Exercise induced bronchoconstriction in childhood asthma
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Chapter 8
Assessment of exercise induced bronchoconstriction in adolescents and young children

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ABSTRACT

Recent research shows important differences in exercise induced bronchoconstriction (EIB) between children and adults, suggesting a different pathophysiology of EIB in children. Although exercise can trigger classic symptoms of asthma, in children symptoms can be subtle and nonspecific; parents, children, and clinicians often do not recognise EIB. With an age-adjusted protocol, an exercise challenge test can be performed in children as young as 3 years of age. However, an alternative challenge test is sometimes necessary to assess potential for EIB in children. This review summarises age-related features of EIB and recommendations for assessing EIB in young children and adolescents.

KEY POINTS

- Adults and children show differences in exercise induced bronchoconstriction (EIB).
- The time course of EIB is age-dependent; the younger the child, the shorter the time to maximal bronchoconstriction and the quicker the recovery from EIB.
- Many children with EIB have breakthrough EIB (bronchoconstriction starting during exercise).
- EIB symptoms are poorly recognised by children, parents and clinicians.
- An age-adjusted exercise challenge test is the first choice test to assess EIB in children, and is feasible in children as young as 3 years.
- Alternative bronchial provocation tests are available when exercise tests cannot be performed.
INTRODUCTION

Exercise induced bronchoconstriction (EIB) is defined as a transient narrowing of the airways that follows vigorous exercise\(^1\). EIB is a common manifestation of asthma in children and adolescents, occurring in up to 90\% of the asthmatic children\(^2,3\). Its prevalence in the general pediatric population is between 6 and 20\%\(^2,4,5\).

EIB compromises the participation of children in play and sports, and may result in a negative influence on quality of life, cardiovascular condition and psycho-motor development\(^6-8\).

In children, EIB is highly specific for asthma\(^9\), and because EIB reflects airway inflammation, it indicates uncontrolled asthma\(^9-11\). Thus the assessment of EIB in children is used to not only diagnose EIB but also to monitor asthma.

Time course of EIB in children

EIB is characterised as a reduction in post-exercise pulmonary function\(^3,12\). The course of EIB in children generally consists of an initial bronchodilatation early during exercise\(^12\). The bronchoconstriction typically begins after cessation of exercise\(^4,13\), but may start during exercise ('breakthrough' EIB)\(^14,15\), and peaks 2 to 15 minutes after exercise\(^2,13,15,16\).

Figure 1. Mean expiratory volume in 0.5 second (FEV\(_{0.5}\)) ± standard deviation during and after exercise in 5-to 7-year-old children with breakthrough exercise induced bronchoconstriction (EIB) (ie, ≥13\% decrease in FEV\(_{0.5}\) during exercise, sustained after exercise; lower graph) and non-breakthrough EIB (ie, ≥13\% decrease in FEV\(_{0.5}\) after exercise; upper graph).

Note that the children with breakthrough EIB have a more severe decrease in pulmonary function and slower recovery from EIB compared with non-breakthrough EIB, indicating severe EIB\(^15\). As percentage of baseline.

* administration of 100 µg salbutamol. SABA, short-acting β\(_2\)-agonist (ie, salbutamol). Data from van Leeuwen et al.\(^15\)
as shown in figure 1. This is followed by spontaneous recovery of pulmonary function, which can last about 30 to 60 minutes\textsuperscript{2,13}. About 50% of the children with EIB subsequently experience a refractory period, which can last between 45 minutes and 3 hours\textsuperscript{2,17}.

Several studies showed that the course of EIB changes with age\textsuperscript{13,18}. Vilozni and colleagues\textsuperscript{13} systematically assessed the relationship between age and time to maximal bronchoconstriction (Nadir-$t$) after exercise. These investigators retrospectively reviewed data of exercise challenge tests in 4-18-year-old children and adolescents, and found a significant relation between age and Nadir-$t$ ($r^2=0.54$, $p<0.001$)\textsuperscript{13}. The mean Nadir-$t$ was at 5.1 ± 2.6 minutes, and none of the children reached Nadir-$t$ later than 12 minutes after exercise\textsuperscript{13}. Another study investigated the spontaneous recovery of pulmonary function after maximal bronchoconstriction, induced by exercise and histamine, in 7- to 12-year-old children with EIB. The recovery rate (ie, % increase in forced expiratory volume in 1 second (FEV\textsubscript{1}) per minute) for EIB decreased significantly with increasing age, in contrast to the recovery rate for histamine\textsuperscript{18}. Thus, the younger the child, the shorter the time to maximal bronchoconstriction after exercise and the quicker the recovery from EIB\textsuperscript{13,18}.

![Figure 2. Relation between age and time to breakthrough EIB, defined as a >13% decrease in FEV\textsubscript{1} or FEV\textsubscript{0.5} during exercise (N=27). r=0.73, p<0.01. Note: data reproduced from different exercise protocols by van Leeuwen et al.\textsuperscript{14,15}](image-url)
Breakthrough EIB in children

EIB has been described as airway narrowing occurring after the cessation of exercise. However, several studies assessing pulmonary function in asthmatic children during exercise have found that EIB often occurs during, and is sustained after, exercise; this is known as breakthrough EIB\(^{14,15,19}\). Breakthrough EIB (defined as a 15% decrease in FEV\(_1\) during exercise) has been described in 8-to 15-year-old asthmatic children, occurring 6-10 minutes after the start of exercise and before cessation of exercise\(^{14}\). Another study, measuring FEV\(_{0.5}\) during and after exercise in 5-to 7-year-old asthmatic children, showed that breakthrough EIB (defined as a 13% decrease in FEV\(_{0.5}\)) in this age group can even occur within 2 minutes of starting exercise, suggesting a shift of the breakthrough phenomenon with age\(^{15}\). The relation between age and time to breakthrough EIB as derived from the data from studies of van Leeuwen and colleagues\(^{15}\) is shown in figure 2. Breakthrough EIB is accompanied by a more severe decrease in pulmonary function and slower recovery from EIB compared with non-breakthrough EIB, indicating severe EIB\(^{15}\). Therefore in children, symptoms of dyspnea within minutes of starting exercise may well be caused by EIB and may result in the child quickly dropping out of play and sports.

Pathophysiology of EIB in children

EIB is thought to be largely caused by dehydration of the respiratory mucosa during exercise induced hyperpnea. This airway dehydration leads to hyperosmolarity of the mucosa and subsequent release of inflammatory mediators, causing bronchoconstriction\(^1\). Another proposed mechanism for EIB is the thermal hypothesis, which states that exercise induced hyperpnea causes airway cooling. After exercise, when hyperpnea ceases, the airways rapidly rewarm, leading to engorgement of the hyperplastic vascular bed in the asthmatic airway wall and subsequent bronchoconstriction\(^{20}\). The quick onset of bronchoconstriction during exercise (breakthrough EIB) and the rapid recovery from EIB after exercise, as observed in young children, are not compatible with the thermal hypothesis. Indeed, rapid rewarming of the airways was not shown to enhance EIB in children\(^{21}\). The thermal phenomenon, however, may contribute to EIB and explain the protracted recovery seen in asthmatic adults, particularly those exercising in a cold environment.

Several mechanisms could explain the quick onset of EIB in young children compared with older children and adults. Exercise induced hyperpnea is associated with the increased urinary excretion of inflammatory mediators\(^{22,23}\). EIB in children has been successfully inhibited by leukotriene antagonists\(^{24}\), loradamine (an antihistamine)\(^{25}\), and mast cell stabilisers, such as sodium cromoglycate and nedocromil sodium\(^{26}\), supporting a role for inflammatory mediators in EIB. Perhaps their release occurs faster in children than in adults, owing to swift changes in osmolarity. Young children may be prone to rapid airway dehydration, as their minute ventilation is relatively high and their capac-
ity to humidify the inspired air low in comparison with adults. Mast cells respond rapidly to a change in osmolarity, as shown many years ago. Furthermore, the airway smooth muscle in young airways could have a shortened response and relaxation time in comparison with adolescents or adults. This rapid hyperresponsiveness of young airways may account for breakthrough EIB and the rapid pattern of bronchoconstriction after exercise in young children. Finally, breakthrough EIB could be explained by a failure of the exercise induced release of bronchoprotective prostaglandins, such as PGE$_2$, as suggested by Larsson and colleagues, to counterbalance the mast cell mediators causing bronchoconstriction during exercise. Further research is necessary to clarify these mechanisms, and particularly to measure the release of bronchoconstrictive and bronchoprotective mediators in children with breakthrough and non-breakthrough EIB.

Assessing EIB in children; recognition of symptoms

The characteristic presenting symptoms of EIB include chest tightness, wheeze, and cough. However, EIB in children can also be accompanied by subtle, nonspecific symptoms, such as fatigue, abdominal or chest pain, or headache. It has been shown that reported symptoms do not correlate with the presence of EIB. For example, most children with EIB cough, but as with adult athletes, this symptom is not specific for EIB. Panditi and Silverman investigated the relationship between parent-reported and child-reported EIB symptoms and laboratory-diagnosed EIB, and concluded that reported symptoms weakly relate to objective measures of severity of EIB. Children seem to have a poor perception of EIB symptoms, and may fail to notice symptoms until taking part in organised sports. About 50% of children with asthma who reported a negative history of EIB had a positive response to an exercise challenge test (ECT). Parents’ perception of the extent and severity of their children’s EIB did not relate to any measurement of lung function. Even clinician-observed symptoms seem to be poor predictors of EIB, leading to both false-positive and false-negative diagnosis and treatment of EIB.

Assessing EIB in children; questionnaires

Asthma control questionnaires, such as the Asthma Control Questionnaire (ACQ) or the (Childhood) Asthma Control Test ((C)-ACT), are widely used and validated measures for the evaluation of asthma control. As EIB is considered to be a sign of uncontrolled asthma, one could expect a significant relation between questionnaires and EIB. However, the ACT failed to detect EIB in a significant percentage of 6-to 17-year-old asthmatic children. A similar study investigated EIB in 5-to 7-year-old children, and showed a poor association between the C-ACT and EIB, even during provocative exercise challenges in cold, dry air. Chinellato and colleagues observed that nocturnal symptoms related better with EIB than symptoms indicating activity limitations, reinforcing
the notion that the occurrence of EIB can be considered a sign of poor asthma control\textsuperscript{9-11}. A limitation of the ACT is the lack of an exercise-specific question. The ACQ does have a distinct question regarding exercise limitations, but also showed no relation with the occurrence of EIB\textsuperscript{43}. This study described a positive predictive value of 51% and a negative predictive value of 59% to predict EIB in adolescents, when using the ACQ cutoff points set by Juniper and colleagues\textsuperscript{38,43}. The relationship between the individual ACQ score and exercise induced decrease in FEV\textsubscript{1} as investigated by Madhuban and colleagues\textsuperscript{43}, is shown in figure 3.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Relation between asthma control questionnaire (ACQ) score and exercise induced decrease in FEV\textsubscript{1}, as percentage decrease from baseline (N=200). Dotted lines represent cutoff value for EIB (ie, 15\% decrease in FEV\textsubscript{1}) and cutoff values for asthma control (<0.75 well-controlled asthma, >1.50 not well-controlled asthma). FEV\textsubscript{1}, forced expiratory volume in 1 second. Figure reproduced by Driessen with data from Madhuban et al.\textsuperscript{43}}
\end{figure}

One may conclude that although EIB is one of the hallmarks of asthma in children and is a clear sign of uncontrolled asthma, children, parents and clinicians seem to be unable to grasp its presence without testing.
Assessing EIB in children; exercise challenge test

ECTs have been studied extensively and are well standardised for children older than 8 years\textsuperscript{5,16,44}. Children younger than 8 years can perform ECTs as well, using an age-adjusted approach\textsuperscript{15,16,45}. Vilzoni and colleagues\textsuperscript{16} performed ECTs in children as young as 3 years.

An ECT consists of pulmonary function measurements before and after exercise. Although an ECT remains the first choice bronchial provocation test (BPT) to assess EIB in children\textsuperscript{2}, it should be interpreted carefully. The advantage of an ECT in the assessment of EIB is that it is a “real-life” test, providing direct insight, for both parents and clinicians, in the severity and course of a child’s EIB. Especially for children, an ECT can be more enjoyable than other BPTs.

The limitation of the ECT lies in standardising the many factors that can affect the airway response to exercise, such as the temperature and water content of the inspired air, and the duration and intensity of exercise. Insufficient attention to these important determinants of EIB may produce false-negative outcomes\textsuperscript{46}. The airway response to exercise is moderately reproducible; the variability in the percentage decrease in FEV\textsubscript{1} for children is 13.4\% (figure 4)\textsuperscript{47}. Therefore more than one ECT may be required to include or exclude EIB\textsuperscript{47}. This variation in airway response could be due to different factors, such as changes in intensity of exercise, environmental or dietary factors, or the

![Figure 4. Variability in the percentage exercise induced decrease in FEV\textsubscript{1} between 2 exercise challenge tests within 4 days in children with mild symptoms of asthma (N=95). The interval defines the 95\% probability that the difference between a single measurement and the true value for the subject is within that range. Figure reproduced with permission from Anderson et al.\textsuperscript{47}](image)
intrinsic reproducibility of an ECT itself. Moreover, particularly in children, variability in airway response could be the result of refractoriness, as children have multiple bouts of physical exercise during the day. Finally, an ECT in its current form does not have a dose response, and ECTs can trigger severe decreases in pulmonary function. The latter could be overcome when measuring pulmonary function during exercise, to identify breakthrough EIB.

**Exercise challenge test; pulmonary function measurements**

The most widely used guidelines for testing are from the 1999 American Thoracic Society statement, and recommend FEV₁ as the primary outcome variable for detecting EIB. A post-exercise decrease in FEV₁ of 10% is generally accepted as diagnostic for EIB, although other cutoffs have been suggested for use in children, such as 13% and 15%. Alternative spirometric measures such as FEV₀.₅ can be used as well, as most young children are unable to perform the required full forced expiration during a total second. In a recent study, 69% of 5-to-7-year-old children showed a baseline Tiffeneau index (FEV₁/forced vital capacity) of 90% or greater, demonstrating that FEV₁ almost equaled forced vital capacity, which could reduce the usefulness of FEV₁ as an index of airway obstruction.

The use of big-breath tests such as FEV₁, to evaluate EIB, may in itself influence the obstruction as a deep breath may lead to bronchodilatation or bronchoconstriction. The forced oscillation technique (FOT) does not rely on forced breathing manoeuvres, and is an elegant method to analyse the patency of the airways, for example in young children unable of performing spirometry. The FOT analyses the resistance and reactance of the airways using acoustical impedance. The resistive component of respiratory impedance (Rrs) depends on the airway caliber. The reactive component of respiratory impedance (Xrs) incorporates the mass-inertive forces of the air column in the conducting airways and the elastic properties of lung periphery, namely lung stiffness, intraparenchymal airway mechanics, and airway-parenchyma interdependence. The FOT has been used to evaluate EIB, and Malmberg and colleagues suggested that an increase of more than 35% in the Xrs at 5 Hz indicated the presence of EIB in young children.

**Schedule of pulmonary function measurements**

Pulmonary function measurements should be performed before (baseline) and serially after exercise, using a standardised schedule. A general recommended appropriate testing schedule is 5, 10, 15, 20 and 30 minutes after cessation of exercise. However, because the time to maximal bronchoconstriction and recovery from EIB in children is age-dependent, the schedule of post-exercise pulmonary function measurements should be cautiously trimmed. Vilozni and colleagues investigated EIB in 3-to-6-year-old children, measuring pulmonary function at 1, 2, 3, 5, 10 and 20 minutes after
exercise. Maximal bronchoconstriction often occurred within 3 minutes after exercise, and could disappear as soon as 5 minutes after exercise. The investigators concluded that the exclusion of measurements up to 5 minutes after exercise may miss or underestimate the severity of the bronchoconstriction. Another study measured EIB and breakthrough EIB in 5-to 7-year-old children, measuring pulmonary function at 2, 4, and 6 minutes during exercise and at 1, 2, 3, 5, 7, 10 and 15 minutes after exercise. In this study the mean maximum bronchoconstriction was at 2 minutes after exercise, which corresponds to data from Vilozni and colleagues. Pulmonary function in most 3-to 7-year-old children recovers within 15 to 20 minutes, which allows earlier termination of pulmonary function measurements in comparison with an adult ECT. Moreover, young children have a short attention span and easily fatigue as a result of repeated forced breathing manoeuvres. Pulmonary function measurements in this age group therefore require special attention, such as the use of incentives, comfortable position (ie, without nose clip), and skilled and patient technicians.

Measurements of pulmonary function during exercise are feasible in children and can identify breakthrough EIB, providing a thorough assessment of EIB in children.

**Modes of exercise**

The exercise performed during an ECT should be of sufficient duration and intensity to provoke a bronchoconstriction response, and preferably be standardised. Current guidelines recommend 6 to 8 minutes of exercise with 4 to 6 minutes at near-maximum target (heart rate of 80-90% of maximum [220 minus age]). The preferred mode of exercise for an ECT in schoolchildren is the treadmill or cycle ergometer. In children younger than 8 years, free-run tests are often used to assess EIB. However, in young children the duration of running seems to be limited by age, and forced running might be overwhelming, which could lead to a high test failure percentage and possibly underdiagnosis of EIB. Alternative modes of exercise in these young children could basically be any exercise that is sustainable, safe, and enjoyable, and during which heart rate can be reasonably maintained above 80% of predicted maximum. For example, one study successfully performed ECTs in 5-to 7-year-old children using a jumping castle, an inflatable platform that children are familiar with and can safely jump on. During exercise, climatic conditions (air temperature and humidity) should be stable. Optimally, the water content of the inspired air should be less than 10 mg/L, which can be accomplished by testing in an air-conditioned room.

**Assessing EIB in children; alternative challenges**

Although an ECT is usually the first choice to diagnose EIB, alternative tests that mimic the dehydrating effect of exercise induced hyperpnea on the airways are available. Standardised BPTs are used to assess bronchial hyperresponsiveness (BHR) through the
administration of bronchoconstrictor stimuli. BPTs are classified into 2 categories: (1) indirect challenges, whereby a stimulus acts on intermediate cells, such as mast cells, to induce airflow limitation through the release of pro-inflammatory mediators; and (2) direct challenges, whereby a pharmaceutical agent such as methacholine or histamine is the provoking agent that induces expiratory airflow limitation through a direct action on effector cells, such as airway smooth muscle and mucous glands.

The response to a direct stimulus reflects airway smooth muscle function and airway caliber. Although these direct tests are sensitive for identifying BHR in an asthmatic population, they are not specific for asthma. For example, methacholine challenges in girls have a sensitivity of between 71% and 77% and a specificity of 53 to 69% for detecting asthma. Subjects with other pulmonary diseases and even healthy subjects may demonstrate BHR to these stimuli. The response to an indirect stimulus is more closely associated with current airway inflammation, as it reflects the presence and active state of inflammatory cells, such as mast cells and eosinophils, in the airway. Indirect BPTs are therefore highly specific for diagnosing asthma that is currently active, and for this reason can be used to monitor the response to anti-inflammatory treatment. As exercise is considered an indirect stimulus, other indirect challenges, such as mannitol, eucapnic voluntary hyperpnea (EVH), hypertonic saline and adenosine monophosphate (AMP), are preferred over direct challenges for assessing EIB.

**Mannitol**

The inhalation of dry-powder mannitol was developed as an indirect BPT, as mannitol can mimic the airway drying provoked by exercise by dehydrating the airway surface and thereby triggering the release of inflammatory mediators. A mannitol test is performed according to a standard protocol, with inhalation of increasing doses of mannitol. The test ends when a 15% or greater decrease in FEV₁ from baseline or a 10% or greater decrease between subsequent doses occurs, or the cumulative dose of 635 mg mannitol has been administered. Sensitivity to mannitol is expressed as the provoking dose to cause a 15% decrease in FEV₁ (PD₁₅%). Reactivity to mannitol is expressed as the response dose ratio, defined as the final percent decrease in FEV₁ divided by the total cumulative dose of mannitol to induce such a decrease in FEV₁. A mannitol challenge is associated with mast cell release of mediators and an increase in urinary concentration of inflammatory mediators. A mannitol challenge is a suitable alternative for an ECT. With a negative predictive value of 91% it is a useful method to exclude EIB in children. A mannitol test has the built-in safety feature of a progressive dose-response challenge, so the test can be stopped before severe decreases in FEV₁ occur. A majority of patients experience coughing during the mannitol challenge, which in some cases causes a delay in the challenge. As the rate of delivery of the osmotic stimulus is an
important determinant for the severity of induced BHR, this could lead to false-negative tests.

**Eucapnic voluntary hyperpnea**
EVH mimics the airway drying provoked by exercise by voluntary hyperpnea of dry air at a high ventilation rate. A sustained 10% or greater decrease in FEV\textsubscript{1} following EVH is considered consistent with a diagnosis of EIB. A positive EVH test is associated with an increase in urinary excretion of the same inflammatory mediators as exercise\textsuperscript{22}. Although EVH tests with dry, and especially with cold air, are feasible in children as young as 2 years\textsuperscript{73,74}, it is technically a difficult test to conduct properly in children. EVH has the potential to provoke severe bronchoconstriction and should only be performed by highly trained specialists, with safety equipment available.

**Hypertonic saline**
Nebulised hypertonic saline acts by increasing airway surface liquid osmolarity, triggering sensitised cells (in particular mast cells) to release inflammatory mediators\textsuperscript{60,67,69}. During a hypertonic saline challenge, an aerosol of 4.5% hypertonic saline is inhaled for progressively increasing intervals of 1 to 8 minutes\textsuperscript{67,69}. The test is terminated after a 15% or greater decrease in FEV\textsubscript{1} is observed, or when a total minimum dose of 23 g has been administered in 15.5 minutes\textsuperscript{67,69}. As with any osmotic stimulus, cough occurs in the majority of patients (73.5%) with 4.5% saline\textsuperscript{68}. Children who are positive to hypertonic saline are 4.3 times more likely to have EIB than those who are negative\textsuperscript{75}. In 348 asthmatic children, the sensitivity of a PD\textsubscript{15} to 4.5% saline to identify EIB (defined as ≥ 10% decrease in FEV\textsubscript{1}) was 53.9%, with a specificity of 87.6%\textsuperscript{75}. In very young children, hypertonic saline may be easier than EVH or exercise to administer. An advantage of hypertonic saline over exercise and EVH is that it can be used to collect sputum for mediator and cellular analysis concurrently with the measurement of BHR\textsuperscript{67}. Furthermore, the hypertonic saline challenge produces a dose-dependent response, thereby preventing a severe decrease in FEV\textsubscript{1}. A disadvantage of the hypertonic saline challenge is that many factors can alter the output of the aerosol, such as the temperature, the volume of fluid in the nebuliser, the tidal volume of the subject, and the size of the valves and tubing\textsuperscript{69}.

**Adenosine monophosphate**
AMP challenge is a nonosmotic indirect BPT. Dry crystalline AMP powder is dissolved in 0.9% saline and is administered in progressively doubling concentrations via a nebuliser. After inhalation, AMP dephosphorylates into adenosine. Adenosine is a protein that binds to specific G-protein-coupled receptors on the cell surface of mast cells, stimulat-
ing degranulation with subsequent release of inflammatory mediators. The response to AMP is expressed as the provoking concentration to cause a 20% decrease in FEV$_1$. AMP challenge is used in research into mechanisms rather than as a routine BPT. There are limited data available on the sensitivity and specificity of AMP challenge in identifying EIB.

**SUMMARY**

Adults and children show marked differences in EIB; the younger the child, the shorter the time to maximal bronchoconstriction and the quicker the recovery from EIB. The weak relationship between exercise induced symptoms and EIB as measured in ECTs in children urges the use of BPTs. An age-adjusted ECT is the first-choice test to assess EIB in children, and is feasible in children as young as 3 years. An ECT is a real-life and revealing test for both children and their parents. Assessing pulmonary function during exercise to identify breakthrough EIB can provide additional important information about the severity of a child’s EIB.
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