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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Indirect Challenge Tests

Airway Hyperresponsiveness in Asthma: Its Measurement and Clinical Significance

Sandra D. Anderson, PhD, DSc

Indirect challenges cause the release of endogenous mediators that cause the airway smooth muscle to contract and the airways to narrow. Airway sensitivity to indirect challenges is reduced or even totally inhibited by treatment with inhaled corticosteroids (ICS), so a positive response to an indirect stimulus is believed to reflect active airway inflammation. The indirect challenges commonly used in pulmonary function laboratories include exercise, eucapnic voluntary hyperpnea, hypertonic (4.5%) saline, and mannitol. Exercise was the first test to be standardized and was used to identify exercise-induced bronchoconstriction (EIB). The inhibition of EIB in young children by sodium cromoglycate led to the concept that mast cells were important very early in the onset of asthma. All of these indirect challenges are associated with the release of mast cell mediators (eg, prostaglandins, leukotrienes, and histamine). The hypertonic saline and mannitol challenges arose from the concept that EIB was caused by an increased osmolarity of the airway surface with release of mediators. These osmotic aerosols simplified testing with indirect challenges in the laboratory, improving the potential to identify currently active asthma. Although hyperresponsiveness to indirect challenges is frequently associated with a sputum eosinophilia, it is not a prerequisite because the mast cell is the most important source of mediators. The mechanism for ICS reducing hyperresponsiveness to indirect challenges likely involves both mast cells and eosinophils. Indirect challenges are appropriate to inform further on both the pathogenesis of asthma and the role of antiinflammatory agents in its treatment. *CHEST 2010; 138(2)(Suppl):25S–30S*

Abbreviations: BHR = bronchial hyperresponsiveness; EIB = exercise-induced bronchoconstriction; EVH = eucapnic voluntary hyperpnea; FENO = fraction of exhaled nitric oxide; ICS = inhaled corticosteroids; LTE₄ = leukotriene E₄; PD₁₅ = provocative dose of saline or mannitol inducing a 15% fall in FEV₁; PD₂₀ = provocative dose of saline inducing a 20% fall in FEV₁; PGD₂ = prostaglandin D₂; SCG = sodium cromoglycate

“Indirect challenges act by causing the release of endogenous mediators that cause the airway smooth muscle to contract, with or without inducing microvascular leakage. Because the responses to these challenges are modified or even completely inhibited

by inhaled steroids, the airway response to these challenges may be a closer reflection of active airway inflammation.”¹ The indirect challenges act on intermediate pathways, such as via mediator release from inflammatory cells and the release of neuropeptides from sensory nerves. The neurally mediated pathway has not been studied extensively because of lack of easy availability of specific antagonists for clinical trial. Both pathways are affected in asthma, and this may be the reason that tests using stimuli that act indirectly are considered to be more specific for asthma than stimuli that act directly on smooth muscle.

The indirect challenges commonly available in pulmonary function laboratories include exercise, eucapnic voluntary hyperpnea (EVH), ultrasonically nebulized hypertonic saline, and dry-powder mannitol

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(Fig 1).² Other indirect challenge tests not readily available for routine challenge testing include adenosine monophosphate (Fig 1), which acts via the mast cell, and agents such as sodium metabisulphite and sulfur dioxide, which are believed to act via a neural pathway.^{1,3} Most stimuli that provoke an attack of asthma in daily life do so indirectly. Medications used to treat asthma and exercise-induced bronchoconstriction (EIB) frequently normalize the response to an indirect challenge. In 2007, the indirect challenges of exercise and mannitol were included in the Global Initiative for Asthma (GINA) guidelines for establishing a diagnosis of asthma.⁴

EXERCISE AS A TEST OF BRONCHIAL HYPERRESPONSIVENESS

Exercise was the first indirect challenge test to be standardized.⁵ It was developed because the mast cell-stabilizing drug sodium cromoglycate (SCG) could not be evaluated for asthma using either a histamine or a methacholine challenge. Allergen, the indirect challenge being used at the time, was considered inappropriate because of its potential to cause a late asthmatic response. Exercise is a common stimulus for provoking bronchoconstriction, and guidelines usually include exercise tolerance as an indicator of

severity and control of asthma. EIB is usually identified as either a 10%⁶ or 15%^{7,8} fall in FEV₁ after 6 to 8 min of vigorous exercise in a dry environment. Many pharmaceutical companies seek an indication for their drug to prevent EIB, so an exercise challenge test is likely to remain in demand. Exercise is the most common cause of an attack of asthma in children, and the severity of attack increases, with increasing numbers of attacks of wheezing per year.⁸ EIB is an early sign of bronchial hyperresponsiveness (BHR) in children⁹ and EIB is one of the last signs to go with treatment with inhaled corticosteroids (ICS).¹⁰

EIB is associated with increased urinary excretion of mast cell mediators, including prostaglandin D₂ (PGD₂), (measured as the metabolite 9 α ,11 β -prostaglandin F₂) leukotriene E₄ (LTE₄), and histamine.¹¹⁻¹³ These same mediators have been identified in sputum, and the concentrations were reduced by acute premedication with a combination of montelukast and loratadine.¹³ In addition to mast cells, EIB is associated with sputum eosinophilia, and EIB severity is reduced in concert with a reduction in eosinophils after chronic treatment with ICS.¹⁴ However, a sputum eosinophilia is not a prerequisite for EIB.¹⁴ EIB was also inhibited in the majority of children following acute premedication with 1,000 μ g fluticasone 4 h before exercise.¹⁵

Although exercise is a natural stimulus for demonstrating BHR, and EIB has a high positive predictive value for presence of asthma, it is often difficult to identify EIB in the laboratory. The type of exercise is usually limited, and neither cycling nor running exercise is relevant to the subject who complains of symptoms after swimming, rowing, skiing, or skating. The inspired air needs to be "dry" and delivered up to a very high flow rate (> 100 L/min), and the intensity of exercise needs to be vigorous (85%-95% maximum heart rate). To overcome these problems, surrogate tests were developed to identify BHR consistent with EIB.

SURROGATES FOR IDENTIFYING BHR TO INFLAMMATORY MEDIATORS OF EIB

The EVH test breathing dry air (~5% CO₂, 21% oxygen, balance nitrogen) for 6 min at a ventilation target of 30 \times FEV₁ was initially standardized to evaluate army recruits for asthma¹⁶ and later to identify EIB in elite athletes.¹⁷ Field exercise at 2°C was compared with EVH in the laboratory at 19.4°C and responses were found to be equivalent for most winter athletes.¹⁸ EVH can provoke severe falls in FEV₁, so its use is confined to evaluate those who regularly exercise at high intensities. The same mediators associated with exercise and EIB were found after 6 min of

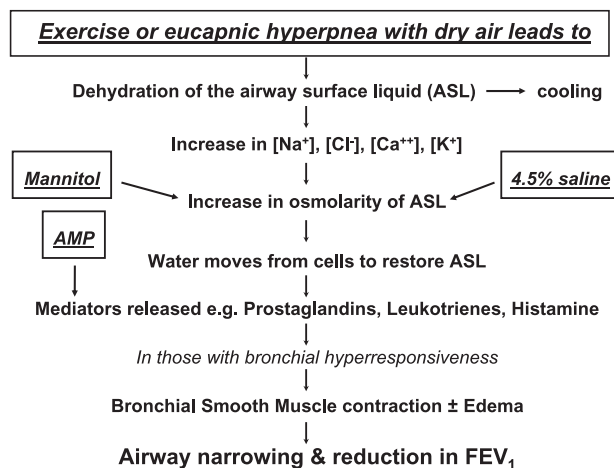


FIGURE 1. The events leading to airway narrowing and a reduction in FEV₁ after indirect challenge tests. During exercise and eucapnic voluntary hyperpnea, airway dehydration occurs as a result of the need to condition large volumes of air in a short period of time. The loss of water by evaporation from the airway surface causes airway cooling and an increase in osmolarity of the airway surface liquid. The stimulus for mediator release is believed to involve the cell volume shrinkage and restoration. Airway cooling may also contribute to the airway narrowing of hyperpnea by causing a reactive hyperemia. Hyperosmolar aerosols increase osmolarity of the ASL directly. AMP acts to release mediators through a specific receptor. Agents like methacholine act directly on the airway smooth muscle. AMP = adenosine monophosphate; ASL = airway surface liquid.

EVH.¹⁹ The response to EVH is also reduced by treatment with ICS.²⁰ The mediator release, particularly PGD₂, and the airway response were both inhibited following 1,500 µg of beclomethasone given 4 h before EVH challenge.¹⁹

The hypertonic (4.5%) saline test was developed to investigate the hypothesis that EIB was caused by a transient increase in osmolarity of the airway surface liquid as a consequence of humidifying large volumes of air during exercise.²¹ The aerosol is generated using a high-output ultrasonic nebulizer and delivered for progressively increasing intervals (0.5, 1, 2, 4, 8 min).²² A positive response, originally defined as a 20% fall in FEV₁, was reduced to 15% after large numbers of healthy subjects had been studied. Subjects with asthma were similarly sensitive to 4.5% saline and EVH.²³ Sensitivity to 4.5% saline was expressed as the provocative dose of saline inducing a 15% or 20% fall in FEV₁ (PD₁₅, PD₂₀, respectively). Children who had a positive response to 4.5% saline (PD₁₅) were 4.26 times more likely to have EIB and 6.96 times more likely to have current wheeze than those who had a negative response.²⁴ The sensitivity (PD₂₀) to 4.5% saline was reduced acutely after 40 mg SCG from PD₂₀ 2.76 mL (control) to 22.2 mL and from 2.76 mL to 16.7 mL after 24 to 56 days of treatment with budesonide 1,000 µg/d. There was a significant correlation between the fold change in PD₂₀ for SCG and budesonide ($r = 0.88$, $P < .01$).²⁵

The hypertonic saline challenge had an advantage over exercise and EVH in that sputum could be collected both in adults and children at the same time as measuring BHR.^{26,27} The sensitivity to 4.5% saline (PD₂₀) after 6 weeks of ICS was related to the percentage of mast cells in the airway epithelium ($r = -0.71$, $P < .05$) and to the percentage of sputum eosinophils reflecting the airway lumen ($r = -0.63$, $P < .05$).²⁷ Asthma duration was related to the epithelial mast cell count ($r = 0.50$).²⁷ The acute effect of 2,400 µg of budesonide was investigated in another study by the same authors, and there was a 2.2-fold shift (95% CI, 1.45-3.33) in the PD₂₀ after 6 h.²⁸ Sputum eosinophils, but not mast cells, were significantly different after this acute treatment with ICS.²⁸ As with EVH, the same mediators associated with exercise have been measured in response to hypertonic saline.²⁹

The mannitol challenge arose from the 4.5% saline challenge and was developed as a point-of-need test requiring no special preparation or clean-up time.³⁰ Mannitol was selected as the osmotic agent as it was generally regarded as a safe molecule for use in both adults and children. Mannitol had suitable properties for encapsulation as a powder and could be delivered through a standard dry-powder inhaler. Mannitol had been shown in vitro to stimulate release of histamine

from human lung mast cells, and this release was enhanced in the presence of anti-IgE.³¹

The mannitol dry powder is delivered in progressively increasing doses (0, 5, 10, 20, 40, 80, 160, 160 mg), with FEV₁ measured 1 min after each dose. A positive response is a 15% fall in FEV₁ at a total cumulative dose of ≤ 635 mg or a 10% fall in FEV₁ from baseline between doses. Sensitivity to mannitol is expressed as the PD₁₅ (mg) and reactivity as the response dose ratio (ie, the final % fall in FEV₁ divided by the total cumulative dose to induce that % fall in FEV₁). The mannitol test has regulatory approval in Australia and 18 countries in Europe and Asia and provides the opportunity for a global standard operating procedure for an indirect challenge.^{32,33} Mannitol as a stimulus acts as a surrogate for exercise, eucapnic hyperpnea, and 4.5% saline.^{30,34,35} Mannitol shares many of the same characteristics of adenosine monophosphate challenge, and the profile of mediators and the effect of pharmacologic agents is similar.^{35,36}

In the original phase 3 study on safety and efficacy, there was also good concordance between responsiveness to 4.5% saline and mannitol in subjects with asthma and healthy subjects.³² In people with signs and symptoms of asthma, but without a definite diagnosis, mannitol had a similar sensitivity and specificity as methacholine (16 mg/mL) for identifying a physician diagnosis of asthma and EIB. However, concordance between different test results in these subjects was not as high as the groups with known asthma or healthy subjects.

Mannitol was shown to release PGD₂, LTE₄, and histamine from cord blood-derived human mast cells and leukotrienes from eosinophils in vitro.^{37,38} Given by inhalation, mannitol is associated with release of PGD₂ and LTE₄ in subjects with asthma and to a lesser extent in healthy subjects.^{39,40} The release of PGD₂, but not LTE₄, is inhibited by SCG and eformoterol (Fig 2).⁴⁰ The consistent finding of mast cell mediators in response to an indirect challenge is in keeping with the current thinking that asthma is a mast cell myositis.⁴¹ The release of mediators from inflammatory cells in association with a measure of BHR gives more information than a test of fraction of exhaled nitric oxide (FENO), which appears to be a reflection of atopy and BHR independent of the diagnosis of asthma.⁴²

BHR to mannitol expressed as PD₁₅ is related to the percentage of sputum eosinophils in patients with asthma not taking ICS.⁴³ A positive response to mannitol can occur, however, in the absence of a significant sputum eosinophilia.⁴³ The reason for this is that the primary mediator for mannitol response is PGD₂, which is of mast cell origin. The resolution of BHR to mannitol over weeks is likely to be associated

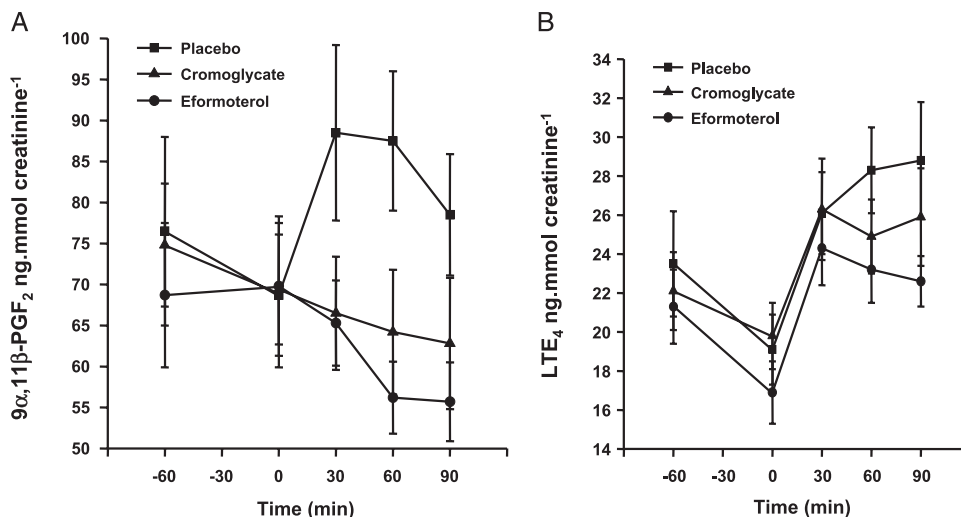


FIGURE 2. Urinary concentration of $9\alpha,11\beta$ -PGF₂ (the major metabolite of the mast cell mediator prostaglandin D₂) (A) and LTE₄ (B) for 60 min before and 90 min after mannitol challenge in 14 subjects with asthma: in the presence of placebo, 2 × 20 mg of disodium cromoglycate, and 2 × 12 μg of formoterol administered as dry-powder aerosols 15 min before challenge with mannitol (252 ± 213 mg). The mannitol and the drugs were delivered using an Inhalator (Boehringer Ingelheim; Ingelheim, Germany). There was a significant increase in $9\alpha,11\beta$ -prostaglandin F₂ ($P < .001$) and LTE₄ following placebo ($P < .001$). The values after challenge were significantly lower at 90 min after cromoglycate ($P < .035$) and at 60 and 90 min after formoterol ($P < .05$). By contrast, for LTE₄, the peak levels vs baseline were not significantly different for the three study days. There was a 32% ± 10% fall in FEV₁ after mannitol after placebo, 11.6% ± 6% after cromoglycate, and 2% ± 3% after formoterol. $9\alpha,11\beta$ -PGF₂ = $9\alpha,11\beta$ -prostaglandin F₂; LTE₄ = leukotriene E₄. (Adapted from Brannan et al.⁴⁰)

with a reduction in sputum eosinophils as with exercise.⁴⁴ A longer time of treatment may be required for resolution of mast cells.²⁷

INTERPRETATION OF A MANNITOL TEST RESULT

Mannitol is used to assess BHR to aid in the diagnosis of asthma. A positive test result to mannitol is consistent with the presence of inflammatory cells (eg, eosinophils and/or mast cells) and their mediators (eg, prostaglandins, leukotrienes, and histamine). Therefore, mannitol is most useful as a test to confirm a diagnosis of currently active asthma in a treated or untreated subject.^{32,33} This gives it an advantage over methacholine. Methacholine is also indicated for the diagnosis of BHR however, its usefulness in clinical practice is in a negative test result ruling out asthma rather than a positive result confirming a diagnosis of asthma.⁴⁵

Although the majority of subjects with mannitol hyperresponsiveness have abnormal FENO > 22 ppb, sputum eosinophilia (> 1%), atopy, and BHR to methacholine, this is not always the case. Hyperresponsiveness to mannitol has been documented in those with a low FENO, with low percentage of eosinophils in sputum, in those who are nonatopic, and in those without BHR to methacholine.^{33,43,46}

A negative mannitol test result indicates a “missing” component (ie, either a bronchial smooth muscle

unresponsive to the endogenously released mediators, as may occur in nonasthmatic eosinophilic bronchitis, or insufficient numbers of inflammatory cells, as may occur in a person treated with ICS).³² Back-titration of ICS dose is likely to reveal the lowest dose that controls BHR to the endogenous mediators. If no BHR returns, then the subject does not have currently active asthma and an exacerbation is unlikely.⁴⁷

A negative mannitol test result in a person not taking treatment can be interpreted as the person being unlikely to have currently active asthma or, if they do, it is only mild. For a person suspected of having asthma on the basis of symptoms, a negative test to mannitol may be a sign to investigate other possible causes of the symptoms, such as obesity and/or gastroesophageal reflux.

For a person with symptoms but a negative test to mannitol, there may be an insufficient number of inflammatory cells or insufficient concentration of mediators and/or the person does not have BHR to those mediators. Some 30% of subjects with mild EIB are not identified with a mannitol test or a methacholine test.³³

An athlete with a positive test result to methacholine but a negative test result to mannitol has BHR but may not have active airway inflammation or significant EIB. Cross-country skiers are good examples of this type of subject.⁴⁸ The BHR in this case may be a sign of airway injury due to conditioning excessive

amounts of air in unfavorable environments.⁴⁹ The inflammation may be a neutrophilia rather than an eosinophilia and reflect airway dehydration. The BHR may not be responsive to treatment with steroids or leukotrienes and usually resolves with cessation of training.⁴⁹

In conclusion, indirect challenge tests have clinical usefulness in identifying BHR that is consistent with airway inflammation responsive to treatment with ICS and with acute administration of mast cell-stabilizing agents. Agents such as mannitol are known to release mediators from both mast cells and eosinophils. In this respect, a mannitol challenge test provides the opportunity for both diagnosis and ongoing assessment of active airway inflammation that may affect both.

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