Bronchial Provocation Testing for the Identification of Exercise-Induced Bronchoconstriction

John D. Brannan, PhD[a], and Pascale Kippelen, PhD[b,c] *New Lambton, NSW, Australia; and Uxbridge, United Kingdom*

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Learning objectives:

1. To explain the primary mechanism of exercise-induced bronchoconstriction (EIB).

2. To select the most appropriate tests that are useful for identifying EIB.

3. To explain the difference between "indirect" and "direct" bronchial provocation tests.

4. To explain why surrogate tests for EIB are more potent than laboratory exercise tests at identifying EIB.

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Exercise-induced bronchoconstriction (EIB) occurs in patients with asthma, children, and otherwise healthy athletes. Poor diagnostic accuracy of respiratory symptoms during exercise requires objective assessment of EIB. The standardized tests currently available are based on the assumption that the provoking stimulus to EIB is dehydration of the airway surface fluid due to conditioning large volumes of inhaled air. "Indirect" bronchial provocation tests that use stimuli to cause endogenous release of bronchoconstricting mediators from airway inflammatory cells include dry air hyperpnea (eg, exercise and eucapnic voluntary hyperpnea) and osmotic aerosols (eg, inhaled mannitol). The airway response to different indirect tests is generally similar in patients with asthma and healthy athletes with EIB. Furthermore, the airway sensitivity to these tests is modified by the same pharmacotherapy used to treat asthma. In contrast, pharmacological agents such as methacholine, given by inhalation, act directly on smooth muscle to cause contraction. These "direct" tests have been used traditionally to identify airway hyperresponsiveness in clinical asthma but are less useful to diagnose EIB. The mechanistic differences between indirect and direct tests have helped to elucidate the events leading to airway narrowing in patients with asthma and elite athletes, while improving the clinical utility of these tests to diagnose and manage EIB. © 2020 Published by Elsevier Inc. on behalf

[a]Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton, NSW, Australia
[b]Centre for Human Performance, Exercise and Rehabilitation, Brunel University London, Uxbridge, United Kingdom
[c]Division of Sport, Health and Exercise Sciences, College of Health and Life Sciences, Brunel University London, Uxbridge, United Kingdom

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Corresponding author: John D. Brannan, PhD, Department of Respiratory & Sleep Medicine, John Hunter Hospital, Lookout Rd, New Lambton, NSW 2305, Australia. E-mail: john.brannan@health.nsw.gov.au.

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Abbreviations used
AHR- Airway hyperresponsiveness
EIB- Exercise-induced bronchoconstriction
ERS- European Respiratory Society
EVH- Eucapnic voluntary hyperpnea
FEV_1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroid
PGD_2- Prostaglandin D_2

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INTRODUCTION

Exercise-induced bronchoconstriction (EIB) describes the transient narrowing of the airways that occurs during or, most commonly, after vigorous exercise.[1] EIB is common in patients with asthma who experience frequent respiratory symptoms (such as cough, wheeze, chest tightness, and mucus hypersecretion), and it is often an indicator of persistent asthma warranting treatment.[2] EIB can occur in otherwise healthy people, including children and adolescents, and in those performing regular exercise (eg, army recruits and elite athletes).[2,3]

EIB is characterized by a transient fall in forced expiratory volume in 1 second (FEV_1). Bronchial provocation tests that induce changes in FEV_1 in response to exercise, or surrogates of exercise (eg, dry air hyperpnea and hyperosmotic stimuli), are recommended for EIB diagnosis.[2,4] This approach is strengthened by observations that exercise symptoms are poor predictors of EIB.[5]

Understanding the mechanisms of EIB is important to select the most appropriate test to assess EIB, as well as to justify and guide therapy.[6] This review is a summary of the pathophysiology of EIB, and describes the advantages and disadvantages of various diagnostic tests available for EIB assessment and management. In addition, this review demonstrates how discrepancies between "indirect" (eg, exercise and its surrogates) and "direct" (eg, methacholine) tests advanced our understanding of the pathophysiology of EIB, and how the development of surrogates for exercise helped to improve clinical practice. According to current guidelines, direct tests are not recommended for the assessment of EIB, because of discordance in the airway response in individuals with EIB alone and in those with mild clinical asthma with EIB.[7,8]

MECHANISMS OF EIB: WHAT HAVE MECHANISTIC STUDIES TAUGHT US?

Water loss from the airway surface in response to conditioning large volumes of air to body conditions (ie, 37°C, 100% relative humidity) during exercise is regarded as the primary stimulus to EIB.[1,9] Severity of EIB varies with the water content of inhaled air,[9] and inhalation of fully conditioned air during exercise completely blocks EIB.[10,11] Because cold air is always dry, EIB is usually more severe during winter[12] and is common in winter athletes.[13,14] In addition to the amplifying effect on respiratory water loss, cold air breathing is thought to create intra-airway thermal gradients that trigger engorgement of the bronchial vasculature and mucosal edema as soon as exercise ceases,[15] thereby exaggerating airway narrowing.

Mechanistically, water loss from the airways is likely to cause transient dehydration and hyperosmolarity of the airway surface liquid in the first 10 to 12 generations where the volume of the periciliary fluid is estimated at less than 1 mL.[16,17] Compensatory water movement across the airway epithelium restores the airway surface lining osmolarity. It has been proposed that this event causes inflammatory cells (eg, mast cells and eosinophils) to release histamine, prostaglandin D_2 (PGD_2), and cysteinyl leukotrienes, and, in susceptible individuals, this leads to airway smooth muscle contraction and airway narrowing.[6] Reasons why patients with asthma are susceptible to EIB compared with healthy subjects without asthma include the following: (1) patients with asthma are likely to be allergic and have activated mast cells and eosinophils in greater numbers in their airways[18,19] (Figures 1 and 2) and evidence of mediator release,[20,21] and (2) their smooth muscle is hyperresponsive (to methacholine or histamine consistent with observations in patients with asthma with EIB).[7] In athletes (particularly endurance-trained athletes), recruitment of the small airways to condition the large volumes of inhaled air in a short time (up to 200 L/min) likely amplifies the osmotic stress.[22]

Evidence to support the osmotic theory from studies in EIB,[2] using the surrogate tests for EIB, is comprehensive, and there (1) is a good relationship between the severity of EIB and the airway sensitivity to surrogate tests in known patients with asthma,[23] (2) are consistent reports of an increase in urinary metabolites of the potent bronchoconstrictors (PGD_2 and cysteinyl leukotrienes) after bronchial provocation with dry air hyperpnea and mannitol challenge,[24-27] (3) is reduced severity and/or duration of induced bronchoconstriction or enhanced airway recovery in individuals with EIB premedicated with either a histamine antagonist (ie, fexofenadine hydrochloride), or a mast cell—stabilizing agent (ie, sodium cromoglycate, nedocromil sodium) or leukotriene antagonist (eg, montelukast),[25,28-30] and (4) is attenuation of EIB using high-dose inhaled corticosteroids (ICSs) acutely or regularly in recommended doses.[31,32] Regular ICS in doses recommended for the daily treatment of asthma can attenuate, or even abolish, airway sensitivity to exercise and to surrogate tests for EIB.[33] A negative airway response after ICS is suggestive of successful attenuation of airway inflammation, which is the source of bronchonstricting mediators. Thus, the abolition of indirect airway hyperresponsiveness (AHR) with ICSs has been proposed an optimal therapeutic outcome.[34]

Clinical implication: EIB is osmotically driven and can be identified using surrogate challenge tests that mimic exercise challenge such as dry air hyperpnea and hyperosmotic stimuli.

CHALLENGE TESTING FOR THE DIAGNOSIS OF EIB: AN HISTORICAL PERSPECTIVE

The development of tests for the diagnosis of EIB was derived from the understanding that exercise was a common stimulus for bronchoconstriction in patients with asthma. Assessing EIB is also useful and important in occupational settings where EIB could put individuals at risk of an attack of asthma (eg, army recruits and scuba divers) and/or impair exercise performance (eg, professional athletes). Prevalence of EIB in all these groups can differ significantly, as does the diagnostic sensitivity of bronchial challenge tests to assess EIB.[35] However, regardless of

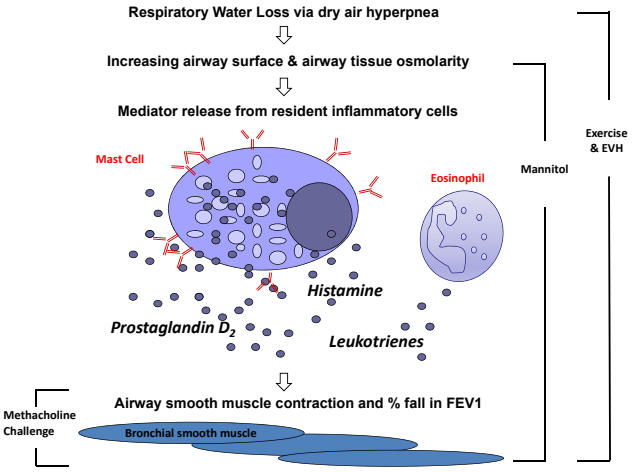

FIGURE 1. A schematic outlining the key events of indirect tests that result in AHR using hyperpnea with dry air that occurs during or after vigorous exercise or an EVH challenge. The osmotic challenge test inhaled dry powder mannitol mimics the effects of dry air hyperpnea by increasing the osmolarity of the airway surface. For all these stimuli, an important feature is the presence of airway inflammation, in particular the mast cell, and when the airway response is more severe, also the eosinophil, in association with a sensitive airway smooth muscle. Direct tests (eg, methacholine) act directly on the airway smooth muscle to cause bronchoconstriction.

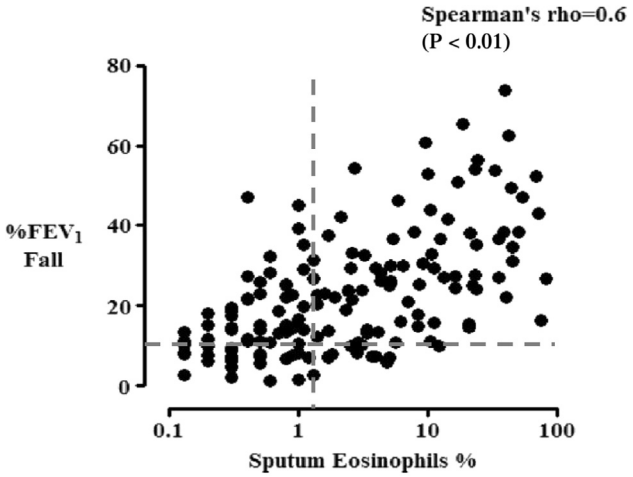

FIGURE 2. An example of the relationship of eosinophilic airway inflammation obtained from sputum induction with the severity of the fall in FEV_1 to exercise in subjects with asthma. Although the mast cell mediators play a key role in the airway response to mannitol, the presence of the eosinophil can augment the airway sensitivity to exercise. Although the absence of eosinophilia (<2% eosinophils representing the cutoff for normal) does not exclude the presence of EIB, the airway response is often milder.[19]

the diagnostic sensitivity and specificity of an individual test for EIB, the documentation of a positive response to exercise, or its surrogates, identifies the need for clinical intervention.[2] Little mechanistic differences exist in the airway response to exercise (or its surrogates) between patients with asthma and athletes. However, it is more likely to observe severe airway responses to "indirect" challenges in those with active asthma and EIB, compared with those with EIB alone. Some patients with asthma may have significant airflow limitation during exercise, which can be observed in falls in minute ventilation. Occurrence of EIB during exercise (also referred to as "breakthrough EIB") seems particularly common in children.[36] Although not comprehensively studied, treatment responses between individuals with EIB alone and those with asthma and EIB do not seem to differ.[25,31]

Tests for EIB have evolved since the early investigations into the stimulus and mechanisms of EIB and the establishment of exercise protocols.[37] Historically, the work began using treadmill exercise to diagnose asthma in children[38] on the understanding that EIB was one of the first clinical features of asthma. Subsequently, EIB in children was also shown to be one of the last features to resolve with regular ICS.[39] This was soon followed by the investigation of surrogate tests to identify EIB, most notably the development of the eucapnic voluntary hyperpnea (EVH) test with dry air for occupational screening of US Army recruits.[40] This development was associated with the emerging understanding that airway drying associated with exercise hyperpnea was the primary stimulus to EIB. This led to the development of osmotic challenges (using nebulized aerosols of hypertonic saline and dry powder mannitol) to identify potential for EIB.[41] Collectively, exercise, EVH, and osmotic challenges are classified as "indirect" tests, because they cause the release of mediators of bronchoconstriction from resident airway inflammatory cells. These mediators act on smooth muscle receptors to cause contraction and airways narrowing (Figure 1).[42,43]

Throughout this period, and before the development of indirect tests, it was common to use bronchial provocation tests using nebulized methacholine or histamine to identify AHR for assessing the potential for EIB.[44,45] The rationale was that EIB is in fact a type of AHR and it can be associated with clinical asthma. Known as "direct" tests for AHR, these pharmacological agents act directly on airway smooth muscle receptors to cause airway narrowing.[43] However, tests using these pharmacological agents are neither sensitive nor specific for identifying EIB (particularly in those with EIB alone or with an early diagnosis of asthma).[7,8] Thus, there is dissociation between airway responses to exercise, or its surrogates (eg, dry air hyperpnea and osmotic challenges), and AHR to methacholine or histamine.[8,35,46,47] Several reasons may serve to explain these findings: (1) pharmacological agents act directly on the airway smooth muscle; thus, a positive response is not dependent on the endogenous release of inflammatory mediators; (2) cysteinyl leukotrienes and PGD_2 are far more potent than methacholine or histamine for provoking bronchoconstriction[48]; and (3) positive responses to direct challenges (in the presence of a negative indirect test result) may result from airway injury from smoking, cold air hyperpnea, or airway remodeling.[49] For example, elite skiers can be positive to methacholine, with signs of airway epithelial injury and remodeling, yet many of these athletes are negative to indirect challenges and do not respond to regular ICS.[50-52]

Clinical implication: Major clinical guidelines on EIB moved away from recommending methacholine or histamine for the assessment of EIB; however, these tests may remain important in identifying airway injury in elite athletes.[2,4]

TABLE I. The recommended withdrawal times for medications, foods, and physical activity before performing challenge testing with exercise, EVH, or inhaled mannitol

Medication/activity/food	Recommended time to withhold before challenge testing
Short-acting beta$_2$-agonist (albuterol, terbutaline)	8 h
Long-acting beta$_2$-agonist (salmeterol, eformoterol)	24 h
Long-acting beta$_2$-agonist in combination with an ICS (salmeterol/fluticasone, formoterol/budesonide)	24 h
Ultra long-acting beta$_2$-agonists (indacaterol, olodaterol, vilanterol)	≥72 h
ICS (budesonide, fluticasone propionate, beclomethasone)	6 h
Long-acting ICS (fluticasone furoate)	≥24 h
Leukotriene receptor antagonists (montelukast, zafirlukast)	4 d
Leukotriene synthesis inhibitors (zileuton/slow release zileuton)	12 h/16 h
Antihistamines (loratadine, cetirzine, fexofenadine)	72 h
Short-acting muscarinic acetylcholine antagonist (ipratropium bromide)	12 h
Long-acting muscarinic acetylcholine antagonist (tiotropium bromide, aclidinium bromide, glycopyrronium)	≥72 h
Cromones (sodium cromoglycate, nedocromil sodium)	4 h
Xanthines (theophylline)	24 h
Caffeine	24 h
Vigorous exercise	>4 h

MEASUREMENT OF CHANGE IN AIRWAY CALIBER

For all bronchial provocation tests it is essential that quality baseline spirometry be performed (ie, strictly using American Thoracic Society/European Respiratory Society recommendations).[53] Baseline FEV_1 should be greater than or equal to 70% to 75% of predicted normal value, and not less than 1.2 L.[2] For both safety and efficacy reasons, the baseline FEV_1 must be stable. FEV_1 should be measured in duplicate at each time point during or after the challenge, with a difference of no more than 150 mL or 5%. Because the primary outcome is a change in FEV_1 from baseline, full forced expiratory maneuvers to vital capacity are not essential.

Medications that can protect against EIB need to be withheld before a diagnostic challenge test[2] (Table I). Postchallenge, bronchoconstriction is usually reversed with a standard dose of inhaled beta$_2$-agonists. Recovery after inhaled beta$_2$-agonist may be slower in individuals with more severe falls in FEV_1 and also in those who are taking inhaled beta$_2$-agonists daily.[2,54]

DRY AIR HYPERPNEA CHALLENGES

Exercise for bronchial provocation

Laboratory exercise tests (usually performed on treadmills or cycle ergometers) require participants to perform a 6- to 8-minute high-intensity effort.[2,4] The warm-up period before reaching the target workload should be short (2-3 minutes maximum), and the remaining exercise (5-6 minutes) should be performed at 80% to 90% of predicted maximum heart rate (calculated as 220 minus age) or 17.5 to 21 times FEV_1 (when ventilation is recorded). The rationale for such protocols is to permit high ventilatory rates to be reached rapidly and to be sustained, to maximize the dehydrating stimulus to the airways. Recommended protocols outlined in guidelines[2,4] are useful to assist in optimizing the dehydrating stimulus and, thereby, potentiating the airway response and avoiding false-negative test results. Of note, absolute humidity should be maintained below 10 mg H_2O/L (<50% relative humidity at 20°C) and a nose clip should be used to avoid humidification of inhaled air from the nasal passage. Postchallenge, serial measurements of FEV_1 are taken (usually at 5, 10, 15, and 20 minutes), with a fall in FEV_1 of 10% or more over 2 consecutive time points considered as diagnostic for EIB (Figures 3 and 4).

It is well known that laboratory exercise tests may not be sensitive enough to identify EIB in some individuals. For example, it is common for elite athletes to have EIB in their chosen sporting activity, yet have a negative running or cycling exercise test result in the laboratory.[55] Negative test results more commonly occur in those with mild disease (ie, when the FEV_1 fall may be close to the 10% cutoff for a positive test result).[56] Possible reasons are that (1) the exercise test in the laboratory may not be sufficiently vigorous to require a ventilation rate to cause adequate airway dehydration[57]; (2) it is not always possible to control water content of inspired air[57]; and (3) airway irritants (eg, airborne allergens, traffic-related pollutants, and chlorination by-products in swimming pools) can enhance EIB in the field.[58] In addition, in individuals with an FEV_1 fall around the 10% threshold, there can be a variation in the airway response when multiple tests are performed.[56,59] Although this is a problem diagnostically, it also suggests that, in these individuals, EIB is likely to be mild.

Clinical implication: After a negative exercise test result, if EIB is still highly suspected, the test should be repeated.[2]

Eucapnic voluntary hyperpnea

The disadvantages of exercise in the laboratory motivated the development of alternative methods to improve diagnostic sensitivity. EVH testing[60] requires individuals to breathe for 6 minutes a dry gas mixture containing 21% O_2, 5% CO_2, balance N_2, at a ventilation level equating 60% of maximum voluntary ventilation (calculated as 21 times baseline FEV_1).[2] In order for athletes to reproduce the ventilatory demand of their field exercise, the target ventilation should be increased to 85% of maximum voluntary ventilation (ie, 30 times baseline FEV_1). Postchallenge, FEV_1 should be measured soon after completion

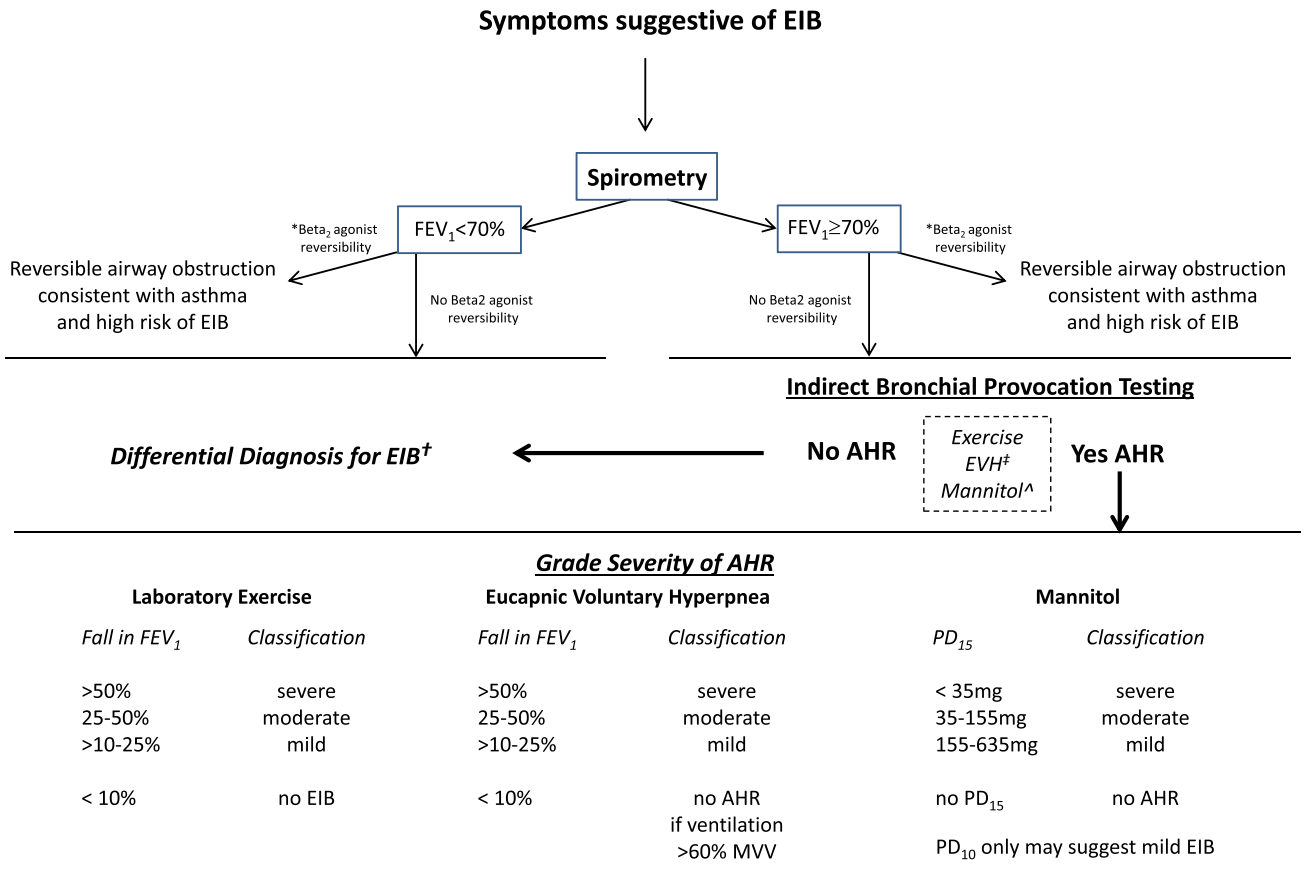

FIGURE 3. An algorithm for the decision to perform an indirect bronchial provocation test in persons with symptoms suggestive of EIB, including the test options and test outcomes, which include the cutoff values for a positive test result and the classification of the airway response to a grade severity of AHR. *MVV,* Maximum voluntary ventilation; *PD15*, the provoking dose of mannitol to cause a 15% fall in FEV_1; *PD10*, the provoking dose of mannitol to cause a 10% fall in FEV_1. Adapted from Weiler et al.[2] *Demonstrating reversibility in FEV_1 of 12% and 200 mL. †Very mild AHR may cause variable responses to all tests, and if EIB is still strongly suspected, a repeat test may be warranted. ‡$FEV_1 \geq 75\%$ for the EVH challenge.

of the test and should be monitored for at least 15 minutes, with recordings taken at 5-minute intervals. The cutoff for a positive EVH test result is a fall in FEV_1 of 10% or greater. In athletes, it is recommended that the fall be sustained over at least 2 consecutive time points.[2,42]

EVH challenge is more sensitive for identifying AHR compared with laboratory exercise. Furthermore, EVH has been demonstrated to be useful in elite athletes for confirming EIB documented during field exercise.[61] However, some individuals (especially young athletes) may not reach the minimum required ventilation (21 times FEV_1), reducing the sensitivity of the test.[62] Furthermore, some have argued that, in elite athletes, the use of a 10% cutoff makes the test too sensitive and that a 15% fall in FEV_1 may be more specific.[63] The variability in the airway response, particularly when the response is mild (ie, around the 10% cutoff), has also led some authors to suggest that more than 1 EVH test should be performed to confirm diagnosis.[57] In some athletes—particularly those engaging in winter and aquatic sports—a negative EVH test result does not always exclude EIB[64,65] (Figure 3).

The apparatus for performing an EVH challenge can be sourced by pulmonary function laboratories and "home-made" set-ups can be easy to assemble.[42] However, they necessitate use of premade gas mixtures, which can be expensive. There are now commercially available devices for gas mixing. These usually require a higher initial cost but potentially they are less expensive due to lower ongoing costs.[66]

EVH has both practical and mechanistic advantages over laboratory-based exercise tests. EVH permits the subject to reach a high rate of ventilation faster than exercise, with an ability to sustain this high level of ventilation more easily, leading to a more reliable dehydrating stimulus to the airway surface. Through the use of compressed air, the inspired water content can be maintained close to 0 and airway dehydration potentiated. It is important to understand that with a more potent stimulus comes the potential for severe falls in FEV_1 (>30%). This is more likely because the EVH protocol is a single-bolus dose of hyperpnea. This is in contrast to dose-response challenge tests (such as mannitol and hypertonic saline), which reduce the possibility of severe falls in FEV_1.

Clinical implication: It is recommended for EVH to be used only in individuals (1) with EIB alone (ie, not in those individuals with established clinical asthma), (2) with normal to near-normal lung function (ie, baseline $FEV_1 > 75\%$ predicted),

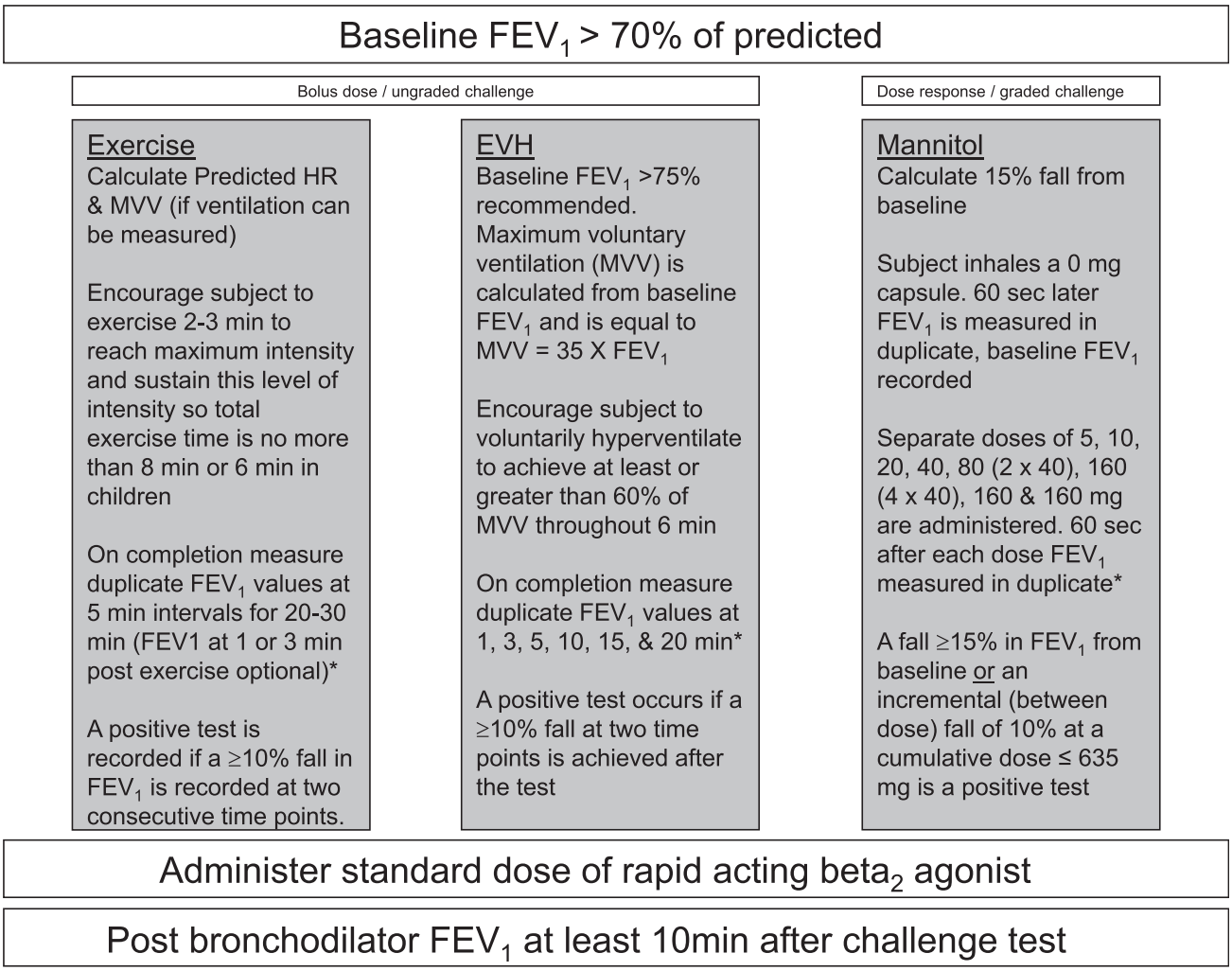

FIGURE 4. A summary of the fundamental similarities and differences in the protocols required to perform indirect tests to identify EIB: laboratory exercise, EVH, and the mannitol bronchial provocation challenge test. *Note:* The highest FEV_1 is taken to calculate % fall in FEV_1 at each time point (*Common to all tests).

and (3) who are not taking inhaled medications regularly.[2] During EVH, ventilation should also be closely monitored throughout the 6-minute period. If falls in ventilation are observed during the test, this may be an early sign of bronchoconstriction and may lead to a severe airway response. It is best in this case to consider ceasing the EVH challenge before the 6 minutes.

OSMOTIC STIMULI (EG, MANNITOL CHALLENGE)

The methodology for the mannitol challenge arose from the need to make indirect tests more practical and accessible.[67] The test is standardized and simpler to perform than exercise or EVH, which both require complex equipment. The mannitol test comes as a kit consisting of increasing doses of mannitol powder (5, 10, 20, and 40 mg in capsules) and a simple low-resistance inhaler.[68] FEV_1 is measured at baseline and 60 seconds after the inhalation of each dose. Because the response to mannitol is dependent on progressively increasing the osmotic gradient at the airway surface, the test should be performed without significant delay between doses. Mannitol provokes cough in some patients.[69] To minimize cough induced by upper airway impaction, individuals should be advised not to inhale the mannitol powder too rapidly.

The fall in FEV_1 required for a positive test result is 15%, which has been validated to aid in a clinical diagnosis of asthma. In individuals (especially athletes) who have a 10% fall in FEV_1 with the maximum dose of 635 mg of mannitol, mild EIB may be present.[70] The mannitol challenge is the only regulatory approved indirect bronchial challenge test that has demonstrated adequate safety and efficacy in identifying asthma and EIB[7,68] (Figures 1 and 4).

The airway sensitivity to mannitol is reproducible[71,72] and relates well to the severity of EIB in patients with asthma and summer elite athletes.[23,70,73,74] Furthermore, in patients with mild asthma with EIB, AHR to mannitol was 1.4 times more likely to identify AHR than a laboratory exercise test.[7] However, in swimmers the relationship between mannitol and field-based exercise reveal discordant responses, which may be a product of mild AHR.[75,76]

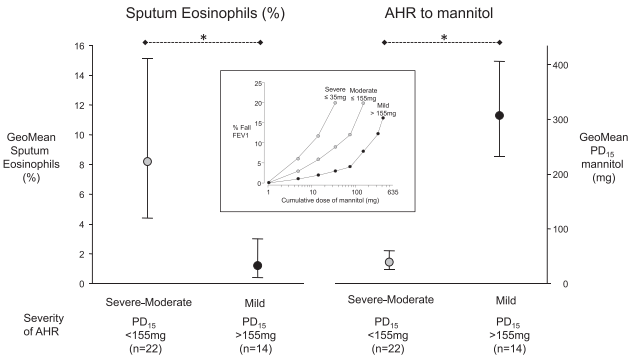

FIGURE 5. Data taken from 2 studies (n = 36) where sputum eosinophils have been obtained in subjects performing a mannitol challenge test who were not taking regular ICSs.[77,78] There is a significantly higher level of eosinophils in patients with severe to moderate AHR to mannitol (n = 22) (gray dots), compared with those who have mild AHR (n = 14) (black dots) who overall are characterized as having normal levels of eosinophils in sputum (<2% eosinophils) (left). It is considered the mast cell is playing the primary role in AHR to mannitol while the eosinophil if present augments the airway response. There was a significant difference in the provoking dose of mannitol (mg) to cause a 15% fall in FEV_1 (PD_{15}) between the severe to moderate group compared with the mild group (right). INSET: A summary of the dose-response curves in those with severe, moderate, and mild AHR to mannitol. *PD15*, The provoking dose of mannitol to cause a 15% fall in FEV_1. *$P <$ .001.

Severity of the airway sensitivity is expressed by provoking dose of mannitol that causes a 15% fall in FEV_1 (with a provoking dose of mannitol in milligrams to cause a 15% fall in FEV_1 < 35 mg classified as severe, 35-155 mg, moderate, and 155-635 mg, mild)[42] (Figure 3). The airway response can also be expressed as response-dose ratio (ie, the % fall in FEV_1/mg of mannitol), which is a measure of airway reactivity. The severity of the airway response can predict the severity of airway inflammation (eg, mast cells and eosinophils),[77-80] (Figure 5) and regular ICS treatment has been shown to reduce the airway sensitivity and reactivity in patients with asthma.[32,34] However, daily treatment with ICSs can abolish the airway sensitivity to mannitol.[32,81] Like the abolition of EIB with ICSs, a negative mannitol test result in the presence of regular ICS has been proposed as a signal for optimal ICS therapy[82] and a potential end point to signal downtitration of the ICS dose.[83]

Clinical implication: Mannitol may be used to identify and monitor ICS treatment in individuals with EIB, a goal for adequate therapy being nonresponsive to the challenge.

FUTURE DIRECTIONS

Future directions in research in EIB have previously been discussed.[84] The role of the small airways in EIB is still unclear, and few studies have used outcome measures other than FEV_1 to quantify the change in airway caliber, such as impulse or forced oscillometry.[85,86] It is still not clear whether these outcome measures can provide complementary information to FEV_1. Future studies could investigate these methods on EIB, in particular those with mild EIB. The threshold for a positive EVH test result, particularly in asymptomatic elite athletes, is still under debate as is the minimum ventilation to be reached by young athletes.[63] The lack of concordance in the response to various indirect bronchial challenges in some athletic groups (particularly swimmers and cold-weather athletes) warrants further investigation, particularly to establish which test (if any) can be considered as a "criterion standard."

CONCLUSIONS

The development of surrogate tests for the diagnosis of EIB has assisted with the understanding of the mechanisms of EIB. EIB is an osmotically driven and inflammatory mediated condition that is primarily triggered by the loss of water from the airways during conditioning of inhaled air during exercise hyperpnea. In spite of some limitations, surrogate indirect bronchial provocation tests (in particular, EVH and mannitol) reproduce in a more standardized manner the osmotic changes that occur with exercise while improving the practical application of the assessment of EIB.

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