durations of protection against EIB were afforded by lower doses. In another study observing the duration of protection, 20 mg of cromolyn provided only 41% attenuation of the postexercise fall in FEV<sub>1</sub> when inhaled 2 h before exercise and no protection when inhaled 4 h before exercise (95). Thus, there is strong evidence that cromolyn provides considerable protection against EIB, provided it is taken shortly before exercise.

It is quite common to treat patients with combinations of cromolyn and beta<sub>2</sub>-agonists to manage EIB. Support for this practice can be found in a study where terbutaline sulphate (1000 µg) and cromolyn (20 mg aerosol) were inhaled either alone or in combination 20 mins before isocapnic hyperventilation and found to have additive protective properties (96). In an attempt to reproduce these findings during exercise, Woolley et al (62) treated patients with terbutaline sulphate (500 µg) and cromolyn (2 mg aerosol) alone or in combination at several times before exercise. These authors did not observe any additive protection from the combination of the two agents. However, the dose of cromolyn in this study was only 2 mg, which is suboptimal (93,94).

**Nedocromil:** Nedocromil, inhaled before exercise, has been shown to attenuate the magnitude and duration of EIB. Inhalation of a range of concentrations of nebulized nedocromil (0.5 to 20 mg/mL), as well as 4 mg of aerosolized nedocromil, offered similar degrees of attenuation of the postexercise fall in FEV<sub>1</sub> (50% to 62% attenuation) (97). While it is clear the nedocromil offers protection against EIB, there is no evidence that this protection is any greater than that provided by cromolyn. In direct comparisons of these agents, there has been no advantage in terms of the degree of protection against EIB (95,98). In one study however, cromolyn still afforded protection against EIB 2 h after treatment, while nedocromil did not (95).

### Nonpharmacological attenuation of EIB

**Conditioning of inspired air:** EIB is thought to be caused by respiratory heat loss, brought about by both the heating and humidification of inspired air. This theory is supported by studies demonstrating that virtually no bronchoconstriction occurs with warm humid air breathed during exercise by individuals who experience bronchoconstriction following the same exercise with cold or dry air (99-101). Several investigators have tried to capitalize on these findings by attempting to reduce the severity of EIB by conditioning the inspired air of patients with asthma. In the simplest of the manipulations, 10 children with asthma experienced significantly less bronchoconstriction following exercise during nasal breathing (8% fall in FEV<sub>1</sub>) than during either spontaneous (16%) or mouth breathing (22%) (102). In another study, nasal breathing appeared to protect children with asthma following exercise of uncontrolled intensity (103). Expanding on these observations, other investigators have observed that a heat and moisture exchanger attenuates hyperpnea-induced bronchoconstriction (104) and that warming masks attenuate postexercise (in cold air) bronchoconstriction by up to 80% (105,106).

**Exercise training:** Bronchoconstriction following exercise is related to the respiratory heat loss, a function of the movement of air rather than the exercise itself. Thus, if patients were able to exercise at a lower minute ventilation at the same level of exercise (as would be expected with increased cardiovascular fitness), they should experience less bronchoconstriction. To determine whether this is the case, several investigators have observed the effect of training on EIB. In several of these studies, results are difficult to interpret, due to lack of a control group (107), failure to demonstrate improved cardiovascular fitness after training (108,109) or failure to ensure that pre- and post-training exercise challenges were at the same absolute work rate (110). In a controlled study, where 22 adults with asthma receiving training experienced a 15% increase in peak oxygen consumption, patients were challenged with the same magnitude of exercise before and after training (111). In this study, the training resulted in a 64% attenuation of the postexercise fall in FEV<sub>1</sub>. In a similar study of children with asthma, exercise training produced a smaller (27%) but still significant attenuation of EIB (112). Obviously, the benefits from training are beneficial only if the patients continued to exercise at their pretraining intensity. When patients are allowed to exercise freely following training, the degree of bronchoconstriction remains unchanged (110). Thus, while training should certainly not be discouraged in patients with asthma, it may not reduce their symptoms or treatment requirements associated with exercise.

**Modifying the pattern of exercise:** In most patients, following an episode of EIB, there is a period where further exercise is followed by a smaller episode of bronchoconstriction (113). This 'refractory period' can be prevented by prior treatment with indomethacin (114), and is likely due to the release of prostaglandin E<sub>2</sub>, which has been shown to protect against EIB (115).

Several investigators have attempted to design exercise programs that use this phenomenon to reduce the severity of

EIB experienced by patients during exercise. The simplest of these modifications involves the introduction of a warm-up period of exercise before a bout of exercise known to produce EIB. The first investigation of the effect of warm-up showed that inclusion of a 3 min bout of moderate work rate exercise before 5 mins of higher intensity exercise had no influence on the magnitude of the subsequent EIB (116). However, in this study, there was no break between the warm-up and the challenge exercise. Current understanding of the refractory period following EIB would predict that some separation between the warm up and the challenge should be allowed for an increased production of bronchoprotective prostaglandins to take place. Presumably, this would also require at least a small degree of bronchoconstriction following the warm-up period. In another study, 10 adults with asthma were required to exercise for 30 mins warm-up at a moderate work rate followed 21 mins later by a 6 min exercise challenge at a higher work rate (117). The postexercise fall in FEV<sub>1</sub> following these two bouts of exercise was 17% and 26% below baseline, respectively. When the 6 min exercise bout was performed without warm-up, the fall in FEV<sub>1</sub> was 46% below baseline. Thus, in this case, the period of warm-up resulting in a modest degree of bronchoconstriction resulted in a 43% attenuation of the magnitude of EIB following a subsequent period of more intense exercise. Other investigators have observed that similar protection is afforded by performing seven repeated 30 s sprints approximately 30 mins before an exercise challenge (118). These findings strongly support a prolonged period of modest exercise 20 to 30 mins before vigorous exercise for both elite and recreational athletes.

In an alternative approach, Morton et al (119) have shown that separating a standard 6 min exercise challenge into progressively smaller components separated by periods of rest can result in a progressively greater attenuation of subsequent EIB. The greatest degree of protection was found when the exercise was performed as 36 repetitions of a 10 s bout of exercise with 30 s rest between each bout. In this case, the postexercise fall in FEV<sub>1</sub> was attenuated by 74%. Certainly, these findings suggest a pattern of exercise that could easily be adopted by patients to reduce their symptoms associated with exercise.

### SUMMARY

The initial management of asthmatic patients with EIB is to manage asthma optimally, which in most cases will involve the use of inhaled corticosteroids. This treatment over a period of weeks will, in most cases, reduce the magnitude of EIB by at least 50%. There will, however, be patients who continue to have symptoms associated with exercise that require further treatment. When the occurrence of these symptoms are infrequent, then control with short acting inhaled beta-agonists provides almost complete attenuation of symptoms. Care should be taken, however, because this protective effect can be diminished with frequent beta<sub>2</sub>-agonist use. This is also the case for the long acting beta<sub>2</sub>-agonist, salmeterol. In patients requiring frequent protection from EIB

despite appropriate steroid use, additional treatment with cromolyn or LT blocking agents should prove beneficial. Where daily prolonged protection is required, particularly in school-aged children, LT blocking agents may be a valuable treatment option. Additional protection may be obtained by the addition of agents including antihistamines and anticholinergic agents, although the additional benefits obtained by

all the possible drug combinations remain to be described. Finally, nonpharmacological interventions are possible and may reduce or eliminate the need for one or more drugs in some patients.

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