Key points

• The primary stimulus for exercise-induced bronchoconstriction (EIB) is water loss from the airway surface liquid with subsequent bronchoconstricting mediator release.
• A symptoms-based diagnosis is not sensitive or specific to EIB.
• The free run can be a very effective stimulus to EIB.
• The dry-air laboratory challenge is an effective test for EIB and allows for more control of test intensity and inhaled air conditions than the field-based challenge.
• A positive challenge is defined by a 10% decrease in forced expiratory volume in 1 s from baseline at two time-points within 3–30 min after the cessation of exercise.
Field and laboratory exercise challenges for identifying exercise-induced bronchoconstriction

Educational aims

- To define necessary conditions for a successful exercise challenge.
- To provide operational procedures for performing an exercise challenge in the laboratory or the field for the identification of exercise-induced bronchoconstriction.
- To compare positive and negative attributes of each challenge.
- To provide spirometric cut-off criteria for positive challenge tests.

Summary

Exercise challenge tests are often used for identification of exercise-induced bronchoconstriction (EIB). Optimal test conditions are: absolute humidity of <10 mg H₂O per L; exercise intensity resulting in a sustained increase in minute ventilation to 14–21 times the forced expiratory volume in 1 s or heart rate (HR) to 80–90% of the estimated maximal HR; and exercise duration of 6–8 min. Variability in fitness level and age necessitate individualisation of the exercise protocol. Field tests are subject to variability in test conditions and may have poorer repeatability than laboratory tests that require expensive equipment. However, either challenge test can be employed for the diagnosis of EIB in conjunction with a critical clinical assessment.

Historical aspects

The association of exercise with asthma was recognised almost 2,000 yrs ago by Aretæus (81–138 AD): “If from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called Asthma” [1]. Any condition associated with dyspnoea was described as asthma until the publication of “A treatise of the asthma” by Sir John Floyer in 1698 [2]. He suffered from asthma, and described how exercise could precipitate an asthmatic attack and that the severity of the attack is related to the intensity of the exercise: “All violent Exercise makes the Asthmatic to breathe short ... and if the Exercise be continued it occasions a Fit”.

The first objective measurement of the effect of exercise on lung function was made by HERXHEIMER [3] in 1946. In addition to the level of hyperventilation, the magnitude of the response, measured as the decrease in lung function that occurs after exercise, was subsequently shown to be dependent on the nature, intensity and duration of the exercise stimulus. Different exercise forms have been investigated. When performed at similar heart rate (HR), minute ventilation and oxygen consumption,
the exercise modality that is most potent for the degree and incidence of bronchoconstriction is free running, followed in decreasing order by treadmill running, cycling, swimming and walking (fig. 1) [4]. With regard to duration and intensity, the maximum effect of treadmill running on lung function occurs after 6–8 min running up a slope of 10-15% at a constant speed [5].

Additional factors that influence the effect of exercise are the water content and quality of the inspired air. The water content of the inspired air determines the extent of the respiratory water loss during exercise. It is complexly related to relative humidity and air temperature. At a given temperature, water content is determined by the relative humidity of the air. However, for a given relative humidity, water content is nonlinearly related to temperature. Thus, the water content is always low in cold air, but can vary from low to high in warm air depending on the relative humidity of the air. In susceptible individuals, air with a low water content is more potent than air with a high water content at provoking bronchoconstriction and cooling of the inspired air enhances the airway response [6]. By contrast, warming of the inspired air to or above body temperature does not prevent bronchoconstriction if the relative humidity is low [7].

Two hypotheses were proposed in the late 1970s and early 1980s for the mechanism of EIB [8, 9]. Both are based on the effects of water loss. In the thermal hypothesis, evaporative water loss during exercise leads to airway cooling and vasoconstriction. After exercise, there is rapid rewarming with bronchial vascular engorgement and airway oedema [10]. In the osmotic hypothesis, water loss causes dehydration of the airways, leading to a transient increase in osmolarity [11] with subsequent release of bronchoconstrictive mediators [12]. Critical review of the experimental work leading to both hypotheses suggests that the increase in airway resistance seen in EIB may be due to both the mechanical effect of the reactive hyperaemia and mediator-induced contraction of the bronchial smooth musculature [13].

EIB

EIB is the transient narrowing of the lower airways that occurs after exercise [14, 15]. Occasionally, transient narrowing can also occur during exercise [16–18]. It occurs in most individuals with recognised asthma, but can also occur in individuals without signs of clinical asthma, such as elite athletes [19].

Cough, wheeze, chest tightness, shortness of breath or excess mucus production are observed symptoms of EIB. However, self-reported symptoms are neither specific nor sensitive for EIB. ~50% of elite athletes who report symptoms in combination with exercise do not have airway narrowing and ~50% who report no symptoms will test positive for EIB [20, 21]. It is therefore important to support the diagnosis of EIB by performing a challenge test.

The exercise challenge test

The exercise challenge test is indicated primarily for the diagnosis of EIB, assessment of EIB severity and the efficacy of prophylactic drug therapy [22]. In some countries it is also used to screen for EIB in elite athletes and in certain occupations, such as firefighters, police and soldiers. It is considered an indirect challenge because it is associated with release of mediators that act on airway smooth muscle to cause contraction. This is unlike the direct challenges of histamine and methacholine, which act directly on the airway smooth muscle receptors to cause bronchoconstriction independent of the presence of inflammatory cells.

Contraindications

Absolute and relative contraindications that are recommended in the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines on bronchial provocation testing [22, 23] are summarised in table 1. If baseline forced expiratory volume in 1 s (FEV1) is <50% predicted or <1.5 L, an exercise challenge should not be performed; a β2-agonist reversibility test should be substituted. A challenge test should only be done if the expected benefit justifies...
the potential risk and complications associated with the procedure. Preferably, exercise challenge should be performed in subjects with lung function 75–100% predicted.

Subject preparation
In addition to antiasthmatic medication and medication with antihistamine effects, the subject should abstain from all food and drinks that contain caffeine, and strenuous exercise. Abstinence times before the exercise test are given in table 2.

Measurement of lung function
Lung function tests should follow ATS and ERS standards for forced vital capacity and FEV1 manoeuvres [24]. Spirometry should be performed at baseline prior to the exercise challenge. The 10% decrease and 50% alert value of FEV1 should be calculated from the pre-exercise baseline FEV1. After challenge, spirometry is performed at defined times, such as 3, 5, 10, 15, 20 and 30 min. It is not recommended at earlier time points after challenge, as the effort could be influenced by respiratory muscle fatigue [25]. Spirometry should continue to 30 min unless the patient has a decrease in FEV1 >50%, at which point a short-acting β2-agonist should be administered to reverse the response. At each time-point, two repeatable FEV1 values should be measured and the greater of the two values recorded. The patient should not be released until FEV1 returns to 95% of the baseline value.

Post-exercise FEV1 values are compared with pre-exercise baseline FEV1 values and calculated as a % change from baseline using the equation:

\[
\text{Pre-exercise FEV1} - \text{post-exercise FEV1} \times 100
\]

A ≥10% decline in FEV1 at any time-point within 30 min of ceasing exercise is considered diagnostic of EIB [22, 23]. The optimal cut-off point in children and adolescents is considered to be a ≥13% decline in FEV1 [26, 27]. The decline in FEV1 is usually sustained over two time-points. An unsustained decline may be due to respiratory muscle fatigue.

### Table 1 Comparison of absolute and relative contraindications to exercise challenge tests from the guidelines of the European Respiratory Society (ERS) and the American Thoracic Society (ATS)

| Factor                                                                 | ATS | ERS |
|------------------------------------------------------------------------|-----|-----|
| Absolute                                                               |     |     |
| Severe airflow limitation (FEV1 <50% pred or <1 L)                     | x   |     |
| Severe airflow limitation (FEV1 <1.2 L in adults)                      | x   |     |
| Heart attack in last 3 months                                          | x   | x   |
| Stroke in last 3 months                                                | x   | x   |
| Uncontrolled hypertension (systolic BP >200 mmHg or diastolic BP >100 mmHg) | x   |     |
| Aortic aneurysm                                                        | x   |     |
| Arterial aneurysm                                                      | x   |     |
| Inability to understand the procedures and the implications of a challenge test | x   |     |
| Unstable cardiac ischaemia or malignant arrhythmias                    | x   |     |
| Relative                                                               | x   |     |
| Moderate airflow limitation (FEV1 <60% pred or <1.5 L)                 | x   |     |
| Moderate airflow limitation (FEV1 < predicted FEV1 – 1.5 L in males, FEV1 < predicted FEV1 – 1.2 L in females) | x   |     |
| Inability to perform acceptable-quality spirometry                    | x   |     |
| Pregnancy                                                              | x   | x   |
| Nursing mothers                                                        | x   |     |
| Current use of cholinesterase inhibitor medication (for myasthenia gravis) | x   |     |
| Recent upper respiratory tract infection (<2 weeks)                    | x   |     |
| During exacerbations of asthma                                         | x   |     |
| Epilepsy requiring drug treatment                                      | x   |     |

% pred: % predicted; BP: blood pressure. #: for safety reasons, exercise challenge tests should preferably be performed in subjects with lung function 75–100% pred.
Field and laboratory field challenges

### Table 2  Minimum abstention times for medication, exercise and nutrients prior to exercise challenge test

| Minimum abstention time | Factor |
|-------------------------|--------|
| Day of test             | Coffee, tea, cola drinks and chocolate Smoking |
| 4 h                     | Strenuous exercise |
| 6–8 h                   | Short-acting, inhaled β2-agonists e.g. salbutamol and terbutaline Long-acting anticholinergics e.g. ipratropium Short-acting anticholinergics e.g. ipratropium Chromones e.g. cromolyn sodium and nedocromil |
| 12–24 h                 | Long-acting, inhaled β2-agonists e.g. salmeterol and formoterol Inhaled glucocorticosteroid |
| 24 h                    | Theophylline |
| 48 h                    | Ultralong-acting, inhaled β2-agonists e.g. indacaterol |
| 72 h                    | Long-acting anticholinergics e.g. tiotropium Leukotriene receptor antagonists Antihistamines and other medications with antihistamine effects e.g. tricyclic antidepressants |

**Exercise testing protocols**

Both the ERS and ATS have published guidelines for exercise test protocols [22, 23]. Preexercise warmup is not allowed, as this has been shown to be protective to EIB in some individuals. A nose clip is always worn during the test to dictate mouth breathing and prevent the inspired air from being conditioned by the nasal mucosa.

The target workload should be sufficient to increase the minute ventilation to 14–21 times the predicted FEV1, which is 40–60% of the maximum voluntary ventilation (MVV), defined as 35×FEV1. It should be achieved within 2–4 min of the start of the challenge and then be sustained for a further 4 min, with a total time of 6 min for children, 7 min for adolescents and 8 min for adults. The work intensity that is necessary to achieve the target work load is dependent on the degree of physical fitness and body weight of the subject. Degree of physical fitness is of equal importance for all exercise modalities, as is the age of the patient. Because of the wide age range of patients, no single standardised protocol pace can be defined. The protocol should be individualised according to fitness level and age. Body weight is of lesser importance for the work intensity on a cycle ergometer.

It is essential that a high level of minute ventilation is rapidly achieved and maintained for the duration of the test in order for rapid recruitment of the lower airways to the 10th generation to occur, allowing conditioning of the inspired air. According to the osmotic hypothesis, the rate of water loss is more important than the absolute water loss for an increase in osmolarity of the periciliary fluid and subsequent release of mediators leading to EIB.

The inhaled air should be dry, with a water content <10 mg H2O per L of air. Relative humidity (RH) and ambient temperature of the inspired air should always be measured. The relationship between these two factors to give an absolute water content of 10 mg H2O per L is shown in figure 2 [26]. For laboratory tests, medical grade air (<5 mg H2O per L) is preferred and is administered using a nonlatex reservoir bag with a two-way, nonrebreathing mouth valve.

Exercise tests can be performed in the laboratory or in the field. Ergometers, such as the motor-driven treadmill or bicycle, are needed for laboratory tests, while field tests are either free running or a sport-specific exercise. For the elite athlete, a sportspecific exercise test is often used and should be performed under conditions that cause symptoms in the subject.

**Monitoring**

It is recommended that minute ventilation is monitored during the exercise challenge to ensure that the exercise targets are achieved. Minute ventilation is typically measured online using a metabolic cart during the laboratory exercise challenge. This allows the technician to increase, maintain or decrease the speed and/or incline of the treadmill to reach the target ventilation of 50–60% MVV. If minute ventilation cannot be monitored, HR in beats per min can be used as a surrogate, with a target HR of 80–90% estimated HRmax (220 – age in yrs) for the last 4 min of the challenge [22]. An exercising HR of 80–90% will allow all but the very fit athlete to achieve and exceed 60% MVV.

HR can be monitored simply by using a wireless HR monitor watch and chest band during laboratory and field exercise tests. Alternatively, ECG equipment with a three-lead or 12-lead placement can be used for laboratory exercise tests.

**Safety aspects**

During all exercise challenges, personnel qualified to administer emergency procedures should be present. Emergency equipment, such as a cardiodefibrillator, materials for intubation and emergency rescue medication, should be readily available.

**Sensitivity and specificity**

For both laboratory and field tests, the minute ventilation achieved and sustained during the exercise, the duration of the exercise and the...
Field and laboratory field challenges

**Treadmill exercise**
The work intensity on the treadmill is determined by the speed and slope of the treadmill and the weight of the subject [28, 29]. General recommendations for starting treadmill speed are 3 km·h⁻¹ for children and 5 km·h⁻¹ for adults at an incline of 2.5% [30]. In some protocols, the desired work intensity is achieved by increasing the slope while running at a constant speed; in other protocols, both slope and speed are increased in order to reach the work intensity within the first 2 min of the challenge. Prior to 2 min, adjustments should be made to achieve the target of 80–90% of predicted maximum HR (HRmax) and a minute ventilation of 50–60% predicted MVV. Further adjustments can be made up to minute 4. The target HR/minute ventilation should be maintained for the remaining 4 min of the challenge.

**Cycle ergometer**
The target workload in W in the healthy untrained subject is calculated using as (53.76 × predicted FEV1) – 1107 [31]. This is achieved within 4 min by beginning at 60% of the target workload and increasing at 1-min intervals to 70, 90 and 100%. The subject should be encouraged to sustain this target workload for an additional 4 min. At this workload the minute ventilation should reach 50–60% of predicted MVV.

**Free-running**
Subjects are encouraged to run as fast as possible on an indoor or outdoor track. In children, the running time is standardised to 6 min and a HR of 85–90% of predicted HRmax is achieved within 2 min, which is then sustained for 4 min [26]. In adolescent athletes, a minimum running time of 6 min or a standard distance of 1 mile of competitive running in groups of four to six subjects has been used [32].

**Sport-specific exercise tests**
Sport-specific tests have been used in athletes in winter sports, such as cross-country and biathlon skiers, speed skaters, ice hockey players, and swimmers [33–38]. All protocols were at competition intensity, but varied regarding presence or absence of warmups. The duration of the exercise test is dependent on the sport of the athlete and can vary from 80 s in speed skaters to >1 h in cross-country skiers [39]. Alternatively, the duration can be constant, being usually 6–15 min [34, 35, 38–40], or it can be a race over a fixed distance [37, 38].

Water content of the inspired air are factors that determine the sensitivity and specificity of the challenge. The currently recommended exercise challenge for EIB is 8 min exercise (either cycling or running) that evokes an intensity >90% HRmax by 2–4 min into the challenge and is maintained for the remaining 4–6 min. The exercise challenge should not be done at ambient conditions with an absolute humidity >10 mg H₂O per L (e.g. 21°C, 60% RH), as this increases the risk of a false negative test [41]. In field-based tests, ambient temperature, wind velocity, and air pollution with allergens, chemicals, ozone and particulate matter are additional factors that may affect the airway response [42].

Irrespective of the type of exercise challenge, it is essential that a high level of minute ventilation is rapidly achieved and maintained for the test duration in order for rapid recruitment of the lower airways to the 10th generation to occur for conditioning of the inspired air.

Effect of HRmax
The sensitivity of the exercise challenge is increased if the HR response to the workload is increased from 85% to 95% HRmax. Carlsten et al. [39] demonstrated that the sensitivity of exercise challenge is increased if the HR response to the workload is increased from 85% to 95% HRmax.
Field and laboratory field challenges

Figure 3
Mean ± SE post-challenge decreases in forced expiratory volume in 1 s comparing a cold-air, field-based exercise challenge to a room temperature (21°C, 50% relative humidity) laboratory exercise challenge (n=18). 18 out of 23 subjects were exercise-induced bronchoconstriction (EIB)-positive after a field challenge and -negative after the laboratory challenge. Only five out of 23 EIB “field”-positive subjects tested positive in both challenges. Data from [39].

al. [44] examined the effect of exercise intensity on EIB by comparing the results of two treadmill challenge tests at 85% and 95% of calculated HRmax in 20 asthmatic children. The peak decrease in FEV1 was significantly greater at 95% than at 85% HRmax (25.11% versus 8.84% decrease); nine out of 20 subjects had decreases >10% at 85% HRmax, while all 20 had decreases >10% at 95% HRmax. This study supports the necessity of standardising the exercise protocol using high exercise intensity and consequent high minute ventilation.

Effect of cold air
The temperature of the inspired air does not affect the sensitivity of the challenge. However, it may affect the severity of the EIB. When exercise challenge was performed at the same RH (40%) but at temperatures of 20.2°C and -18°C, the severity of the EIB was significantly greater after exercise at -18°C than at 20.2°C, suggesting an additive effect of cold air [45]. Thus, it may be prudent to assess individuals who have symptoms only under cold conditions with an exercise challenge with cold air inhalation if the challenge test with warm air with an absolute humidity <10 mg H2O per L is negative. In contrast, no additive effect was observed by Evans et al. [46], who reported that the severity of EIB was related to water content and not the temperature of inhaled air during exercise.

Repeatability
In a study examining the repeatability of % decrease in FEV1 in 373 subjects with mild symptoms suggestive of asthma but without a definitive diagnosis, Pearlman et al. [47] identified agreement between two laboratory exercise challenges of 76.1%. 56.8% of the subjects were negative on both challenges, 19.3% were positive on both challenges and 23.9% had a positive test on only one challenge [47].

In another study of subjects with symptoms suggestive of asthma, a well controlled laboratory exercise challenge demonstrated reasonable repeatability, but intersubject variability suggests that two tests may be needed to make a diagnosis of EIB [48].

Using a 15% decrease in FEV1 as the cutoff criterion for a positive test, Haby et al. [49] showed good validity and short-term reliability of free running in evaluating EIB in large groups of children 8-11 yrs of age. However, the uncontrolled nature of the stimulus and changing ambient conditions may impose variability that limits the free running test as a means of monitoring therapy.

Conclusion
The exercise challenge test for identification of EIB can be problematic. If the inhaled air is not sufficiently dry, or if the exercise intensity is not sufficient to achieve a minute ventilation of 14-21 x FEV1 or 80-90% estimated HRmax, then false negative tests are likely. If these conditions are met then the test can be highly sensitive. Because of variability in patient fitness level and age of patients, it is not practical to have a defined laboratory challenge protocol in terms of treadmill speed and incline or cycle ergometer intensity. Even with consistent within-patient protocols, the agreement between two laboratory treadmill challenges is 76%. The ease in administering the field-based challenge and the lack of required expensive equipment make this challenge attractive. This challenge has been called the “gold standard”. However, because of the variability in exercise intensity and ambient conditions from one test day to another, this test is not ideal for monitoring therapy. In conclusion, the exercise challenge can be a useful tool for the identification of EIB, but as with all challenge tests, it is only one piece of the diagnostic puzzle, which includes close evaluation of symptoms, atopic status, family history and clinical examination, together with response to bronchodilators and oral corticosteroids.
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