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Bronchial Challenge Testing

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1. Introduction

Airways hyper-responsiveness (AHR) is found in almost every patient with asthma. The degree of AHR is variable between individuals with asthma and can correlate to the severity of the underlying asthma. Equally treatment of asthma can modify the degree of underlying AHR. Measures of Airway hyper-responsiveness or bronchial challenge testing are therefore important in both the assessment and management of asthma.

The appraisal and assessment of the currently available bronchial challenge testing is hampered by the lack of a 'gold standard' for the diagnosis of asthma. In addition to basing this overview on published evidence, we are also integrating some of our own research and clinical experience as clinicians and director of a respiratory physiology laboratory.

Some tests including the **direct challenge tests** with methacholine or histamine are highly sensitive; this makes them particularly useful to exclude a diagnosis of asthma. The disadvantage of these tests is a general lack of specificity. Although one is unlikely to miss asthma using these highly sensitive tests, the clinical importance of a positive test is not always clear. In addition, the methacholine challenge test may be positive in physiological scenarios which cause airways reactivity.

At times it is clinically more meaningful to choose a less sensitive but more specific test, which reflects the physiological airway response such as one of the **indirect challenge tests** for example; exercise challenge, hypertonic saline, adenosine or mannitol testing. These tests are particularly helpful if one wishes to assess the response to treatment. If asthma is well controlled these tests are often negative and are not useful in excluding asthma.

The performance of bronchial challenge testing requires adherence to international quality guidelines for the performance of spirometry and well trained staff. Most tests use a change in the FEV₁ by 200mls as the minimum cut-off, which reflects the historic belief that spirometry, (in particular FEV₁) is only reversible within 200mls; i.e. 200mls is thought to be the minimum standard of a coefficient variation of these tests. However, new equipment and the latest ERS / ATS guidelines suggest a variability of 150ml or even 100mls could be achieved. This becomes particularly important if one were to comment on trends within a series of tests.

Finally, as in any other clinical tests the risk benefit ratio needs to be considered. Although it may be interesting to know whether a patient with advanced COPD still has significant

reversibility, a possible positive response to methacholine may cause distressing respiratory compromise. Challenge testing should not be performed if the baseline FEV₁ is less than 1.5 L or less than 60% of the predicted FEV₁. The expected response should also be taken into account when performing tests, particularly the methacholine challenge and eucapnic voluntary hyperventilation test can potentially cause significant changes in a susceptible airway. Many laboratories will only perform a eucapnic voluntary hyperventilation (EVH) test when other tests like hypertonic saline are negative, and a clinical suspicion of asthma persists.

2. History of challenge testing

Much of this chapter, actually much of this book, is devoted to preventing the smooth muscle cells contracting or maybe turning the process of altogether. Considering the mental energy spent controlling contraction of the airway smooth muscle cells and witnessing the, at times devastating clinical outcome may lead the clinician to relate to this metaphor of the airway smooth muscle cell described by Seow and Fredberg “ ... we might think of the airway smooth muscle as the Hell’s Angels of cells, sitting on a Harley-Davidson, unshaven, a cigarette in one hand, a can of beer in the other, and a tattoo on its arm reading ‘Born to Lose’ ” (Seow & Fredberg, 2001).

The same authors argue the airway smooth muscle cell, although first described in 1804, may not have a specific physiological function. It seems plausible that there is no explanation for the utility of airway smooth muscle. It is probably that during the ontological development of the lung from the foregut, some of the vestigial gut smooth muscle may have become displaced into the airway as an ‘accident of nature’ not fulfilling any useful function in the lung.

It was during the 1940’s that Curry first reported a greater degree of bronchoconstriction to inhalation of histamine and methacholine in patients with asthma compared to those without asthma (Curry, 1947). In the same decade Tiffeneau described the change in the airway using either histamine or methacholine by describing the provoking concentration (PC) to induce a 20% reduction in the FEV₁ (PC₂₀). (Tiffeneau & Pinelli, 1947). From then onwards bronchial challenge testing started to make its way from a research tool into the clinical arena.

In 1987 Pauwels and colleagues proposed that bronchoprovocation tests could be divided into direct and indirect stimuli. Direct stimuli like methacholine, histamine, leukotrienes and prostaglandins act directly on the smooth muscle receptors. Indirect stimuli act through one or more intermediate pathways which cause a release of mediators from inflammatory cells and cause bronchial constriction. Many naturally occurring stimuli in asthma cause symptoms through indirect mechanisms and these tests may correlate better with clinical features of asthma. Indirect tests include exercise, hypertonic saline, adenosine monophosphate, eucapnic voluntary ventilation and mannitol.

The current Global Initiative for Asthma Guidelines (GINA) include these indirect challenges as a diagnostic and management tool because the response to these challenges is modified or even completely inhibited by inhaled steroids. The availability of dry powder mannitol capsules has the potential to bring challenge testing from the specialist laboratory to the patient bedside or more relevant the ambulatory setting.

3. Reversibility testing

Bronchodilator reversibility testing is clinically easier to perform and generally safer than bronchial challenge testing. Although the sensitivity is only approximately 50% to detect asthma, the specificity is approaching 90%. We have included a short description on reversibility testing in this chapter because depending on the clinical question, a positive bronchodilator response may make a bronchial challenge test redundant.

The bronchodilator response is complex and dependent on the interaction between airway epithelium, nerves and smooth muscle. The relationship between bronchoconstriction and bronchodilator response is not straightforward as the presence of one cannot guarantee the presence of the other. In general when performing reversibility testing the referrer is looking to answer one of the following questions:

1. Is there evidence of reversible airflow limitation?
2. Can the subjects' lung function be improved by the addition of a bronchodilator?

3.1 Methods

The ERS/ATS consensus guidelines (Pellegrino 2005) suggest that prior to giving a bronchodilator, baseline spirometric measurements are taken including FEV₁, FVC and PEF_R. After baseline measurement, 400mcg salbutamol or 160mcg ipatropium is given via a spacer in four divided doses at 30 second intervals. Spirometry is then repeated after 10-15 minutes if using a short acting beta agonist or 30 minutes if using a short acting anticholinergic drug.

When testing is being performed to assess for the presence of a possible therapeutic benefit, then it is suggested that the subjects' usual drug, dose and mode of delivery is used. The class of drug, dose and mode of delivery vary widely. The repeat testing should be performed according to the time of the reported drugs onset of activity.

Nebulised bronchodilators are sometimes used in reversibility testing however there are a number of issues surrounding their use. The administered dose can vary widely depending on rate and output, particle size, distribution and concentration, respiratory rate, and inspiratory to expiratory ratio. The administration of bronchodilators without nebuliser or spacer is not recommended as in general the respirable fraction is low and heavily technique dependent (Pellegrino 2005). Spacers are preferred because of the reduced risk of aerosol generation of infected particles.

3.2 What defines a positive response?

Current ATS/ERS guidelines use an increase in FEV₁ and/or FVC (not due to an increased expiratory time) of 12% **and** 200ml as being suggestive of significant bronchodilatation.

The definitions of significant reversibility vary surprisingly widely in standard consensus guidelines. For example the British NICE COPD guidelines suggest that significant reversibility suggestive of asthma is achieved with a change in the FEV₁ of 400ml (NICE COPD guidelines 2010). Many studies have investigated the appropriate cut-off for significant reversibility. The choice of cut-points needs to balance the chance of an event occurring by random variation; the co-efficient of variant of the measurement has its upper

limits approaching 8% or 150ml. Even if bronchodilator testing is positive it may not infer a symptomatic improvement or proof of a diagnosis of asthma as increasingly it is recognised that other pathological processes including COPD can result in significant bronchodilator reversibility.

Our own research suggests that the ATS / ERS definition is sensitive, meaning that significant bronchodilation is unlikely to be missed. It does however come at the cost of reduced specificity. If one were to use mid-flow parameters like the FEF₂₅₋₇₅ or even the volume based standard FEV₂₅₋₇₅, the co-efficient of variation is significantly reduced and this improves the positive predictive value (Swanney 2003). Most of these parameters are measured routinely by the software of modern electronic spirometers, therefore making them easy to measure and apply. However, clinical experience with these new parameters is lacking.

The lack of a bronchodilator response should not be used to withhold the use of this class of agent in clinical practice as they may still produce a clinical response including improved symptoms and performance. If it is clinically important to accurately determine the response then referral for bronchial challenge testing should be considered.

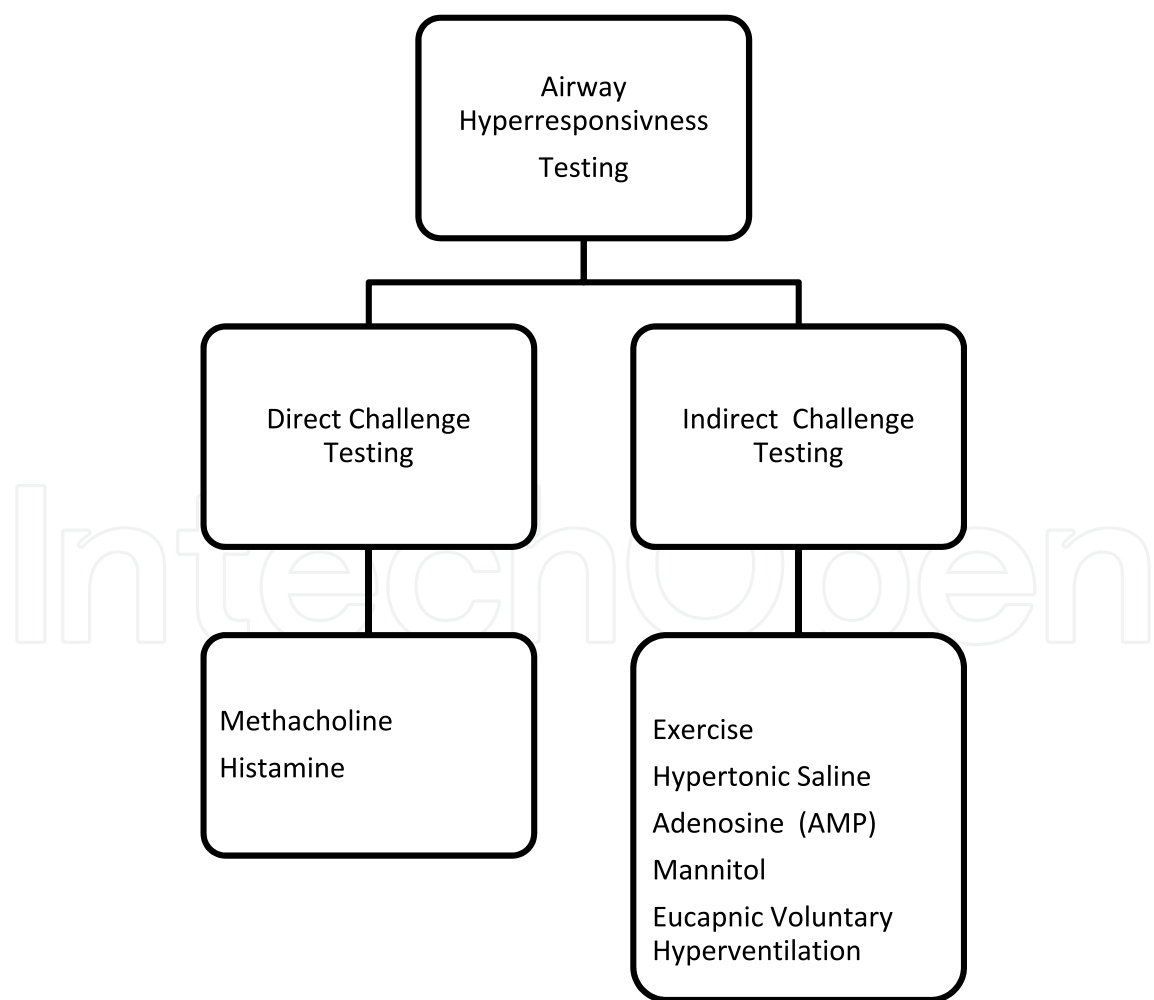


Fig. 1. Diagram of direct and indirect challenge testing

4. Direct bronchial challenge testing

In 1987, Pauwels distinguished bronchial challenges for AHR into direct and indirect testing (Pauwels et al., 1988). Direct stimuli act on the airways smooth muscle causing contraction. Indirect stimuli act via the inflammatory cells within the airway. The two main components of AHR are persistent and variable (O'Byrne et al., 2009). The persistent component consists of the anatomical and structural changes including airway remodelling and smooth muscle hypertrophy. The variable component is thought to be related to external or environmental influences and the subsequent inflammatory process involving mast cells and eosinophils. These processes are not independent. We know that over time, persisting airways inflammation contributes to structural changes within the airway (Grainge et al., 2011).

4.1 Use in the diagnosis of asthma?

In our experience, the main clinical utility of direct challenge testing is to exclude asthma. The direct challenge tests stimulate the airway smooth muscle cell directly and have significant negative predictive power for the diagnosis of asthma; i.e. almost all patients who are asthmatic will have a positive test. The most commonly used direct stimuli are histamine and methacholine. As they act directly on the smooth muscle it is thought that their effects are predominantly via the persistent or structural changes associated with AHR.

In contrast, indirect challenge tests exert their effect through inflammatory cells, epithelial cells and bronchial nerves, which release mediators like leukotrienes or interleukins subsequently resulting in bronchial smooth muscle constriction. Indirect challenges may therefore reflect the degree of bronchial hyper responsiveness and the effect of treatment more accurately (Joos et al., 2003).

4.2 Methacholine challenge testing

Methacholine challenge testing (MCT) is a type of direct bronchial challenge testing. Methacholine is a muscarinic agonist. In our experience, the MCT is a sensitive test with high negative predictive value, better for ruling asthma out rather than ruling it in. The MCT has its maximal diagnostic content in those patients with a pre-test probability of asthma i.e. between 48-70%. (Perpina, 1993). One of the difficulties with the MCT is its poor positive predictive value. It is difficult to determine the false negative response rate as there is a wide variability in the literature of the definition of "current asthma symptoms". This necessitates the need to remain open to idea of repeating the test or escalation to other forms of bronchial challenge testing if the clinical suspicion remains high.

Methacholine powder with Food and Drug Administration (FDA) certification validating it for human use and purity should be used. The two most common methods published by Crapo et al (Crapo et al., 2000) and Cockcroft (Cockcroft, 1977) which involves tidal breathing and inhalation of an aerosol from a nebuliser at an output of 0.13 mL/min. The other method is the dosimeter method (Chai, 1975) which involves inhalation of an aerosol with 5 breaths to TLC with a 5 second breath hold for each. Otherwise the methods are the same with saline as control and doubling of concentrations from 0.03mg/mL to 16mg/mL and 5 minutes between each inhalation. The FEV₁ is measured at 30 and 90 seconds after completed inhalation. The percentage decline in FEV₁ is calculated and the test is stopped

when a drop of 20% in FEV₁ occurs, or the highest concentration is administered. The PC20 can be calculated from a log concentration vs. dose response curve.

The two methods were previously believed to give similar results based on a single study with small numbers using histamine. More recently it has been shown that the tidal breathing method can produce a lower PC20. The reasons for this are thought to be a combination of a greater dose with the tidal breathing method and the potential for the 5 breath hold method to produce bronchodilatation in subjects with mild AHR to methacholine (Allen, 2005).

A number of contraindications to methacholine challenge test exist. According to the ATS guidelines the following are considered to be absolute contraindications; severe airflow obstruction with FEV₁ <50% or 1L (this is controversial and varies within the literature from 60% to 80% predicted), myocardial infarction or stroke within 3 months of testing, uncontrolled hypertension or aortic aneurysm. Relative contraindications include an FEV₁ <60% or <1.5L, the inability to perform adequate spirometry, pregnancy or current breastfeeding and the current use of cholinesterase inhibitor for myasthenia gravis.

Methacholine testing should only be performed by trained staff in an appropriately equipped Bronchial Challenge Laboratory. Serious side-effects of MCT are rare. Transient symptoms such as wheeze, cough, and dyspnoea are reported. Very rarely death after Methacholine exposure has been reported. (Becker, 2001)

There are a number of other factors which can lead to an increase in AHR and therefore false positive MCT. These factors include exposure to environmental antigens, occupational or environmental sensitizers, respiratory tract infection, allergic rhinitis and smoking related lung disease. In general the MCT has a poor positive predictive value.

Conversely, there are other agents which can reduce airways hyper reactivity, therefore potentially giving a false negative result. On the whole this is not as great an issue as that of false positives. The negative predictive value exceeds 90% when the pre-test probability of asthma is 30-70%. If the patient has current symptoms present over the previous 2 weeks and the MCT is negative, one can be fairly confident in ruling out asthma as the diagnosis. Agents which can modify the result of the MCT include oral or inhaled bronchodilators such as cromolyn sodium, nedocromil, hydralazine, cetirizine and leukotriene modifiers. In addition some foods can reduce bronchial hyper reactivity including coffee, tea, cola and chocolate. Inhaled or systemic corticosteroids can modify the effect of MCT, however in general it is not necessary to stop them prior to MCT. (Crapo 2000).

The MCT does have a number of other limitations which should be considered when interpreting the result. As it is a direct challenge test, it is predominantly testing the smooth muscle contraction and fixed component related to airways remodelling. This is highly likely to relate to the chronicity of the problem and may therefore be absent in those with recent onset of their disease or alternatively in those with chronic asthma and fixed airflow obstruction with airways remodelling. AHR can also have significant variability within a subject. This is important to acknowledge, particularly in children where the presence of a negative direct bronchial challenge may be heavily dependent on recent exposures.

There are other factors that need to be taken into consideration when interpreting the MCT; firstly the pre-test probability, the interpretation of the results may be different depending

on whether you are screening an asymptomatic population or testing on the basis of symptoms. Other important issues include the presence or absence of any post-test symptoms and the degree of recovery in symptoms and lung function after bronchodilator is given.

The cut-points for a positive test have been chosen to produce the highest sensitivity. Initially the cut point was set at 8mg/mL (Cockcroft et al., 1985 & Cockcroft, 1977). This produces a very high sensitivity, however the specificity was lower with a large number of positives in patients with rhinitis and up to 5% of asymptomatic individuals. This has now been modified to include the 4-16mg/mL as a borderline positive result. At a level of 16mg/mL up to 20% of asymptomatic people from a random population will have a positive test (Cockcroft, 1992). The best PC20 cut point to give highest positive and negative predictive values based on ROC curve analysis is 8-16mg/mL.

The ATS guidelines suggest that in the presence of no baseline airways obstruction a PC20 greater than 16mg/mL should be considered normal, values between 4-16 indicate a borderline response and should be interpreted in the light of the clinical history and pre-test probability as above, between 1-4mg/mL indicates mild AHR and PC20 of less than 1mg/mL demonstrates moderate to severe AHR.

For example, if the PC20 is less than 1mg/mL and the pre-test probability is high then you can be relatively confident of a diagnosis of asthma. However if there is a low pre test probability and PC20 is between 1-16mg/mL then the interpretation is less clear. Options would include poor perception of symptoms, other causes of AHR, a subject who has never previously been exposed to triggers, or a number of individuals with subclinical disease who may go on to develop asthma in the future.

It is difficult to interpret a positive MCT when the baseline spirometry is abnormal or demonstrates significant airflow obstruction and in the presence of a positive bronchodilator challenge. In these situations MCT may be inappropriate and unnecessary.

Many patients with COPD and fixed airflow obstruction will have a positive MCT but no asthma symptoms and no bronchodilator response. These two diseases are best differentiated on the basis of the clinical history including patient age, smoking history, allergies and triggers.

4.3 Histamine challenge

In the 1940's it was first observed that histamine had the potential to induce bronchoconstriction; it has been used in laboratories since the 1960s. It was the use of histamine by Tiffeneau in 1947, who introduced the concept of incrementally increasing the provoking dose in order to induce a 20% reduction in the FEV₁. As discussed, one of the main limitations of direct tests is that a positive response is not necessarily specific for identifying asthma and can occur in healthy people with no symptoms, smokers and in the presence of a number of other lung diseases. A recent article in the NEJM suggests that we need to keep an open mind regarding the role of airways remodelling rather than airways inflammation as a cause of asthma symptoms (Grainge 2011). The authors used the direct challenge agent, Methacholine, to induce bronchoconstriction because it doesn't cause airway inflammation or eosinophilia. They even went to the lengths of taking bronchial

biopsies to show the absence of inflammation but there is still evidence of airway remodelling and increased mucus production. The clinical implications are wide; it raised the possibility of airway remodelling secondary to airway injury after a chronic cough and the importance of addressing bronchial constriction in addition to inflammation. It may ultimately lead to new therapeutic approaches, bearing in mind that anti-inflammatory treatment has not been shown to modify the natural history of lung function changes in prospective studies (Guilbert 2006).

Practically, methacholine and histamine have a very similar action on the airway smooth muscle. By chance they can even be used in equivalent doses to cause an effect on the airway. Histamine acts not only on airway smooth muscle, but also on sensory fibres in the airway. So although it is classified as a direct stimulus it may actually have some of its effects via an indirect pathway. Histamine is associated with more flushing and systemic side effects.

Many laboratories prefer the use of methacholine over histamine for the lack of these systemic reactions, if they wish to perform a direct bronchial challenge test. Others continue to use histamine as they are familiar with its use. Histamine is not licensed as a medical product in all countries, in particular the United States.

5. Indirect challenge testing

5.1 Overview of indirect challenge testing

A number of indirect stimuli are also used to detect airways hyper-responsiveness including exercise challenge, hypertonic saline, adenosine monophosphate (AMP), mannitol, and eucapnic voluntary hyperventilation. Exercise testing was the first standardized indirect bronchial challenge test. Following this, there has been an increase in the use of osmotic agents such as hypertonic saline and mannitol, stemming from the theory that exercise induced bronchoconstriction (EIB) is induced by an increase in airways osmolality.

These agents act indirectly on smooth muscle via the existing inflammatory cells in the airway causing release of inflammatory mediators such as histamine, leukotrienes and prostaglandins. AMP also acts by direct stimulation of mast cells in an IgE independent fashion. They result in smooth muscle contraction and consequently reduction in airway calibre.

Indirect tests are felt to be more physiological and clinically relevant than direct testing as they stimulate both neural and inflammatory pathways. Most asthma stimuli in 'real life' are more likely to be indirect than direct stimuli; the bronchoconstricting effect of endogenous mediators like prostaglandins or leukotrienes display a stronger effect on the smooth muscle than methacholine or histamine. The presence of a positive indirect test infers the presence of inflammation, and an airway which is responsive to inflammatory mediators. AHR to indirect tests tends to improve or resolve with the use of inhaled corticosteroids (ICS). This implies that an improvement in airways inflammation leads to subsequent benefits in the variable component of AHR. Although a positive indirect challenge test infers the presence of airways inflammation and a positive response to ICS, this is not always due to eosinophilic inflammation as mast cells are often also important in the pathogenesis. Many indirect tests are dose limited, meaning the dose cannot be

increased any further due to the inherent limits of the test such as the solubility of AMP or the physiological limits of an individual for exercise.

Other uses of indirect stimuli are in those individuals who present with diagnostic uncertainty and have ongoing symptoms whilst taking ICS. If the indirect test is positive it confirms the presence of ongoing active inflammation with asthma. In contrast a negative test may indicate that either their asthma is not currently active at the time, or an alternative diagnosis should be considered.

5.1.1 Guide to therapy?

We know that AHR in response to indirect testing decreases and can resolve after the use of inhaled corticosteroids (ICS), in contrast to direct testing. EIB also improves after use of ICS (Koh 2007). The degree of AHR to indirect stimuli correlates with the degree of airways inflammation. For example, the numbers of eosinophils and mast cells present in the airway. These markers of airways inflammation are in turn known to reduce in number with the use of ICS. Therefore indirect bronchial challenge testing can be used as a meaningful measure to assess control of airways inflammation and could potentially be used as a tool in clinical decision making regarding ICS dose. Tests including fraction of exhaled nitric oxide (fENO) and sputum eosinophils have been used as measures of ongoing airways inflammation in eosinophilic asthma. Indirect tests of AHR have the advantage that they can be used in all phenotypes of asthma as AHR to indirect stimuli has been shown to be present in non-eosinophilic asthma when fENO may be normal. This observation suggests the involvement of mast cells amongst others in non-eosinophilic asthma.

5.2 Exercise challenge testing

Exercise challenge testing is one of the oldest forms of challenge testing, with the intention of reproducing the physiological response of the airways during exercise. Exercise causes airway narrowing in the majority of patients with asthma. It is generally believed that exercise related hyperventilation causes a drying of airway mucosa, thereby creating a hypertonic environment which in turn leads to airways bronchoconstriction (Crapo 1999). Clinically this is of particular relevance to people who have to perform demanding or even life saving work in adverse conditions like police persons, military personal, CUBA divers or fire fighters. This is also of concern in athletes, and tends to be aggravated in people exercising in cold environments, particularly cross country skiing or ice-skating.

5.2.1 Indications

Exercise testing is particularly useful in patients with a history of exercise induced symptoms. In our experience exercise testing is more useful in people who perform recreational exercise rather than high performance athletes. These tests are intuitive for the patient, and don't need expensive equipment or administration of medication.

5.2.2 Methods

Whilst several protocols exist, the most widely accepted protocol is based on the Guidelines for Methacholine and Exercise Challenge Testing, produced by the ATS in 1999. The guiding

principle is to create a degree of hyperventilation by pushing the participants quickly to perform high cardiac output exercise. This is classically done on a treadmill or exercise bike with the aim of achieving 80 – 90% of the maximal heart rate in 4 – 6 minutes (Crapo 2000).

The heart rate is normally monitored through an ECG or pulse oximetry and the test is stopped when the patient has achieved 80 – 90% of the maximal cardiac output. However although the end of test criteria is dependent on heart rate, the respiratory rate is also very important. Some protocols suggest measuring the respiratory rate aiming for 40 – 50% of the maximal calculated respiratory rate. It is equally feasible to allow the athlete to perform his or her usual exercise, like swimming, canoeing or track running. Since the aim of the asthma exercise testing is to create hyperventilation, protocols designed for cardiac testing, like the Bruce protocol, are not meaningful in this setting.

The principle outcome variable of exercise testing is the FEV₁. Baseline spirometry should be performed prior to exercise, not during testing and then at 5, 10, 15, 20 and 30 minutes post exercise. This is important as a significant percentage of patients have a late reaction to exercise with a significant fall in their FEV₁. The criteria for a positive response has been extensively discussed. While most laboratories have now adopted greater than 10 % from baseline to be abnormal, a fall of 15% appears to be more diagnostic of exercise induced bronchospasm (Crapo 2000).

The contraindications to exercise testing are similar to those for other forms of challenge testing, in particular a low baseline FEV₁ of less than 60% and less than 1.5L. In addition patients with unstable cardiac ischemia or malignant arrhythmias should not be tested. Patients with orthopaedic limitation are not likely to achieve exercise ventilation high enough to elicit airway narrowing. Bronchodilator medication should be withheld up to 48 hours prior to testing.

High performance athletes often find it difficult to reach a high degree of cardiac output and hyperventilation under laboratory conditions, particularly when an exercise bike is used. In our experience with elite athletes, although the clinical utility of this test is meaningful when the test is positive, the sensitivity is not high. False negative exercise tests have been reported in patients who are in a stable phase, patients who are on treatment and also athletes who clearly do have airway related problems at high performance but don't reach a state of hyperventilation under laboratory conditions.

5.3 Hypertonic saline testing

Hypertonic saline testing (HTS) was developed to establish whether EIB was caused by an increase in osmolarity of the airway surface liquid when humidifying large volumes of dry air during a period of exercise.

5.3.1 Methods

A high-output ultrasonic nebuliser of hypertonic saline is delivered for progressively longer intervals from 0.5 up to 8 minutes. The ultrasonic nebuliser integrates analog devices to control ultrasonic nebulisation. An oscillator develops electrical power, which is transmitted to a transducer in the nebuliser chamber. When energised by the high frequency electrical signals (approximately 1.63 MHZ), the transducer changes its thickness, oscillating at the

frequency of the applied voltage. This results in an energy transfer between the transducer and the liquid in the chamber, causing the liquid to be nebulised into minute droplets.

The patient is asked to inhale the fine hypertonic saline mist through a mouth piece (a towel is provided) for 30 seconds. You must ensure the output setting and airflow of the nebuliser is set to maximum. Nebulisation is stopped and two spirometry manoeuvres are performed. If no significant fall in the FEV₁ has been detected further hypertonic saline is nebulised. The exposure time doubles at each level: 30secs, 1min, 2mins, 4mins, 8mins.

The test is positive when the patient demonstrates a 15% reduction in FEV₁. The test should be stopped when the patient has had a total exposure time of 15.5 minutes and >20 g saline has been delivered.

The major indications for using hypertonic aerosols are to identify bronchial hyper-responsiveness consistent with active asthma or exercise-induced asthma and to evaluate bronchial responsiveness that will respond to treatment with anti-inflammatory drugs. In a study by Riedler (1994), children with a history of current wheeze were seven times more likely to have a positive response to hypertonic saline than asymptomatic children. In an occupational study in people responding positively to the question "have you ever had an attack of asthma" the mean percentage fall in FEV₁ was 17.6% compared with 5.8% for those who responded negatively. From the evidence to date, it would appear that bronchial responsiveness to a hypertonic aerosol is consistent with an asthma diagnosis.

A challenge with a hypertonic aerosol can be used in the assessment of a patient with a past history of asthma that wishes to join the armed forces. The hypertonic saline test has become the test of choice in some states in Australia. A positive test confirms the suspicion of asthma. If the test becomes negative with appropriate anti-inflammatory treatment it also confirms that the airways disease can be controlled and applicants are not discriminated against.

An interesting variant highlighted by the ERS task force report is that the hypertonic saline challenge may play a particular role in assessing people with chronic cough. Hypertonic saline may prove the presence of asthma by causing a fall in the FEV₁. It may also provoke excessive cough in the absence of airway narrowing and indicate that the cough is not due to asthma but a different airway mechanism (Joos et al., 2003).

The benefit of HTS when compared to exercise testing is the ability to also collect sputum for analysis. The PD20 to HTS after 6 weeks of ICS reflects the percentage of airways mast cells and sputum eosinophilia. (Gibson, et al., 2000).

Finally, testing with hypertonic saline may be the agent of choice if a bronchial challenge is indicated during pregnancy.

5.4 Adenosine (AMP) challenge testing

Unlike the previous indirect challenges mentioned, the mode of action for the inhaled AMP challenge is not osmotic. When inhaled, AMP quickly dephosphorylates into adenosine causing mast cells to degranulate and release histamine and leukotrienes, which have a potent effect on bronchoconstriction.

AMP is prepared for inhalation by mixing AMP with a phosphate-buffered solution. It is administered by doubling concentration doses within the range of 0.09 to 800 mg/mL. The doubling concentrations of AMP are delivered to the participant via nebulizer for 2 minutes with spirometric measurement every two minutes until a 20% fall in FEV₁ is recorded.

AMP may provide a good demonstration of airway inflammation based on sputum eosinophils. AMP is cheap and may be a good way to monitor inflammation. It can also cause sputum eosinophilia within 1 hour of the challenge. An inflammatory response after the AMP challenge could present a problem and needs to be considered before using the AMP challenge as a diagnostic tool. AMP is not widely licensed around the world. (Mohsenin & Blackburn, 2006)

It has been shown that mannitol produces results similar to those from the AMP challenge in terms of airway hyper-responsiveness and recovery time without airway eosinophilia and may potentially replace adenosine testing in the future.

5.5 Mannitol testing

The Mannitol challenge test was developed in an attempt to imitate the physiological response to exercise by creating a hypertonic airway environment but avoiding the inherent limitations of exercise testing and allowing testing to leave the specialised laboratory to become a point of care test. Mannitol is a natural sugar which is not normally absorbed in the airways and slowly causes an increasingly hypertonic environment. In susceptible subjects, it induces bronchoconstriction. (Anderson et al., 1997)

Mannitol testing has been well researched, has excellent data available and is a commercially available product. Mannitol testing is leaving the research environment and lung function laboratories and entering the clinical arena. Laboratories that work with mannitol have found it easy to use and in general patients report finding it acceptable. Some patients are not able to tolerate testing with mannitol due to significant coughing (Anderson 2010).

5.5.1 Methods

As in other challenge test, mannitol challenge should also not be performed if the FEV₁ is less than 60% of the predicted value. Using the dry powder capsule and the inhaler device which is part of the Bronchial Challenge Test Kit (aridol™, Pharmaxis Ltd, Frechs Forest, Australia) the participant is asked to inhale an escalating dose of Mannitol. The typical regime is an inhalation of 5mg, 10mg, 20mg, 40mg, 80mg, 160mg, 160mg and 160mg of mannitol leading to a total cumulative dose of 635mg. The FEV₁ is measured 60 seconds after inhalation.

A test is positive if the FEV₁ falls more than 15% from baseline or the FEV₁ falls more than 10% between two incremental doses of mannitol. The test is negative when no significant fall, i.e. a fall of less than 15% from baseline, has been observed after 635mg of mannitol has been administered.

The limitations of the mannitol test are related to the availability of the medications, and also the response from the patients. Since mannitol testing is a form of indirect testing by

monitoring a physiological response, it can be negative in patients with well-controlled asthma. This feature can be used clinically, as a mannitol challenge test, similar to an exercise, and hypertonic saline challenge test can be negative in patients whose asthma is very well controlled. If a clinical suspicion of exercise induced asthma persists then performance of the Eucapnic Hyperventilation Test should be considered.



Picture 1. Eucapnic Voluntary Hyperventilation testing

Picture showing the setup for Eucapnic Voluntary Hyperventilation. In the background is a gas cylinder with 5% CO₂ and 21 % O₂ balanced with N₂, a large, (golden), non-diffusing gas bag and a two way non-rebreathing valve. The patient is instructed to actively hyperventilate through the mouthpiece inhaling the balanced gas mixture for six minutes.

5.6 Eucapnic Voluntary Hyperventilation

This test has been developed as a physiological test to assess the airways response to exercise. During episodes of hyperventilation the airways mucosa can dry out, creating a hypertonic environment. In exercise challenge testing this is often limited by the inability to reach an appropriate level of hyperventilation, as exercise is usually cardiac limited, however we are looking for the respiratory stimulus. We have previously discussed the role of hypertonic saline testing and mannitol testing which use different methods to mimic this

response. Normal hyperventilation is limited by the development of hypocapnoea which can cause significant dizziness, neurological symptoms and syncope. Bronchial provocation testing using eucapnic voluntary hyperventilation came into favour when it was realised that exercise is not needed to achieve high respiratory rates. The possible side effects of hyperventilation were counteracted with the addition of 4.9% Carbon dioxide (Phillips, et al., 1985).

5.6.1 Method

The eucapnic voluntary hyperventilation test allows significant hyperventilation at a rate of approximately 30 - 60 per minute. The rate to be achieved can be calculated assessing $30 \times \text{FEV}_1$ or $.85 \times \text{MVV}$, whichever is greater. Using a large, non-diffusing gas bag filled with 5% CO_2 and 21 % O_2 balanced with N_2 , and a two way non-rebreathing valve the patient is instructed to actively hyperventilate through the mouthpiece inhaling the balanced gas mixture. The patient is encouraged to maintain this hyperventilation for six minutes. The FEV_1 is measured immediately after the end of test (two manoeuvres within 150ml), and then at 5, 10, 15 and 20 minutes. The test is positive if the FEV_1 falls more than 10% from the baseline.

Although the test is relatively easy to set up, responses can be very profound with reductions in FEV_1 in excess of 50% after only a minute of hyperventilation. Cardio-respiratory emergencies have been described. Given the potentially strong reaction to the EVH, it is common to only perform an EVH test, if the participant has a negative hypertonic saline or methacholine challenge test.

This test has been shown to be particularly useful if a high clinical suspicion of EIB persists despite negative simple challenge tests like hypertonic saline or methacholine challenge. In the setting where asthma needs to be excluded, for example amongst commercial divers or where asthma persists and patients wish to continue taking asthma medication, for example in elite athletes during competition, the eucapnic voluntary hyperventilation may be a simple, elegant and useful tool. After careful consent has been obtained, the patient is instructed to hyperventilate whilst carbon dioxide is added and removed in order to maintain a eucapnic environment.

The eucapnic voluntary hyperventilation test is usually restricted to tertiary laboratories given the need for balanced gas mixture and resuscitation equipment. One limitation of EVH is that it can be modified by the use of certain agents used in asthma management. Athletes therefore may need to stop their asthma medication prior to performance of a eucapnic hyperventilation test which may interfere with their training schedule. Because EVH has demonstrated high sensitivity it is currently the IOC Medical Commission-recommended challenge to identify EIB among Olympic athletes (Rundell & Slee, 2008).

6. Summary and clinical vignettes

The choice of bronchial challenge test will be determined by a number of factors including the physicians experience, the skill set in the local laboratory and also by emerging evidence. Evidence on the best use of bronchial challenge testing is still emerging,

highlighted by some more recent publications (Grainge 2011). A very important aspect when choosing a challenge test is the patients medical background and the specific clinical question being asked.

In this last section we outline some clinical vignettes which focus on the choice and interpretation of bronchial challenge testing. These are based as much on our clinical experience as on evidence and certainly remain open for interpretation. If these clinical vignettes inspire discussion and debate we would be delighted and we will endeavour to engage in correspondence. We also accept that our approach may change as new evidence comes to light.

Chest tightness in a runner

A 24 year-old female presents to respiratory outpatients with 9 months of paroxysmal exertional dyspnoea and chest tightness. She is a competitive marathon runner and her symptoms are only present after running over 10km. She has been given a clinical diagnosis of asthma and prescribed inhaled corticosteroids and sodium chromoglycate with little effect. How would you further investigate her?

The assessment of exercise induced asthma in elite athletes can pose some difficulties and it is known that symptoms often correlate poorly with the results of challenge testing. The use of clinical exercise testing is of high specificity but only moderate sensitivity due to the frequent inability of available testing protocols to achieve adequate workload to induce symptoms. The current test of choice by the international Olympic committee's medical commission (IOC-MC) is eucapnic voluntary hyperventilation (EVH) (Fitch et al 2008). The advantage of EVH is the increased ability to achieve minute ventilation of a magnitude equivalent or in excess of that obtained at extreme levels of exercise. Other options in centres where EVH may not be available would include the use of a "field exercise challenge" or an indirect challenge tests such as hypertonic saline or mannitol. In the event of these tests being negative with ongoing symptoms, supervised withdrawal of her current inhaled medications could be considered prior to repeating the testing.

Shortness of breath after treated sleep apnoea

A 45 year old man is referred from the sleep unit. After successful treatment for sleep apnoea he increased his activity levels and noticed wheezing and shortness of breath on exercise. His current body mass index is 45; he is planning on losing weight and wonders if he can improve his exercise tolerance with asthma treatment.

Shortness of breath in an obese person is a common problem. The additional load on the upper airway, which already has the highest resistance, can cause airway narrowing and exertional wheeze. However fat tissue itself also releases pro-inflammatory cytokines which can cause airways inflammation in susceptible subjects. Spirometry can be helpful as it may show a restrictive pattern. In that case measurement of the total lung capacity is frequently reduced, with a marginally reduced DLCO but well maintained and often high kCO. If spirometry shows an obstructive pattern the test of choice here would be a direct test, like methacholine challenge test. If no other clinical features are suggestive of asthma besides wheeze on exercise, a negative methacholine test would exclude asthma and the patient could be reassured to continue exercising and attempting to lose weight, which will ultimately improve his respiratory function.

Chronic cough in a never smoker

A 55 year-old female who has never smoked, presents with a 3 year history of chronic cough, worse at night. There are no symptoms of breathlessness, wheeze, gastro-oesophageal reflux or nasal drip. She is worried about the possibility of underlying asthma.

In the first instance baseline spirometry with reversibility testing may be useful if positive due its high specificity. If the reversibility testing was negative, given the intermediate pre-test probability of asthma a direct challenge test could be considered. If a methacholine challenge test was negative this could be helpful in ruling out asthma as the cause of her cough. Many excellent guidelines are available to help the physician to investigate chronic cough. The evidence based Australian cough guidelines suggest that the most remediable causes which respond well to specific treatment include protracted bacterial bronchitis, angiotensin-converting enzyme inhibitor use, asthma, GORD, obstructive sleep apnoea and eosinophilic bronchitis (Gibson 2010).

Asthma in a police recruit

A 21 year old man comes to see you after applying for the police force. In the screening questionnaire he answered that he'd had mild asthma since early childhood. He has always taken a small dose of inhaled corticosteroids and his asthma has never caused him to miss any school, wake him at night, or have any unscheduled visits to medical facilities. He has been successful in competitive sports.

This is a frequent question in a respiratory laboratory and the choice of test may be influenced by the regulatory authorities. From a patient advocate point of view a direct challenge test with methacholine for example would only confirm that he indeed has asthma. Several medical examiners within the armed forces request indirect testing either with mannitol or hypertonic saline. If he did have asthma and it was poorly controlled, he would demonstrate a fall in his FEV1 indicating a positive test. However even if he did have underlying asthma and it was well controlled, no fall in the FEV1 would be shown. This is seen by medical examiners as reassuring that his asthma would be well controlled (or absent) and he will not be discriminated against during the selection process.

7. Conflict of interest

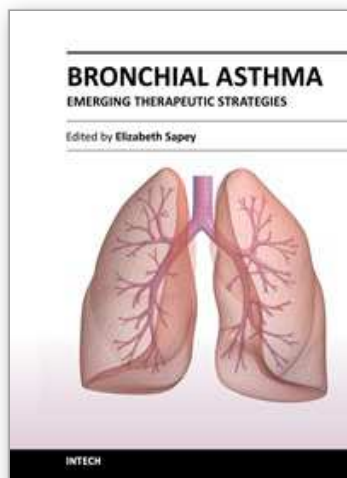
The authors have no conflict of interest to declare.

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Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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