Alternatives to exercise challenge for the objective assessment of exercise-induced bronchospasm:
eucapnic voluntary hyperpnoea and the osmotic challenge tests

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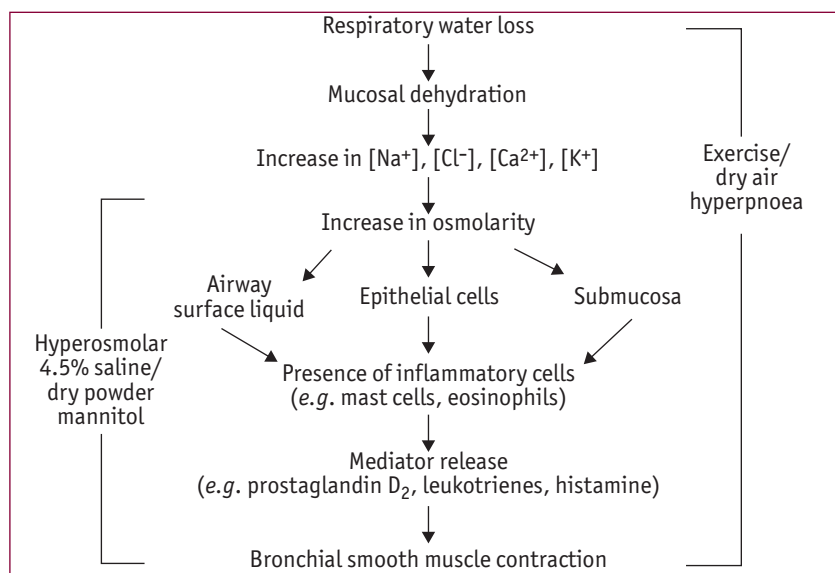
Educational aims

❭ To describe alternative tests for the assessment of exercise-induced bronchoconstriction and to describe the mechanisms by which bronchoconstriction is caused.
❭ To describe how these tests are performed and how to interpret the test results.
❭ To choose the most appropriate test for a given clinical problem.

Summary

Exercise-induced bronchoconstriction (EIB) is caused by evaporative water loss due to conditioning large volumes of air in a short period. This leads to an increase in osmolarity of the airway surface, which provides a favourable environment for release of bronchoconstricting mediators from inflammatory cells in the airways. Thus, stimuli that mimic this water loss or increase the osmolarity of the airway surface may be used as 'surrogates' for exercise challenge testing. The most widely used tests are eucapnic voluntary hyperpnoea (EVH) or osmotic challenges (*e.g.* hyperosmolar saline and mannitol). However, there are some differences in the methodology that need to be considered when using these tests. Importantly, EVH and the osmotic challenge tests overcome some of the practical and safety limitations of performing exercise testing at high intensity. The utility of these alternative tests for assessing EIB is discussed.

❮Exercise testing protocols were developed in the 1970s to identify exercise-induced bronchoconstriction (EIB), as this was a common feature of persons with currently active asthma [1, 2]. While exercise testing could be performed both in children and adults, there were practical difficulties with using exercise testing, both in the laboratory and in the field, as well as in the primary care setting, where asthma is most commonly diagnosed and treated, and access to such testing is limited [3].

By the late 1970s, it was realised that water loss by evaporation from the airway surface was the stimulus for EIB and exercise itself was

Figure 1
A schematic outlining the key events that result in bronchial hyperresponsiveness due to hyperpnoea with dry air in persons with asthma that occurs during or following vigorous exercise or a eucapnic voluntary hyperventilation challenge. The osmotic challenge tests using hypertonic saline or mannitol mimic the effects of dry air hyperpnoea by increasing the osmolarity of the airway surface. For all these stimuli, the presence of airway inflammation in association with a sensitive airway smooth muscle is important. Reproduced from [4], with permission from the publisher.

not necessary to provoke the response. This recognition led to the development of the eucapnic voluntary hyperpnoea (EVH) test which utilises dry air to mimic the airway dehydration of hyperpnoea during exercise. Dehydration of the airway surface liquid leads to an increase in osmolarity, which causes inflammatory cells in the airways to release bronchoconstricting mediators. This understanding formed the basis of the subsequent development of hyperosmolar saline and dry powder mannitol as alternatives to EVH in the diagnosis of EIB (fig. 1).

These alternative tests also proved useful for identifying subjects who were at risk of EIB. Specifically, among groups such as elite athletes, defence force recruits and divers with self-contained underwater breathing apparatus (SCUBA), for whom EIB may be hazardous, an objective measure is important. The development of EVH and the osmotic challenges provided practical advantages over exercise testing.

Forced expiratory volume in 1 s ($FEV1$) is the preferred measure of airway calibre for each test and at least two reproducible $FEV1$ values are recorded, and the best $FEV1$ value is used to calculate the airway response. Furthermore, medications for the treatment of asthma need to be avoided at different times prior to testing, such that these drugs do not influence the airway response to these tests (table 1). Testing for EIB requires a subject to perform exercise vigorously for 6–8 min, a requirement that limits usefulness in some children and adults, particularly the elderly or impaired (e.g. obese). Furthermore, the "bolus dose" of the exercise stimulus for EIB testing is such that large decreases in $FEV1$ may occur post-exercise. Testing for EIB requires several trained personnel to be in attendance for up to an hour, adding significantly to the expense of the test. Finally, the equipment required to perform the exercise adequately (e.g. treadmill or bicycle ergometer) can be expensive and occupies a large amount of space. Both EVH and the osmotic challenges have improved access to bronchial provocation testing while maintaining or improving the diagnostic utility of testing.

EIB is common in persons with clinical signs and symptoms of asthma, but it also occurs in persons who do not have clinical signs and symptoms. In both subject groups, the clinical decision for treatments to prevent EIB is similar, i.e. by using medications effective for the treatment of clinical asthma. It has been appreciated more recently that the clinical signs and symptoms of asthma are not reflective of the degree of pathophysiology that is sensitive to inhaled corticosteroids. However, airway responses to exercise and these alternative tests have been demonstrated to relate to the degree of steroid-sensitive inflammation [5, 6]. Thus, such tests hold some

Table 1 Required periods for withholding medications, food and activity before challenge tests

	Time
Medication	
Inhaled, nonsteroidal anti-inflammatory agents e.g. sodium cromoglycate and nedocromil sodium	6–8 h
Short-acting β_2-agonists e.g. salbutamol and terbutaline	8 h
Inhaled corticosteroids e.g. beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide and mometasone furoate	12 h
Ipratropium bromide	12 h
Inhaled corticosteroids plus long-acting β_2-agonists e.g. fluticasone and salmeterol, budesonide and eformoterol	24 h
Long-acting β_2-agonists e.g. salmeterol and eformoterol	24 h
Theophylline	24 h
Tiotropium bromide	72 h
Antihistamines e.g. cetirizine, fexofenadine and loratadine	72 h
Leukotriene-receptor antagonists e.g. montelukast sodium	4 days
Food and activity	
Caffeinated drinks e.g. coffee and cola drinks	6 h
Strenuous exercise	12 h

promise to more effectively identify the need for treatment and to monitor efficacy of treatment in those with EIB [7].

This review covers only indirect stimuli as an alternative to exercise. It is not intended to be a comparison between direct and indirect tests for identifying bronchial hyperresponsiveness (BHR) and for this the reader is referred elsewhere [8].

EVH

EVH (also known as eucapnic hyperventilation or isocapnic hyperventilation) was developed from the understanding that the ventilation reached and sustained, and the water content of the air inspired were important determinants of bronchoconstriction in asthmatics with documented EIB [9, 10]. EVH is now well established as a surrogate for exercise in the diagnosis of EIB [11–14]. The characteristics of the airway response to these stimuli are very similar, although there are differences in the physiological and metabolic demands between EVH and exercise: for example, the maximum airway response, measured as a decrease in FEV1, usually occurs within 10 min of cessation of hyperpnoea, with the median time to achieve the maximum response being only 4 min for EVH. The airway sensitivity to a progressive challenge with EVH can be predictive of the decrease in FEV1 in response to exercise (fig. 2) and the drugs that inhibit EIB also inhibit the response to EVH. Refractoriness to the stimulus, usually defined as <50% of the initial FEV1 response, is observed with repeated exercise and EVH within 1–4 h.

Rationale and development

A standardised protocol, originally developed to screen defence force recruits for EIB, uses a special gas mixture inhaled at room temperature for 6 min with a target ventilation of 30 times the FEV1 [12]. While cooling the air can reduce the time of the challenge and the ventilation required, it is expensive and, for most assessments, unnecessary. However, in young children, a protocol of 4 min hyperpnoea in cold air has been developed and used very successfully [16] and there is even a protocol for 2-yr-olds [17]. The equipment required to perform an EVH challenge requires less space than exercise equipment and only one person is required for testing (fig. 3) [14]. It is important that eucapnia (38–42 mmHg) is maintained during an EVH challenge, as hypocapnia is a well-known bronchoconstricting stimulus. Eucapnia is maintained by providing a source of
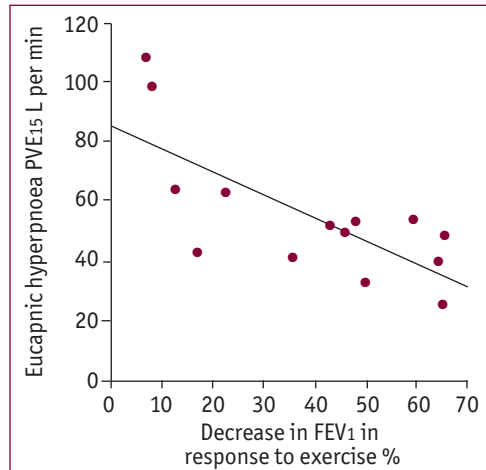
Figure 2
The relationship between PVE15 (the provocative ventilation required to induce a 15% decrease in FEV1) obtained during a multi-stage eucapnic voluntary hypopnoea challenge test in known asthmatic subjects and its relationship to the decrease in FEV1 following 8 min of exercise on a cycle ergometer breathing dry air. r= -0.73; p<0.001. Reproduced from [15], with permission from the publisher.

dry air containing 4.9–5.0% carbon dioxide (CO_2) and 21% oxygen, balanced with nitrogen. This mixture keeps end-tidal CO_2 levels within the normal or eucapnic range when minute ventilation is 40–105 L per min, provided a subject has an FEV1 of 1.5 L or more [18]. If a subject has a level of ventilation value beyond this range (*e.g.* elite athletes) then a mixing device can be used to adjust and monitor the CO_2 concentration to maintain eucapnia. The level of ventilation that is required depends on the subject tested: for elite athletes and others performing high-intensity exercise it is calculated as 30 times the FEV1, which represents 75–85% of the achievable maximum voluntary
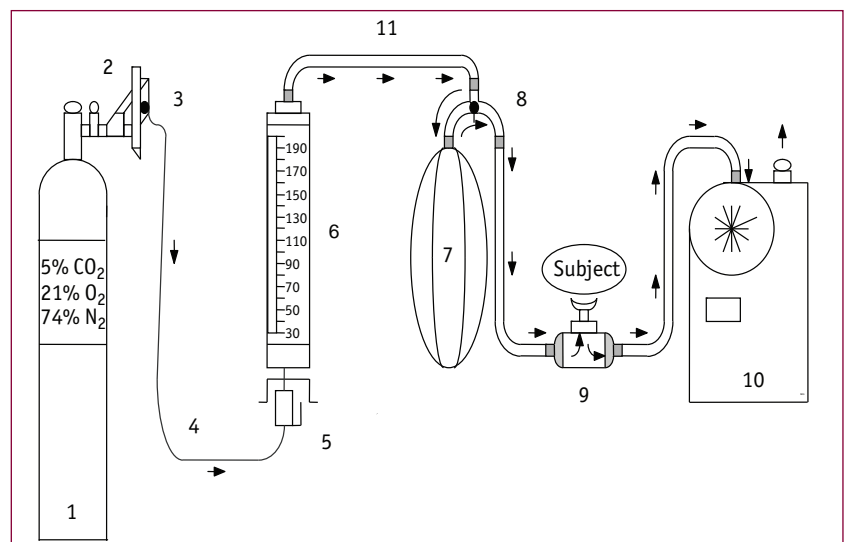
Figure 3
An example of the basic equipment used to perform a eucapnic voluntary hyperpnoea test. 1: compressed gas mixture; 2: regulator; 3: demand resuscitator, 30–150 L per min; 4: high-pressure tubing; 5: demand valve; 6: rotameter, 30– ~200 L per min; 7: meteorological balloon, 100–300 g; 8: metal connector with tap that simultaneously allows gas both to enter and leave balloon; 9: low-resistance, low dead-space breathing valve; 10: gas meter accurate to 1 L; 11: hoses, minimum diameter 1.25 inches. Arrows indicate direction of gas flow. Note: equipment substitutions can be made for 1 and 10 by using a commercial gas mixer and a high flow-rate meter turbine to measure ventilation, which will add cost to the basic equipment. Reproduced from [15], with permission from the publisher.

ventilation (MVV). For most subjects not competing at elite level, a ventilation exceeding 21 times the FEV1 (60% MVV) is likely to be close to the maximum ventilation achieved during exercise in a test for EIB [19]. In a pulmonary function laboratory setting, 81% of the patients referred for testing for EIB were able to achieve this target [20]. The minimum level for a valid test may be set as low as 17.5 times the FEV1 for 6 min to be consistent with exercise ventilation [19]. The actual target ventilation is based on the subject's reproducible pre-challenge FEV1 and is independent of the subject's physical fitness.

It should be noted that the reduction in FEV1 following EVH is not related to the pre-challenge FEV1 and even in those with normal predicted values for FEV1, the decreases can commonly exceed 30%, and sometimes 50% [21, 22]. This may be important to consider when testing subjects who are taking β_2-agonists on a daily basis, as it has been observed that these subjects can have a more pronounced decrease in FEV1, as well as a slower airway recovery following EIB with a standard dose of rescue β_2-agonist [23].
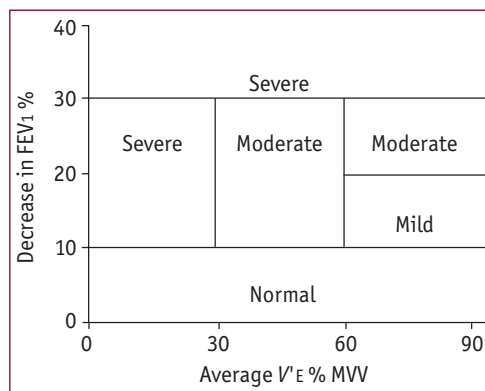
Protocol

The single 6-min protocol is the most commonly used [12, 14]; however, in persons with suspected asthma, a multistage protocol has been developed which requires 3-min periods of ventilation at 10.5, 21 and 31 times FEV1 [24]. A 4-min protocol at 21 times FEV1 has also been used in known asthmatics to evaluate the protective effect of drugs [25].

Some systems use demand valves directly attached to the source of gas and incentive devices on computer screens to help the subject achieve the target ventilation. One fairly inexpensive system (fig. 3) [26] uses a large, powder-free meteorological balloon as a reservoir. The balloon is filled with ≥90 L of the dry air containing CO_2. The subject inhales the air through a two-way valve and is asked to hyperventilate voluntarily to keep the balloon at a constant volume while the gas from the cylinder refills the balloon *via* a rotameter at the target rate. An advantage of systems that measure ventilation during the EVH test is the ability to observe sudden decreases in ventilation that may be due to bronchospasm. In such cases, the test should be stopped and FEV1 should be measured immediately. At the end of the period of ventilation, FEV1 is measured in duplicate immediately post-challenge and for 3, 5, 10, 15 and 20 min. If using a multistage protocol in known asthmatics, measurements of

FEV1 are made more at 1, 3, 5 and 7 min, and if there is no further decrease at 7 min, the subject proceeds to the next level of ventilation [26]. However, progressive protocols can induce refractoriness at the higher ventilations [27].

Interpreting the response to EVH tests

A decrease in FEV1 from the pre-challenge value of ≥10% is defined as a positive test result based on the mean plus two standard deviations of healthy, nonasthmatic subjects. When minute ventilation is ≥60% of MVV, decreases in FEV1 of 10–19.9% and 20–29.9% are classified as mild and moderate, respectively. A decrease in FEV1 >30% is considered severe at any ventilation (fig. 4) [14, 26]. The decrease in FEV1 should be sustained, with the subject having a 10% decrease in FEV1 recorded at two consecutive time points post- challenge [28]. EVH has been observed to identify more cases of EIB than laboratory exercise tests and is as sensitive as field exercise testing [29]. This is probably due to the higher levels of ventilation that can be achieved rapidly and sustained using EVH compared with exercise on a bicycle or treadmill in a laboratory. Thus, persons with mild EIB and a negative response to a laboratory exercise protocol may have a positive response to the 6-min dry air voluntary hyperpnoea EVH protocol.

Figure 4

The classification of severe, moderate and mild EIB for an EVH challenge for either a single- or multistage protocol. Severity is based on the level of ventilation required to induce a positive response. For example, if a subject has a 10% decrease in FEV1, the response is classified as severe if the ventilation required was <30% of MVV, moderate if it is <60% MVV or mild if >60% MVV. A decrease in FEV1 of >30% is considered severe, independent of the level of ventilation. V'E: *minute ventilation*

Hyperosmolar saline challenge test

Hyperosmolar saline was established as a laboratory-based test for identifying the presence of asthma without the need for tests using a source of dry air [30, 31]. The immediate practical advantages are that this test requires a small amount of equipment and the progressive dose–response nature of the protocol means that severe decreases in FEV1 can be avoided. The hyperosmolar saline challenge has been used safely in epidemiological studies of BHR [32, 33]. The safety of hyperosmolar saline has been established in phase 3 clinical trials [34]. While assessing BHR with hyperosmolar saline, the associated induction of sputum can also be performed for the identification of sputum cell types [35].

Rationale and development

The protocol for the delivery of hyperosmolar saline as a bronchial provocation test was established in the 1980s [30]. It was found that the rate of change of airway osmolarity was the most important determinant of the response. A standardised protocol was developed using a concentration of 4.5% saline [31]. Higher concentrations caused the FEV1 to decrease too quickly and, for lower concentrations, the time for testing was too long. The aerosol is administered in progressively increasing doses with the subject inhaling for increasing time intervals until the desired minimum decrease in FEV1 is achieved. This progressive dose–response protocol has advantages of safety over both EVH and exercise, where the stimulus is given as a bolus dose over 6–8 min. Initially, a value of 20% decrease in FEV1 from the pre-challenge value was used for 4.5% saline [31]. This value was reduced to a 15% decrease in FEV1, as it became evident that healthy subjects with normal lung function had little response [36]. This value of 15% was confirmed in a later study in healthy subjects based on the mean plus two standard deviations of the % decrease in FEV1 [34].

Protocol

The equipment required is a large-volume (200–250 mL) ultrasonic nebuliser with a detachable canister (for weighing) that generates particles 2–6 μm in diameter and delivers 1.5–2 mL per min to the inspiratory port of the two-way valve. The canister is filled with 200 mL of 4.5% saline at ~21^{0}C and the subject breathes tidally through a two-way valve for different periods of exposure. The aerosol is inspired through tubing with a smooth interior about 60–70 cm long and 22 mm wide to avoid excessive impaction of the aerosol. All of the specifications reduce variability of the output of the nebuliser [26].

The pre-challenge FEV1 is measured in triplicate. The initial exposure is 30 s followed 60 s later with two reproducible FEV1 measurements. If the reduction in FEV1 is <15% of the pre-challenge FEV1, then the next exposure time is doubled (*e.g.* the remaining doses are 60 s, 2 min, 4 min and 8 min). If the FEV1 decreases ≥10% but <15% between each dose, the previous dose is repeated. The test is completed when a 15% decrease in FEV1 is achieved or a minimum dose of ≥23g (~23 mL) of aerosol has been delivered following the final dose of 8 min (total exposure time 15.5 min). The dose is measured by reweighing the detachable canister and tubing (without the two-way valve) making sure that any aerosol that has deposited in the tubing is permitted to fall back into the canister and not be excluded from the reweighing procedure. The dose delivered in mL per exposure time is calculated [26].

Interpreting the response to hyperosmolar saline

A dose–response curve is constructed relating the percentage fall in FEV1 to the cumulative dose of aerosol delivered in mL. The provocative dose causing a 15% decrease in FEV1 (PD15) is calculated *via* linear interpolation. A PD15 value <2 mL is classified as severe, 2–6 mL as moderate and >6 mL as mild (fig. 5) [26]. Epidemiological studies have demonstrated that a positive response to hyperosmolar saline is associated with currently active asthma [33, 37]. Subjects hyperresponsive to 4.5% saline have been shown to be less responsive following treatment with inhaled corticosteroids (ICS) [36, 38, 39]. For subjects already taking ICS who are also hyperresponsive to 4.5% saline, it is likely they could benefit from a higher dose of ICS or improved adherence to ICS. A negative response to hyperosmolar saline in the presence of ICS may suggest very mild or controlled asthma [40]. There have been a number of studies demonstrating a relationship with the airway sensitivity to hyperosmolar saline and the airway response to exercise [41–43]. In one study of 365 school children who exercised and had a hyperosmolar (4.5%) saline test, the sensitivity and specificity of hyperosmolar saline to identify EIB was 54% with a specificity of 85% [32]. To

Figure 5

The classification of the airway response to hypertonic saline. This is calculated using the dose of aerosol required to provoke a 15% decrease in FEV1 from the pre-challenge value. The delivered dose (in mL) is cumulative and is calculated by dividing the total dose delivered over the total time required to administer the challenge. An abnormal response is two standard deviations over the mean healthy response (normal <15%). Circles: severe (<2 mL); squares: moderate (2.1–6 mL); diamonds: mild (>6 mL). Reproduced from [15] with permission from the publisher.
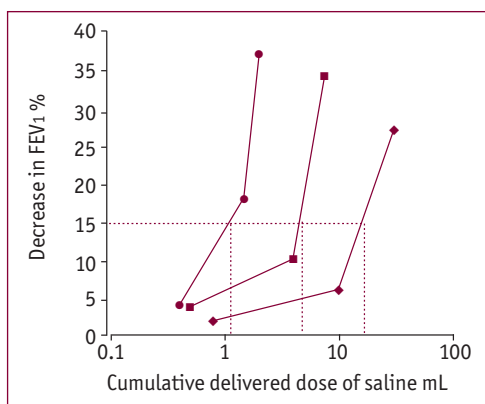
date, there have been no studies assessing the efficacy of hypertonic saline to diagnose EIB in athletes. The sensitivity and specificity of hyperosmolar saline has been assessed in a population of adults where it was found to have a specificity of 65% to identify a clinical diagnosis of asthma, with a specificity of 95% [34]. In this study, the mean decrease in FEV1 was 21.0±5.7%; a 15% decrease was the target for diagnosis.

Mannitol airway challenge test

The mannitol challenge test uses capsules of dry-powder mannitol delivered *via* a simple inhaler. ANDERSON *et al.* [44] first developed the mannitol bronchial challenge test in 1996. A mannitol test kit (Aridol™/Osmohale™) is now commercially available in Australia and 18 countries in Europe and Asia (fig. 6)

Rationale and development

The mannitol challenge test was developed in an attempt to make a bronchial provocation test that used one standardised protocol, gave reproducible findings and that was easy to perform as well as safe to use at the point of need [44]. Mannitol is a sugar alcohol and, like sodium chloride (saline), can act as an osmotic agent in physiological systems. In contrast to sodium chloride, mannitol is nonionic and is not easily or rapidly absorbed through the airway mucosa. Mannitol has advantages over sodium chloride in that, when prepared as a dry powder, it does not readily take up water and is stable and suitable for encapsulation to be used for inhalation. The dry powder formulation overcomes the technical problems in relation to variation in output of the wet aerosol particles over time using ultrasonic nebulisers. Finally, a dry-powder test overcomes the hygienic problems related to the generation of wet aerosols and the exposure of technical staff to these aerosols.

Protocol

For the mannitol test, the patient inhales increasing doses of dry-powder mannitol, with FEV1 measured in duplicate after each dose. The test protocol consists of 0 mg (empty capsule), after which the baseline FEV1 is established, then 5, 10, 20, 40, 80 mg (2–40-mg capsules) and three doses of 160 mg (4– 40-mg capsules) mannitol. The maximum cumulative dose of mannitol that is administered is 635 mg. The patient's FEV1 is measured 60 s after administration of each dose,

Figure 6

Examples of equipment used to perform a) laboratory exercise testing, b) exercise testing in the field, c) eucapnic voluntary hyperpnoea, and d) hypertonic saline and e) mannitol challenge tests.
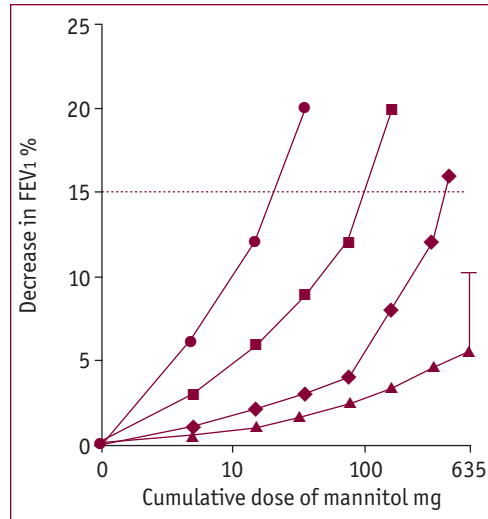
and the percentage change from the value measured after the 0-mg capsule is calculated [44]. The mannitol test needs to be performed in a timely manner so that the osmotic gradient is increased with each dose. The repeatability of the response to mannitol is one doubling-dose [45, 46].

The time to complete a positive test as observed in a large phase 3 trial was 17±7 min for a positive test and 26±6 min for a negative test [34]. A test taking >35 min may lead to a false negative result [47]. Sputum can also be collected for cell analysis during and after the mannitol challenge [48].

Interpreting the response to mannitol

A positive test result is defined as either a decrease in FEV_1 of 15% from baseline (*i.e.* after 0 mg capsule) or a 10% decrease in FEV_1 between two consecutive doses [47]. The response to mannitol is expressed as the cumulative dose of mannitol that provokes a 15% decrease in FEV_1 (PD_{15} expressed in mg). The severity of the airway response to mannitol is described in figure 7. The mean decrease in FEV_1 was 21.3±5.9%; when a 15% fall was the target for diagnosis in a large phase 3 study [34].
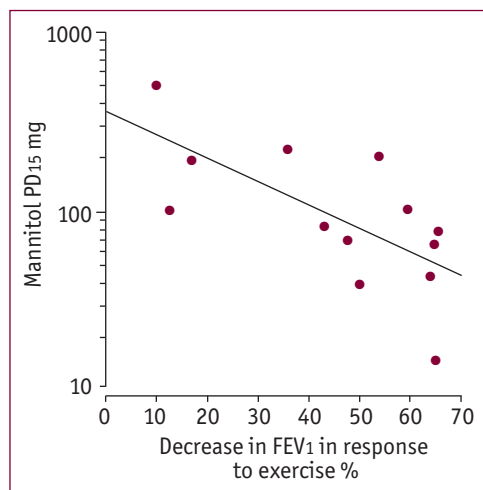
The diagnostic validity of the mannitol challenge test has been assessed in three large clinical trials [34, 47, 49], which have consistently shown that the rate of false-positive tests in non-asthmatics is very low and that the mannitol test has a high specificity for currently active asthma. The sensitivity of mannitol to identify EIB in 375 adults and children with symptoms identified as possible, but not definite, asthma, was 59% when EIB was defined as a 10% decrease in FEV_1 on at least one of two exercise tests [47]. The sensitivity increased to 69% when EIB was defined as a 15% decrease after exercise and to 75% when those with a mannitol test time of ≥35 min were excluded. However, the frequency of a 15% decrease in FEV_1 in response to mannitol was greater than that of a 15% fall to exercise. The lower than expected sensitivity of mannitol to identify EIB in this population may reflect the mild nature of EIB, as 50% of subjects had a decrease of <15% after exercise. Furthermore, the exercise response was variable, in that EIB, on the first exercise test, had a 62% sensitivity of identifying EIB on the second test. By contrast, in adults with known asthma and exercise-induced symptoms who had either a positive exercise test and/or a positive EVH test, 97% responded to mannitol and there was a good relationship with airway

responses, particularly among steroid-naïve asthmatics (fig. 8) [24, 50]. In children with a clinical diagnosis of asthma and exercise-induced symptoms, nine out of 10 children (90%) with a positive exercise test also responded to mannitol (15% decrease in FEV_1) [51].

In a group of elite athletes, the mannitol challenge test had a sensitivity of 96% and a specificity of 92% for detecting EIB defined as a positive EVH test, when using a cut-off of 10% for defining a positive mannitol test [22]. The sensitivity was reduced to 84% when a cut-off of a 15% decrease for mannitol was used. By contrast, a recent study of elite swimmers found little concordance between the mannitol test result and a swimming exercise test result; of the 14% responding to mannitol and the 16% responding to swimming exercise, only one swimmer responded to both tests [52]. Likewise, a study of cross-country skiers found that out of 23 subjects responding to methacholine, only two had a positive response to mannitol [53]. These

Figure 7

Classification of the airway response to a dry-powder aerosol of mannitol. This is calculated using the cumulative dose of mannitol (in mg) that is encapsulated and delivered using a dry powder inhaler to provoke a 15% reduction in FEV_1 from the FEV_1 obtained following administration of the 0-mg capsule. The abnormal response is two standard deviations over the mean healthy response (normal; triangles). Circles: severe (≤35 mg); squares: moderate (≤155 mg); mild (>155 mg). Reproduced from [24], with permission from the publisher.

Figure 8

The airway sensitivity to inhaled mannitol in relation to the % decrease in FEV_1) following 8 min vigorous exercise in steroid-naïve subjects with established clinical asthma and exercise-induced bronchospasm. r= -0.68; p<0.01. Data from [24].

findings may be due to the different cut-off points used or different mechanisms being responsible for EIB in elite-level swimmers and cold-weather athletes [54]. The strongest relationship between airway sensitivity to mannitol and airway reactivity to exercise is in known asthmatics [24]. Elite athletes generally have milder EIB and the reproducibility of the responses may not be a feature of mild responses to indirect challenge tests [47]. EIB in elite athletes may be due to airway injury, such that there may be differences between those with EIB alone and subjects with EIB plus more chronic symptoms of asthma.

The mannitol challenge test has also been studied in groups working in occupations where EIB needs to be ruled out. In a group of firefighters, the mannitol test had a sensitivity of 92%, a specificity of 97% and a positive predictive value and negative predictive value (NPV) of 86% and 98%, respectively, for detecting asthma defined as a combination of symptoms and at least one objective sign of asthma [55]. The inclusion of BHR in the definition of the clinical diagnosis of asthma may explain the high sensitivity in this study. In comparison, a study using a primarily symptom-based diagnosis of asthma in 235 military conscripts found that the mannitol test had a low sensitivity (43%) to detect subjects with a clinical diagnosis of asthma, but a high NPV (88%) [56].

Which test is the most appropriate to identify EIB?

The choice of test will often depend on which tests are locally available and the overall test strategy may also depend on the need for an objective diagnosis of asthma (fig. 9). EVH is the most sensitive alternative test for EIB, particularly for elite-level athletes with good lung function. However, EVH requires specialised equipment and should be performed in a laboratory, which may limit its use to certain specialist clinics. Furthermore, there are safety issues in relation to large decreases in FEV_1 with any provocation test where the stimulus is given as a bolus
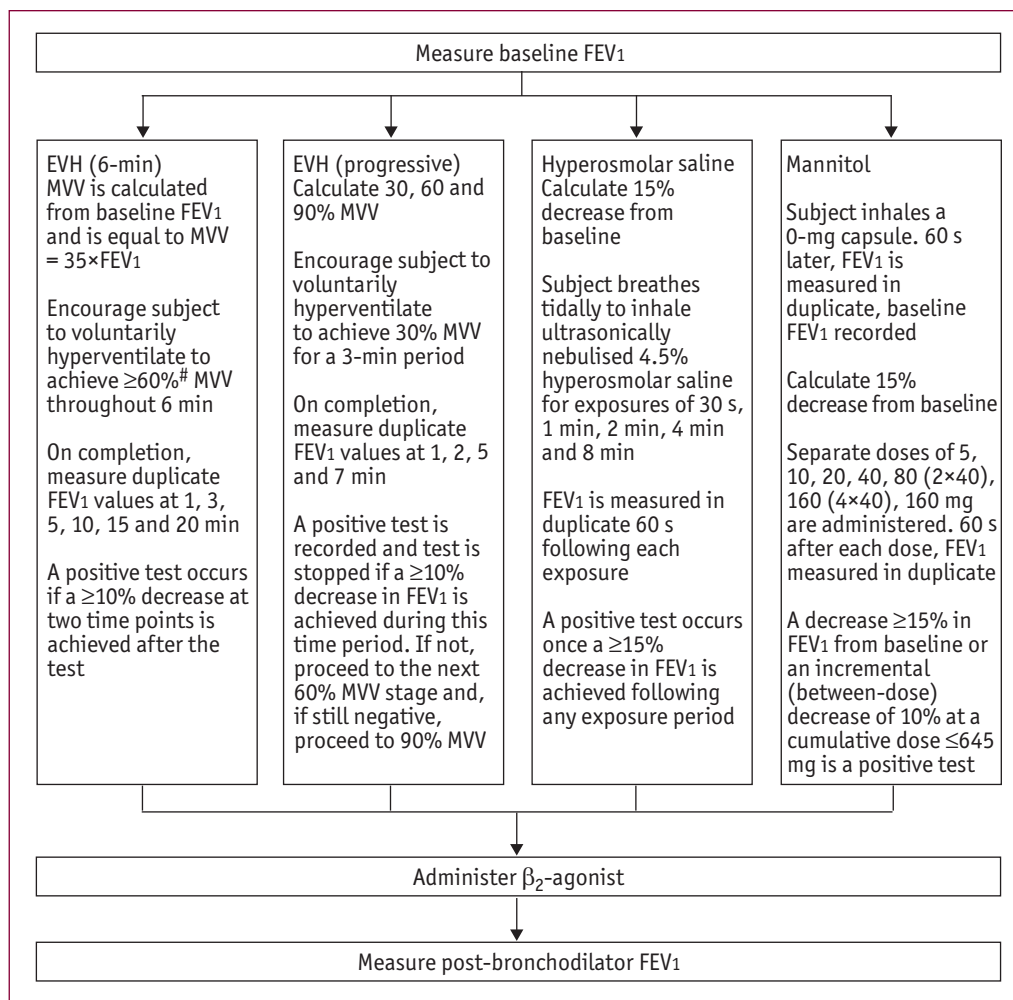
Figure 9
Choice of test. #: 85% used for healthy elite athletes and recruits.

rather than in progressively increasing doses. This safety issue applies equally to athletes and nonathletes, as the maximum airway response to EVH cannot be predicted from the baseline lung function. The hyperosmolar aerosol challenge tests are safer alternatives to EVH, which makes them preferable in asthmatics in general and in nonelite athletes being assessed for BHR and EIB. Both hyperosmolar saline and mannitol require less equipment and the mannitol test can be performed in any clinical setting, as well as in the field. Both aerosol tests have been reported to have a low percentage of adverse events in phase 3 trials [34, 47]. The mannitol test has practical advantages in being a simple, single-use test kit that is standardised and commercially available, and with regulatory approval that has made it more accessible to clinicians.

The hyperosmolar aerosol challenge tests have a lower sensitivity for detecting documented EIB compared with EVH. The agreement between a positive hyperosmolar test and a positive exercise test (*i.e.* positive responses to both tests) is highest in persons with classical asthma symptoms, and the agreement is least in persons without a definite diagnosis of asthma but who have mild symptoms.

The need for obtaining an objective diagnosis of asthma will determine the choice of test strategies: for instance, in the elite athlete, EVH is the most sensitive test to identify EIB and should be the test of choice if it is available. If EVH is not immediately available, a hyperosmolar aerosol challenge test may be applied first and, if it is negative, the athlete may be referred for EVH. In elite athletes applying for a Therapeutic Use Exemption (TUE) certificate to use asthma medications, both the EVH test, hypertonic saline and the mannitol test are recognised by the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA) as appropriate objective tests for identifying asthma. Methacholine and histamine are also accepted by the IOC and WADA for identifying BHR.

In asthmatics and non-elite athletes, hyperosmolar aerosols may be considered the first-choice tests for practical reasons. Due to their lower sensitivity compared with EVH, retesting or assessment with several challenge tests may be required in cases where the suspicion of asthma is high based on symptoms or in cases where it is important to rule out asthma for persons who may be at risk of EIB due to an occupation or sporting activity.

Suggested Answers

1. It may be difficult to obtain a sufficient level of exercise intensity to induce sufficient airway dehydration to cause bronchoconstriction, especially in young children and older adults or in those who are unfit. The equipment required for the test is space occupying and expensive. Large falls in FEV1 can result and may give cause for safety concerns in some patients.

2. The advantage of EVH is that the stimulus is of a shorter duration than exercise and a positive response is defined as only a 10% decrease in FEV1; for the osmotic challenge tests, a positive response is 15%. EVH is thought to be a more sensitive test for identifying EIB compared to laboratory exercise protocols, as a high level of ventilation can be reached and sustained more rapidly than exercise; thus, it may be a more potent dehydrating stimulus.

3. EVH induces evaporation of airway surface liquid, which in turn increases the osmolarity of the airway surface liquid. The osmotic challenge tests increases osmolarity of the airway surface. The increase in osmolarity leads to the release of bronchoconstricting mediators from inflammatory cells in the airways which act on receptors on airway smooth muscle to cause bronchoconstriction.

4. The advantage of EVH is that the stimulus is of a shorter duration than exercise and a positive response is only a 10% fall in FEV1, whereas for the osmotic challenge tests, a positive response is 15%. EVH is thought to be more sensitive to identify EIB compared to laboratory exercise protocols as a high level of ventilation can be reached and sustained more rapidly than exercise; thus, it may be a more potent dehydrating stimulus.

5. The osmotic challenge tests are easier to perform from a practical perspective and require less patient effort. They also require less equipment and are safer than EVH, as they are progressive dose challenge tests.

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