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Diagnostic Exercise Challenge Testing

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Abstract This article reviews the diagnostic challenge methods—both exercise and surrogate—for diagnosis of exercise-induced bronchoconstriction (EIB) and EIB with known asthma. Indirect challenges that release the entire repertoire of mediators representative of EIB and asthma are more specific for diagnosis and are recommended over direct challenges such as methacholine challenge, which are sensitive but nonspecific. Self-reported history and empiric therapeutic trials are not adequate for diagnosis of EIB with or without known asthma. Objective pulmonary function documentation with bronchodilator reversibility or exercise or surrogate challenge are optimal for diagnosis of EIB or EIB with known asthma. Such objective pulmonary function documentation is optimal for the proper management and healthy lifestyle of the exercising athlete or individual.

Keywords Exercise-induced bronchoconstriction · Exercise · Asthma diagnostic challenge · Surrogate · Pulmonary function · Athlete · Exercise challenge · Testing

Introduction

A critical need exists to provide reliable and reproducible diagnostic testing for exercise-induced bronchoconstriction (EIB) with and without known asthma. Ideally, this testing should be adaptable to the office or clinic setting. Asthma in sports has been documented as being both overdiagnosed and underdiagnosed [1••, 2••, 3, 4, 5••, 6]. Self-report or history and/or empiric trials of therapy are not sufficient to make a diagnosis [2••, 7, 8]; objective confirmation by appropriate pulmonary function testing with bronchodilator or exercise challenge is recommended for elite and less competitive sports participants [2••, 7, 8]. However, the exercise challenge encompassing treadmill, cycle, free running, or sports-specific challenge requires skill in the exercise and often specialized equipment, facilities, and personnel that are not easily adaptable to an office or clinic setting [1••, 2••, 3, 4, 5••, 6–9, 10••, 11•• 12••, 13, 14].

The impact of underdiagnosis is to be deprived of beneficial therapy. Overdiagnosis risks labeling an individual with the inherent social and economic consequences, as well as the adverse reactions stemming from unnecessary therapy. The extension of the need for appropriate diagnosis to the larger laboring community, as summarized by Anderson and Brannan [1••], includes firefighters, police, and other defense occupations, as well as those involved in sports and recreational pursuits such as scuba diving. Appropriate diagnosis is essential for these professions with negative impact from overdiagnosis and underdiagnosis. Thus, there is an urgent need for proper diagnosis with bronchoprovocation [1••, 2••, 3, 4 5••, 6–9].

Exercise is a natural challenge, with a high positive predictive value for asthma acting as trigger in up to 90% of asthma patients, particularly in children, and is the earliest sign of exacerbation and often the last to resolve. However, it is difficult to standardize and reproduce, requiring specialized equipment, skills in the exercise challenge, intensity, and personnel that make it cumbersome for a clinical setting. Therefore, surrogate testing procedures have evolved [1••, 10••, 12••]. This review updates our current knowledge of newly available, as well as existing

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diagnostic challenge testing or bronchoprovocation for asthma diagnosis in sports or with exercise in general.

Bronchoprovocation

There are two forms of bronchoprovocation, direct and indirect, that signify the mechanisms by which bronchoprovocation provokes bronchoconstriction (Table 1). A direct bronchoprovocation agent such as methacholine or histamine is a pharmacologic agent that acts directly on the bronchial smooth muscle receptors, provoking contraction and airway narrowing. Direct airway responsiveness provides an index of airway smooth muscle functionality, and a more variable aspect is related to airway inflammation [1••, 10••, 11•• 12••, 13–16]. These agents or challenges (eg, methacholine) are useful predominantly to exclude current asthma when the outcome is negative.

In contrast, the indirect bronchoprovocation agent or exercise challenge agent, such as exercise, mannitol, or eucapnic voluntary hyperpnea (EVH), provokes release of mediators such as prostaglandins, leukotrienes, and histamine that act on the smooth muscle receptor to initiate contraction. The indirect bronchoprovocation agent elicits the release of the entire spectrum or array of mediators, including histamine, leukotrienes, and prostaglandins, that are pathogenetic and intrinsic to EIB. In contrast, the direct challenge or bronchoprovocation utilizes only a single pharmaceutical agent such as methacholine or histamine. The indirect challenge, such as exercise, requires the presence of a responsive smooth muscle, as with direct challenge, but is more critically dependent on the presence of the broad array of airway inflammatory cells [10••, 11••]. The indirect challenge, with its requirement for responsive smooth muscle and elicitation of a broad array of mediators and inflammatory cells, simulates EIB. Thus, the indirect bronchoprovocation challenges are more specific for diagnosis of EIB and asthma than the direct challenge, though they are less sensitive in excluding asthma [1••, 7, 10•• 11•• 12••, 14–18].

Unlike direct challenges, indirect challenges are negative in nonasthmatics with fixed airway obstruction [1••, 11••, 12••]. Indirect challenges have a higher correlation with eosinophilic inflammation typical of asthma and demonstrate greater amelioration with allergen avoidance and use of inhaled corticosteroids, which are characteristic of asthma [1••, 11••, 12••, 19]. Therefore, these challenges, particularly mannitol, may be utilized for diagnosis and for serially evaluating or monitoring asthma therapy, specifically for adherence to inhaled steroid therapy [1••, 10•• 11•• 12••]. However, indirect challenges such as mannitol are dose limited and induce refractory periods with repeated testing, and cross-refractoriness between different indirect challenges has been demonstrated [20, 21].

Direct Challenges

Methacholine challenge is regarded as a highly sensitive test to elicit bronchial hyperresponsiveness (BHR). Currently, a negative methacholine challenge test is regarded as a sensitive method to rule out asthma [10••, 11••]. However, it is not a specific test for asthma, particularly EIB, which may be overdiagnosed, with important ramifications for occupational or recreational pursuits or settings [1••].

By comparison, there is a high reported prevalence of methacholine-positive tests among elite skiers without EIB [22•, 23] and in individuals without asthma [22•]. These findings suggest that the bronchial hyperreactivity to methacholine may be related to airway injury secondary

Table 1 Comparison of direct versus indirect challenges

Aspect	Direct challenge	Indirect challenge
Mechanism	Single mediator bronchoconstriction	Entire inflammatory cascade
Airway caliber	Minimal importance	Intrinsic
Cost	Inexpensive	Variable (mannitol<methacholine)
EIB diagnosis?	Yes	No
Asthma diagnosis	Used to make diagnosis	Used to rule out asthma
Office use?	Not usually	Yes for mannitol; others require special centers
Sensitivity for asthma/EIB	High	Less sensitive
Specificity for asthma/EIB	Low	Usually higher specificity than methacholine
Equipment	Laboratory usually	Mannitol: less equipment in office
Safety	Safe	Safer, declining FEV_1<30%
Time needed	≥30 min	Shorter, usually <30 min
Exercise?	No	No for surrogates but required for exercise challenge

EIB exercise-induced bronchoconstriction, *FEV_1* forced expiratory volume in 1 s

to ventilation of large volumes of air rather than the pathophysiology of asthma related to EIB [24].

Indirect Challenges

The stimuli for indirect challenges to BHR encompass exercise, hypertonic saline, adenosine monophosphate (AMP), dry powder mannitol, and hyperpnea of cold or dry air or EVH (Table 2). Bronchoprovocation testing that acts indirectly is more specific for characterizing the presence of inflammation that is a corroboration of asthma than methacholine. Indirect challenges are recommended to confirm the diagnosis of asthma [1••, 10•• 11•• 12••] and to monitor response to therapy [25, 26]. The common stimuli for an asthma episode in everyday life act indirectly; this is consistent with the utility of indirect bronchoprovocation to characterize or define BHR [1].

Indirect stimuli are now utilized to evaluate athletes [6, 20, 21, 22•, 23, 27, 28], firefighters [4], defense force personnel [5••], smokers [29], and children [30••, 31••]; to assess cough [32]; to confirm asthma [30]; to evaluate new modalities for measuring airway narrowing [33]; and to evaluate two different bronchial provocation tests on day 1 [34] and define efficacy of medications [35–37]. This enhanced utilization of indirect tests is related to increased commercial availability of a standardized test kit for mannitol inhalation and also the increased need to define or identify EIB. This enhanced utility may also be related to the physician's need to corroborate asthma or EIB so as to justify therapeutic decisions [38] or document the need for therapy [39].

The use of exercise challenge to elicit EIB using free running, treadmill, or cycle ergometry has been standardized since the 1970s [40], when it was developed to evaluate the efficacy of pharmaceutical agents [1••, 12••]. EIB is the most common trigger of asthma, particularly in children, and the earliest sign of exacerbation as well as the last to resolve [1••, 12••]. However, it is difficult to standardize and reproduce and requires specialized equipment, personnel, and the ability to exercise at 85% to 95% maximum heart rate with dry medical grade air and high flow rates (>100 L/min) [1••, 12••]. Surrogate tests have been developed (eg, mannitol) to overcome these obstacles. The laboratory protocol utilized for exercise testing has a higher rate of underdiagnosis than occurs in the field [41]. For this purpose, EVH and mannitol are currently being assessed as surrogates for exercise to identify EIB [6, 28, 30••, 31••, 36, 37, 42••].

Table 2 Comparison of indirect challenges

Factor	LBEC	SSEC	EVH	Mannitol	Saline	AMP
Sensitivity for EIB diagnosis	++++	++++	++++	+	+	+
Specificity for EIB	++++	++++	++++	+++	+++	+++
Sensitivity for asthma	++	++	++	+++	+++	+++
Specificity for asthma	+++	+++	+++	+++	+++	+++
PPV EIB	+++	+++	+++	++	++	++
PPV asthma	+++	+++	+++	+++	+++	+++
NPV EIB	+++	+++	+++	+	+	+
NPV asthma	+	+	+	+	+	+
DR curve?	No	No	No	Yes	Yes	Yes
Exercise requirement?	Yes	Yes	No	No	No	No
FDA approved?	N/A	N/A	N/A	Yes	N/A	No
FEV_1 decreases >30%?	Yes	Yes	Yes	No	No	No
Cough?	Yes	Yes	Yes	Yes	Yes	Yes
DR ratio?	No	No	No[a]	Yes	Yes	Yes
Office?	No	No	No[a]	Yes	No	No
Expense	Yes	Variable	Unknown	No	Unknown	Unknown
Correlation with airway inflammation	High	High	High	High	High	High
Current EIB symptoms correlation	MI	MI	MI	MI	MI	MI

[a] Generally no, but DR and in office EVH (see Rosenthal and Howe [76])

+—fair, ++—good, +++—very good, ++++—excellent, *AMP* adenosine monophosphate, *DR* dose–response, *EIB* exercise-induced bronchoconstriction, *EVH* eucapnic voluntary hyperpnea, *FDA* US Food and Drug Administration, FEV_1 forced expiratory volume in 1 s, *LBEC* laboratory-based exercise challenge, *MI* minimal, *N/A* not applicable, *NPV* negative predictive value, *PPV* positive predictive value, *SSEC* sports-specific exercise challenge

(*Adapted from* Weiler et al. [2••])

BHR to mannitol and to exercise has been correlated with a high fractional concentration of exhaled nitric oxide (FE_{NO}) and a high percentage of sputum eosinophils [43, 44]. These are both markers of inflammation sensitive to inhaled corticosteroids [45]. However, BHR to mannitol and exercise is also sensitive to inhaled corticosteroids and can develop even in the absence of high FE_{NO} or a high percentage of eosinophils [43, 44, 46, 47]. These developments suggest that BHR to mannitol and exercise transpires early in the onset of asthma, when mast cell numbers increase in the epithelium of the airway. Mast cells are significant for the release of bronchoconstrictive mediators, as well as cytokines contributing to BHR and inflammation [48].

BPTs thus act via release of mast cell mediators and are a surrogate for their presence [1••]. Therefore, though, there is no gold standard for objective evaluation for EIB. The indirect challenges, including exercise, EVH, inhaled powdered mannitol, nebulized hypertonic saline, or AMP, are more specific for diagnosis than direct challenges such as histamine and methacholine [10••, 48, 49, 50••]. Furthermore, indirect challenges are recommended [50••] for assessing asthma therapy because airway responsiveness is associated with inflammation that is decreased by inhaled corticosteroid therapy [51], while indirect challenges reflect inflammation intrinsic to EIB, and asthma direct challenges reflect predominantly bronchoconstriction rather than inflammation [50••]. Indirect challenges, including mannitol and EVH currently applied and utilized in clinical settings, will be discussed. These challenges, including exercise and mannitol, were approved by GINA (Global Initiative for Asthma) in 2007 for the diagnosis of asthma [12••].

Exercise Challenge

Exercise challenge, usually with treadmill, has been standardized by the American Thoracic Society for duration, intensity by standardizing minute ventilation, and water content of inhaled air [52–59]. Spirometry is performed at baseline before exercise, then at postchallenge times 1 to 3, 5, 10, 15, 20, and 30 to 45 min after 8 min of exercise following two repeatable FEV_1 (forced expiratory volume in 1 s) efforts at each time point. The International Olympic Committee Medical Commission Independent Panel on Asthma recommends that FEV_1 be recorded at 3 min after the completion of the challenge to overcome the problem of postchallenge respiratory fatigue. A 10% or greater decline in FEV_1 from a forced vital capacity or FEV_1 maneuver at any two consecutive time points within 30 min of ceasing exercise may be considered diagnostic of EIB [2••]. The American Thoracic Society and European Respiratory Society [60, 61] recommend a 10% decline in FEV_1 after exercise as a criterion for EIB based on two SDs from the mean percentage decline in FEV_1 in healthy individuals [62]. Standardized laboratory-engendered EIB challenges have been conducted using 6 to 8 min of exercise with ambient conditions (20–25°C, relative humidity <50%) at 80% to 90% of estimated maximal heart rate as a surrogate standard for Ve [1••, 2••, 50••, 56, 57]. Maximum heart rate is computed by the following formula [63]:

220—Age or (More Accurate) 208—Age in Years×0.7

Current recommendations, especially in children and competitive athletes, are for an 8-minute exercise challenge that approximates 90% to 95% maximum heart rate achieved in 2 min and maintained for up to 6 min [41, 64, 65]. A more abbreviated challenge of 6 or 7 min can be used in children. The treadmill velocity and incline are selected to achieve a total testing duration of minutes, with the final 4 to 6 min at intensity equal to at least 80% to 90% of estimated maximum heart rate. A typical protocol is to begin with a speed of 2.5 mph with an incline of 2.5%, adjusting speed and incline to achieve a heart rate of 80% to 90% maximum heart rate within 2 min and maintained for 8 min [37]. Inhaled medical grade dry air (<5 mg H_2O/L) administered by a gas cylinder with a reservoir bag (Douglas bag) and a one-way valve apparatus is optimal for all exercise challenges to provide optimum sensitivity for diagnosis [50••, 66].

Field-Based Challenges

Free running [40, 57, 66, 67] and sports-specific exercise challenges [68, 69] have been demonstrated to be valid for the evaluation of EIB. These challenges have been validated as more sensitive than laboratory challenges at ambient temperature and relative humidity in the laboratory in elite winter athletes [66]. A comparative study was conducted of sports-specific, field-based exercise challenges of varied duration to a standardized 6- to 8-min laboratory exercise challenge. Laboratory conditions were 21°C, 60% relative humidity, and exercise intensity of 95% of peak heart rate. Eighteen of 23 athletes tested positive by field and negative by laboratory challenge. Sports-specific challenges have been utilized for Olympic athletes in Nordic skiing, speed skating, ice hockey, and ice skating to evaluate EIB [68]. Free running has demonstrated good validity and reliability to assess airway responsiveness in children 8 to 11 years of age [57–61]. Investigators assessed 8 studies with 232 children with asthma with a

decrease in FEV_1 of 13% after exercise, providing sensitivity of 63% and specificity of 94% [60]. However, the difficulty in standardizing the stimulus and the changing ambient and environmental conditions led to a variability that may limit the free running test as a method for monitoring therapy. The need for more reproducible stimulus and physiologic parameters than free running has made mannitol a promising diagnostic modality for EIB and monitoring therapy [51].

Laboratory Challenges

Laboratory challenges for EIB can have specificity and sensitivity when standardized with the level of minute ventilation achieved and maintained and should be 60% to 85% of maximum voluntary ventilation, which can be estimated by multiplying FEV_1 by 21 and 30, respectively [53, 64]. These challenges can include treadmill (as delineated previously) or cycle ergometry.

The challenge methods using exercise have a variety of problems that limit their utility. The exercise challenge test was utilized by the US Army, but the problems were as follows:

1. Lack of consensus for a gold standard
2. Requirement for instructed personnel to conduct the test
3. Specialized equipment needed
4. Patient inability to perform the test
5. Decreased sensitivity and reproducibility related to numbers 1 to 4 when used in a clinical scenario led to a search for a surrogate or alternative method of diagnosis.

The mechanism of EIB is now postulated to be the evaporative water loss or dehydration and subsequent hyperosmolarity of the airway, with degranulation of mast cell and mediator release impacting the airway. Intensity, duration, and workload of exercise are only related to this mechanism. Therefore, a surrogate method of diagnosis that does not require exercise was developed using hyperosmolar agents, in particular EVH and mannitol, but also hypertonic saline and AMP. These hyperosmolar agents create a hyperosmolar environment that simulates exercise while avoiding the necessity and obstacles of a natural exercise challenge [1••, 17, 20, 70–72].

Surrogate Challenges

Eucapnic Voluntary Hyperpnea Challenge

EVH challenge was designed and standardized by the US Army to evaluate EIB in recruits with asthma [71]. The EVH challenge was later characterized as a diagnostic test for EIB in elite athletes who could not be exercised sufficiently with an appropriate ergometer with natural exercise challenge [41, 70, 72, 73]. EVH has been recommended by the Independent Panel on Asthma of the International Olympic Medical Commission as the gold standard to identify EIB in athletes who request evaluation to utilize an inhaled β-agonist prior to competing in their event [64]. It has demonstrated the greatest sensitivity and positive predictive value of available diagnostic tests for the elite athlete, including swimmers [74], collegiate athletes [42••], and other athletes [6, 62, 75]. It has been compared with physician diagnosis, postbronchodilator, and field or sports-specific exercise such as swimming, exercise challenge in the laboratory by treadmill or cycle, and mannitol, with more favorable sensitivity and positive predictive value [6, 42••, 62, 74, 75]. However, it requires a specialized gas mixture and apparatus, has limited commercial availability, and is conducted only in specialized centers at present. Prototypes are in development in the United States [76].

The EVH challenge demands that the individual breathe dry medical grade air containing 4.9% to 5% carbon dioxide and 21% oxygen, with the remaining balance as nitrogen, at an exercising ventilation rate of between 21 and $30\times FEV_1$ or 60% to 80% maximum voluntary ventilation, respectively. A recommended rate of $30\times FEV_1$ is optimal for trained or highly competitive elite athletes. The lower rate of $21\times FEV_1$ is designed for known asthmatics or individuals with a history of EIB who are not on daily medication. A reproducible decline of at least 10% in FEV_1 is considered positive for diagnosis [50••, 64]. All indirect challenges require an FEV_1 of at least 80% predicted (Fig. 1) for sufficient reliability and safety.

Inhaled Powder Mannitol Challenge

Mannitol is a sugar alcohol that is a stable ingredient in most vegetables and a hyperosmolar agent that has been utilized for bronchial provocation challenge [1••, 2••]. The mannitol provocation test has been approved in the United States, Europe, Asia, and Australia for evaluation of BHR. As with exercise, EVH and hypertonic saline mannitol as an inhaled powder represent an indirect challenge that creates a hyperosmolar environment leading to mediator release from inflammatory cells of the airway with resultant smooth muscle contraction [1••, 2••].

Mannitol is administered as a dry powder inhaled in progressively doubling doses of 5, 10, 20, 40, 80, 160, 160, and 160 mg with a maximal dose of 635 mg, depending on airway response [1••, 2••, 39]. One minute after each dose, the FEV_1 is measured in duplicate by FEV_1 maneuver. The

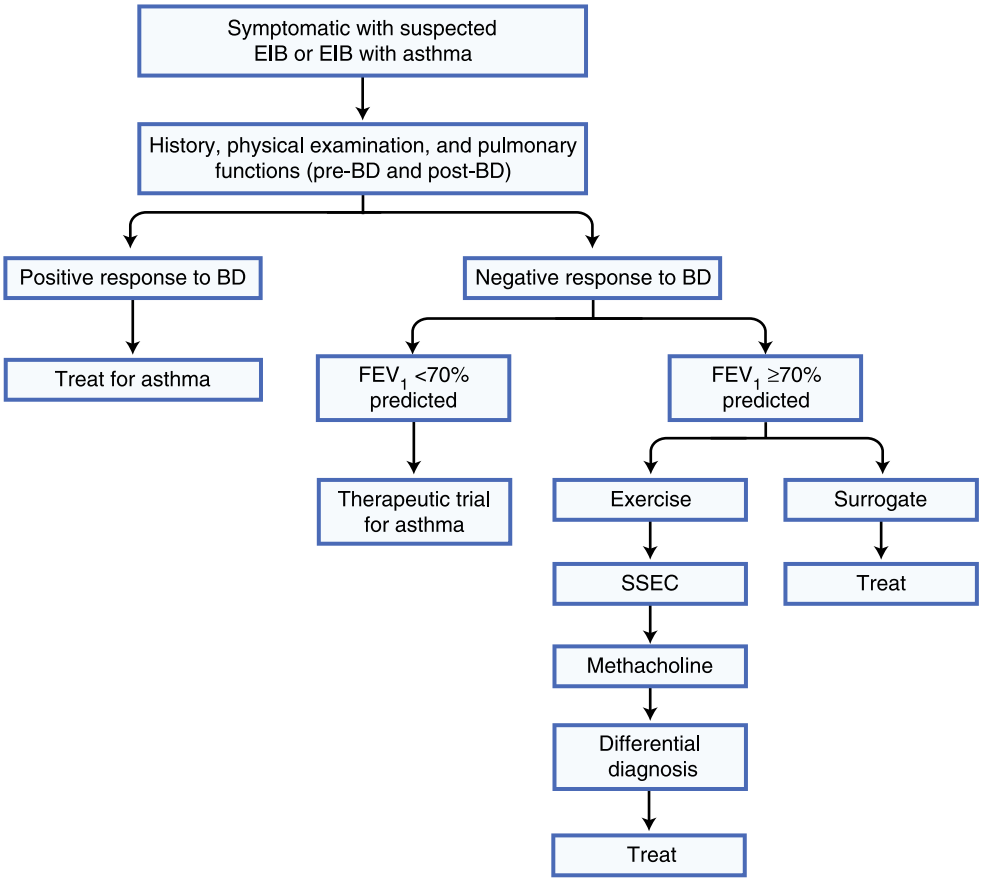

Fig. 1 Treatment algorithm for suspected exercise-induced bronchoconstriction (EIB) or EIB with asthma. *BD* bronchodilator, *FEV_1* forced expiratory volume in 1 s, *SSEC* sports-specific exercise challenge

baseline FEV_1 is obtained after the initial capsule containing placebo is utilized to calculate the target for the 15% decline in FEV_1 after subsequent doses (0.85×0 mg FEV_1 dose). The challenge is completed and discontinued when there is a 15% or greater decline in FEV_1 from baseline, or a between-dose decline of 10% or greater in FEV_1, or when a cumulative dose of 635 mg is administered [1••, 2••, 39]. The dose necessary to provoke a 15% decline in FEV_1 (PD_{15}) is determined by plotting the change in FEV_1 against the log cumulative dose of mannitol administered.

The intrinsic advantages of the mannitol provocation are that it is practical for administration in the office setting because of the ease of application, the short duration to perform the challenge, and the absence of specialized or expensive equipment as with treadmill or cycle ergometer. The necessary equipment includes a spirometer, nose clips, calculator, and mannitol kit [2••].

Additionally, there is a well-documented association between sensitivity to mannitol and exercise reactivity in those with known asthma who are not receiving treatment with inhaled steroids [1••, 2••]. Mannitol has been utilized to define EIB in elite asthma [75]. A decreased sensitivity for mannitol is noted in identifying EIB in individuals without known asthma [1••, 2••]. Mannitol has been successfully used to define BHR in individuals with exercise-induced wheezing [46]. Furthermore, mannitol may be utilized to monitor therapy to establish therapeutic effectiveness [77]. Because bronchial hyperreactivity is a reflection of airway inflammation, a decrease in sensitivity to mannitol may be used as an index to measure decline in airway inflammation. This can be established as a change in PD_{15} and response–dose ratio (RDR), which is calculated by dividing the percentage decline in FEV_1 by the cumulative dose of mannitol resulting in the decline. There is a significant decline in sensitivity (PD_{15}) and airway responsiveness (RDR) in asthmatics after inhaled corticosteroid therapy. The PD_{15} was enhanced from a pre-therapeutic value of 78 mg to 289 mg post-therapy, and there was a 4.2 fold-increase in RDR [77].

EVH is the preferred surrogate provocation test for elite athletes participating in competitive sports. EVH is considered the most efficient and reliable among the indirect challenges with regard to predictiveness, including sports-specific field exercise, laboratory exercise, and inhaled powder mannitol [1••, 2••, 6, 8, 67]. With its high sensitivity, it is the challenge recommended by the International Olympic Committee Medical Commission Independent Panel on Asthma [9]. The intensity of challenge for the elite athlete should be 95% or greater than actual or estimated maximum heart rate and dry

medical grade air for the last 4 min of the 8-minute test. This heart rate assures adequate ventilation for an accurate test. Cycle ergometry should be reserved for cyclists, skaters, or alpine skiers. Treadmill testing should be utilized for Nordic skiers and runners. Tri-athletes may use treadmill or cycle ergometry testing. A positive challenge is regarded by the International Olympic Committee Medical Commission as a 10% or greater decrease in FEV_1 3 to 30 min after exercise [1••, 2••, 7]. Sports-specific, field-based challenges at race pace have been utilized successfully but lack environmental control and reproducibility [62]. Sports-specific challenge in swimmers was not effective in diagnosis [67]. EVH was more accurate in producing a positive response than swim challenge or laboratory challenge with more than 85% maximum heart rate, temperature of 21°C, and relative humidity of 50%, with 1 of 33 athletes with positive field swim challenge, 18 of 33 with positive EVH challenge, and 4 with a positive laboratory cycle challenge result [67]. EVH and all indirect challenges should be performed with caution in patients with FEV_1 below 80% and should not be performed in patients with FEV_1 less than 70% of predicted [1••, 2••].

Thus, hyperosmolar aerosols may be utilized as surrogates for exercise. The mannitol challenge has been utilized as a surrogate for EIB in elite athletes [75]. A decrease of 15% or greater in FEV_1 after inhaling mannitol, 635 mg, is considered positive for EIB by the International Olympic Committee Medical Commission. The mannitol response documented as PD_{15} or a between-dose fall of 10% [39] and these tests are approved by the International Olympic Committee Medical Commission [41, 62].

Conclusions

In summary, a diagnosis of EIB and EIB with asthma when standard pre- and postbronchodilator spirometry is not diagnostic requires confirmation with an objective pulmonary function measure utilizing a standardized indirect challenge whenever possible. Although the standardized dry air exercise challenge and EVH are reliable in diagnosing EIB with and without known asthma, the equipment required is often specialized, costly, and may not be practical at this time for the typical office setting. EVH is probably the most sensitive bronchprovocation challenge for EIB and EIB with asthma and is approved as the gold standard for the International Olympic Committee and the elite athlete [1••, 2••, 6, 12••, 41, 72, 74, 75]. However, it is currently only available in specialized centers, although prototypes are in development [76] and wider commercial availability and affordability for a practice setting may soon become reality. However, inhaled powdered mannitol requires less equipment and can readily be conducted in an office setting. Mannitol is currently approved by the US Food and Drug Administration and is commercially available and reimbursable in an inexpensive kit that is easily adaptable to an office setting with reliable diagnosis for symptomatic asthma, especially in an exercise setting [2••].

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