REVIEW

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Nonspecific Bronchoprovocation Test

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Bronchial asthma is a disease characterized by the condition of airway hyper-responsiveness, which serves to produce narrowing of the airway secondary to airway inflammation and/or various spasm-inducing stimulus. Nonspecific bronchoprovocation testing is an important method implemented for the purpose of diagnosing asthma; this test measures the actual degree of airway hyper-responsiveness and utilizes direct and indirect bronchoprovocation testing. Direct bronchoprovocation testing using methacholine or histamine may have superior sensitivity as these substances directly stimulate the airway smooth muscle cells. On the other hand, this method also engenders the specific disadvantage of relatively low specificity. Indirect bronchoprovocation testing using mannitol, exercise, hypertonic saline, adenosine and hyperventilation serves to produce reactions in the airway smooth muscle cells by liberating mediators with stimulation of airway inflammatory cells. Therefore, this method has the advantage of high specificity and also demonstrates relatively low sensitivity. Direct and indirect testing both call for very precise descriptions of very specific measurement conditions. In addition, it has become evident that challenge testing utilizing each of the various bronchoconstrictor stimuli requires distinct and specific protocols. It is therefore important that the clinician understand the mechanism by which the most commonly used bronchoprovocation testing works. It is important that the clinician understand the mechanism of action in the testing, whether direct stimuli (methacholine) or indirect stimuli (mannitol, exercise) is implemented, when the testing is performed and the results interpreted.

Keywords: Airway Hyper-responsiveness; Bronchial Asthma; Bronchial Provocation Tests

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Introduction

Nonspecific bronchoprovocation test is an important test for diagnosing asthma by measuring airway hyperresponsiveness[1-3], consists of direct bronchoprovocation test with high sensitivity and low specificity, and indirect bronchoprovocation test with low sensitivity and high specificity, respectively[1].

1. Asthma and bronchoprovocation test

Bronchial asthma is a disease characterized by airway hyperresponsiveness that airway narrows by airway inflammation and various inducing stimulus[1,4]. Since the airway hyperresponsiveness is caused by inflammation of airway, the degree is proportional to severity of asthma, and reduced by the treatment[1,4-6]. Therefore, measuring the airway hyper-

responsiveness is important in diagnosing the asthma, assessing the severity, and determining the response to treatment. Methods for measuring the airway hyperresponsiveness can be largely divided into the method for observing an improvement of airflow limitation by bronchodilator, and the bronchoprovocation test in which airflow limitation is induced by pharmacologic or non-pharmacologic stimuli[7-9].

2. Indications and contraindications of bronchoprovocation test

Indications and contraindications of the bronchoprovocation test are represented (Table 1)[1,2].

3. Types of nonspecific bronchoprovocation test

Nonspecific bronchoprovocation test is performed using a number of inducing stimuli, and there are advantages and disadvantages. Direct bronchoprovocation test using methacholine or histamine is very sensitive since it directly stimulates airway smooth muscle cells, but it also has a disadvantage of low specificity. However, because the indirect bronchoprovocation test using mannitol, exercise, hypertonic saline, adenosine, and hyperventilation cause reactions in airway smooth muscle cells by liberating mediators with stimulation of airway inflammatory cells other than the airway smooth muscle cells, airway epithelial cells and nerves; although it shows low sensitivity but has an advantage of high specificity[7-10]. The direct and indirect stimuli are represented (Table 2)[7,9,11].

Table 1. Indications and contraindications of bronchoprovocation test

Indications
Diagnosis of asthma (airway hyperresponsiveness)
Airway hyperresponsiveness severity assessment
Determining relative risk of asthma
Response assessment of asthma treatment
Absolute contraindications
Severe airflow limitation (FEV_1 <50% of predicted normal value or <1.0 L)
Myocardial infarction or ischemic stroke during the past 3 months
Diagnosed aneurysm
Relative contraindications
Moderate airflow limitation (FEV_1 <60% of predicted normal value)
Acute exacerbation of asthma
Recent upper respiratory tract infection within 2 weeks
Uncontrolled hypertension
Pregnancy or breast-feeding
Epilepsy requiring medications
If spirometry measurement cannot be performed in acceptable level

FEV_1: forced expiratory volume at 1 second.

1) Direct bronchoprovocation test

Direct bronchoprovocation test is particularly useful to rule out the diagnosis of asthma due to high sensitivity. In contrast, because of the disadvantage of low specificity, it is hard to evaluate the clinical significance even if the test result is positive. Methacholine, as a muscarinic agonist, has a high diagnostic value to the patient with high probability of asthma on pre-test[7,8,10].

2) Indirect bronchoprovocation test

Indirect bronchoprovocation test is suitable to assess the response to treatment, because it has high specificity and low sensitivity. Asthma patient can be negative in well-controlled state, so that it is unsuitable to rule out asthma[9,10].

Methacholine Provocation Test

1. Introduction

Methacholine provocation test is one method for measuring the airway hyperresponsiveness, and airway hyperresponsiveness is one of the features that can help in the diagnosis of asthma. Even though it can vary depending on the time, typically increases in exacerbation but deceases during the treatment with anti-inflammatory drugs[2,12].

Methacholine provocation test, as traditional methods that is frequently considered on high likelihood of asthma, is more useful to rule out the diagnosis of asthma than to diagnose the asthma. This is because the negative predictive power is higher than the positive predictive power[2,12].

2. Indications

Methacholine provocation test is a useful tool to assess the occupational asthma. In addition, it can also be used to determine the relative risk of asthma, even though a clinical significance is not yet established clearly, it can used to assess the response to treatment of asthma[2].

In patients with moderate possibility of asthma, results of the methacholine provocation test cannot be predicted accurately, even if by the asthma specialists. Methacholine provocation test has very excellent sensitivity for asthma, but positive predictive power is relatively poor[2].

Most people with asthma symptoms have the bronchial hyperresponsiveness. However, bronchial hyperresponsiveness may be observed in other diseases, such as chronic obstructive pulmonary disease (COPD), congestive heart failure, cys-

tic fibrosis, bronchitis or allergic rhinitis[2].

Because clinical improvement of asthma is associated with improvement in airway hyperresponsiveness, clinical asthma research often used the change of airway hyperresponsiveness as an objective result index. However, the use of the methacholine provocation test in the clinical evaluation of asthmatic patients will have to wait for additional research on the usefulness of the test[2].

3. Contraindications

Contraindications of the methacholine provocation test is the same as the contraindications of general bronchoprovocation tests mentioned in the "Introduction," and cases of current using of cholinesterase inhibitors (in case of myasthenia gravis) specifically are included in the contraindications. In other words, all the situations that may decrease a quality of test or increase risk and discomfort of patients are included; therefore, these points should be identified through interviews or questionnaires before the test. If the contraindication is confirmed, it is necessary to consult with a medical doctor or a laboratory director before conducting the test[2,3].

Rapid reduction in forced expiratory volume at 1 second (FEV_1) can occur sometimes during the methacholine provocation test, this risk occurs frequently in people who have low baseline lung function. But because even worse lung function has the low risk of serious side effects, low lung function is a relative contraindication of the methacholine provocation test. There is controversy about the level of lung function that is contraindications of the methacholine provocation test. Typically, the basal FEV_1 <1.5 L or predicted normal value <60% in adults are used as a relative contraindication, The National Asthma Expert Panel Report 2nd edition has recommended FEV_1 <65% as a relative contraindication[2,3].

1) Airway obstruction

Because airway responsiveness shows a strong correlation with the degree of basal airway obstruction in COPD, positive methacholine provocation test can be difficult to interpret. If there are the clinical aspects consistent with asthma, airway obstruction at baseline spirometry test and significant bronchodilator response (FEV_1 or forced vital capacity >12% and increase >0.2 L), these can be confirmed as asthma and the methacholine provocation test is not necessary[2,3].

Table 2. Overview of direct and indirect stimuli

	Stimulus
Direct stimuli	Cholinergic agonist (methacholine, etc.)
	Histamine
	Prostaglandin D_2
	Leukotriene $C_4/D_4/E_4$
Indirect stimuli	Physical stimuli
	Exercise
	Anisotonic spray (hypertonic or hypotonic distilled water, mannitol)
	Hyperventilation under dry atmosphere
	Drug stimuli
	Adenosine
	Tachykinins
	Bradykinin
	Metabisulphite/SO_2
	Propranolol
	Endotoxin (LPS)
	Platelet activating factor
	Ozone
	Specific drugs
	Aspirin, NSAIDs
	Allergen

SO_2: sulphur dioxide; LPS: lipopolysaccharides; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table 3. Factors that decrease bronchial responsiveness

Factor	Minimum time intervals from the last dose to test
Drugs	
Short-acting inhaled β2 agonists (isoproterenol, metaproterenol, albuterol, terbutaline)	8 hr
Short-acting inhaled anticholinergics (ipratropium)	24 hr
Long-acting inhaled bronchodilators (salmeterol, formoterol, tiotropium)	48 hr (more than 1 wk in case of tiotropium)
Oral bronchodilators	
Medium-acting theophylline	24 hr
Long-acting theophylline	48 hr
Oral β2 agonists	12 hr
Long-acting oral β2 agonists	24 hr
Cromolyn sodium	8 hr
Nedocromil	48 hr
Hydroxyzine, cetirizine	3 days
Leukotriene modifiers	24 hr
Corticosteroids (oral or inhaled)	Duration of action is unknown. It should be suspended for weeks to eliminate anti-inflammatory effect.
Foods	
Coffee, tea, cola, chocolate	On the day of test

2) The quality of spirometry tests

The methacholine provocation test of acceptable level depends on the patient's ability to perform an appropriate spirometry test. Patients unable to perform the appropriate spirometry test on baseline step should reschedule a test or consider other diagnostic methods[2,3].

3) Cardiovascular disease

History of cardiovascular disease may also be a contraindication. Additional cardiovascular stress by the induced airway constriction may exacerbate the cardiovascular problem in the patients with history of uncontrolled hypertension or recent heart attack and stroke. If the airway constriction is induced, it becomes the cause of ventilation-perfusion imbalance that can result in arterial hypoxia and changes in blood pressure, cardiac output and heart rate.

4) Pregnancy and breast-feeding

Methacholine is a pregnancy category C drug. It is not yet known whether methacholine is excreted in breast milk[2,3].

Drugs or conditions represented in Table 3 should be avoided before methacholine provocation test[2]. Because these factors decrease airway reactivity, it should be stopped by each time interval before the test. Table 4 is represented the factors that may increase the airway reactivity[2].

Table 4. Factors that increase bronchial responsiveness

Factor	Duration of action
Exposure to environmental antigens	1–3 wk
Exposed to occupational causes	Several months
Respiratory infections	3–6 wk
Air pollution	1 wk
Smoking	Not sure
Chemical stimuli	Several days to several months

4. Interpretations

FEV_1 most commonly used as bronchoprovocation test results, is easy to test and shows excellent reproducibility. When the dose-response curve is obtained with inhaled drug concentration and FEV_1, the inhaled drug concentration is represented on X-axis as log scales and the reduction ratio of FEV_1 is represented on Y-axis as numbers, respectively. Methacholine concentration at the point that FEV_1 is decreased to 20% of baseline in the dose-response curve is called PC_{20} (provocation concentration causing a 20% fall in FEV_1), and it is regarded as an index of the bronchial hyperresponsiveness[2].

If PC_{20} is less than 1.0 mg/mL, specificity and positive predictive value almost close to 100%, so that the diagnosis of asthma can be confirmed. If PC_{20} is less than 8–16 mg/mL, it is considered to have airway hyperresponsiveness. If PC_{20} is not

less than 10 mg/mL, it is very likely that there is no apparent asthma[2,13,14].

Since the effect is shown by the accumulation of the dose from the start of inhalation in the methacholine provocation test, it is also represented by using a accumulated dose instead of the density, and the accumulated dose of methacholine to the point that the bronchoconstriction is induced may appear as PD_{20} (provocation dose causing a 20% decline in FEV_1)[2,15].

Mannitol Provocation Test

Mannitol provocation test is a type of indirect provocation test, which has high specificity and the advantages of being simple and safe, but low sensitivity. If FEV_1 is decreased by 15% or more compared to baseline with 635 mg or less of mannitol, it is determined that airway hyperresponsiveness to the mannitol is shown[3,16,17].

1. Introduction

Mannitol provocation test, which is a type of indirect bronchoprovocation tests, is to access the reaction acting on airway smooth muscles cells by liberating mediators with stimulation of inflammatory cells[9,16,17].

It has higher specificity than the methacholine provocation test on the diagnosis of asthma, and it is closely related to eosinophilia or increased exhaled nitric oxide (eNO) levels, which reflect the inflammatory status of airway[7,17,18]. Therefore, if the mannitol provocation test is positive in a patient with symptoms that asthma can be suspected, it means that there is asthma accompanied by progressive airway inflammation, and it may determine that the anti-inflammatory treatment is necessary.

Mannitol provocation test has the advantages of high specificity and being simple and safe, while there are disadvantages of relatively low sensitivity that only about 60% of asthma patients can be found[3,16,19]. Therefore, negative mannitol provocation test cannot rule out the asthma.

Although methacholine, histamine, etc. induce bronchoconstriction by directly stimulating the bronchial smooth muscle receptors, indirect stimuli such as hypertonic saline, exercise, adenosine, mannitol stimulate mast cells etc. to secrete inflammatory mediators, then these mediators cause a contraction of bronchial smooth muscles by acting as strong bronchoconstrictors, which result in a reduction of the inner diameter of bronchus[9,16,17]. Mannitol is not absorbed into the body as sugar alcohols ($C_6H_6(OH)_6$), thus it remains in the airway surface when inhaled into the airway and increases the osmotic pressure. Water in the cells is moved out of the cells by the osmotic pressure difference, which results in cellular contraction[3,16].

2. Interpretations

If FEV_1 is decreased by 15% or more compared to baseline with 635 mg or less of accumulated mannitol dose in the repeated tests, it is determined that airway hyperresponsiveness to the mannitol is positive[3,16,17].

PD_{15} is defined as the mannitol dose (mg) which is inhaled until the time when FEV_1 is reduced by 15% of baseline[3,17,20].

Response dose ratio (RDR) is defined as FEV_1%/mannitol dose (mg) of the time when FEV_1 is decreased by 15% of baseline. If FEV_1 is reduced by 15% compared to the baseline after using mannitol 635 mg, it is denoted by PD_{15} 635 mg, RDR 0.024%/mg (15%/635 mg)[16,20].

Because the mannitol provocation test means asthma caused by eosinophilic airway inflammation and shows moderate sensitivity (60%), well-controlled asthma, mild asthma, non-eosinophilic asthma can show negative results[16,19]. In addition, if the test time exceeds 35 minutes or the excessive movement is performed before the test, test result may be false negative and it is known that smoking and chronic cough increase the response to the mannitol[9,16]. If the mannitol provocation test is performed in the normal group, FEV_1 reduction usually does not exceed 10%[9,16,21].

Although about 83% of examinee experiences cough during the test, severe cough enough to stop the test only occurs in 1.3%[3,16,20,22]. The other side effects may appear such as headache (6.1%), sore throat (2.6%)[3,16,20].

Exercise Provocation Test

Exercise provocation test is an indirect provocation test to determine the occurrence of nonspecific airway hyperresponsiveness by airway cooling and drying[1,2]. Contraindications and prior stopped drugs of the exercise provocation test are the same as the bronchoprovocation test[1,2]. Exercise provocation test is performed using a treadmill or bicycle ergometer, in accordance with the appropriate protocol in safe facilities and personnel conditions. If decrease by 15% and more of baseline FEV_1 is induced, it is determined as positive[1-3].

1. Introduction

Exercise induces airway constriction in the majority of patients with asthma, exercise-induced airway contractions is called as exercise-induced asthma or exercise-induced bronchoconstriction (EIB)[1-3].

There are ventilation by exercise and moisture content and temperature of the inhaled air as the main factors that determine the severity of the EIB, and if the large amount of air loses the moisture in a short time due to the exercise, the airway contraction occurs by osmotic effects caused by temperature changes (cooling and re-heating) and dehydration[1-3,23].

Airway cooling and drying are considered to stimulate the liberating of inflammatory mediators such as histamine and leukotriene, eventually the exercise itself is also an important provocation test to evaluate the effect of the anti-inflammatory agents and other asthma prescription[1-3,24,25].

2. Indications

It is used as a provocation test for the diagnosis of EIB in the asthma patient with a history of shortness of breath during or after exercise[1,2].

The EIB test is required if working ability is impaired due to suspected asthma symptoms associated with exercise in certain occupational groups (occupations to deal with emergency situations such as armed forces, police, firefighting)[2,26,27].

It is used to determine the effectiveness and optimum dose of drugs that are prescribed to prevent the EIB, and to evaluate acute (such as cromolyn sodium and nedocromil sodium) or chronic (steroid and leukotriene antagonists) anti-inflammatory effects of the treatment[2].

3. Contraindications

Contraindications are the same as the general bronchoprovocation tests mentioned in the "Introduction"[1,2]. In addition, the test should not be performed in cases of the unstable ischemic heart disease or malignant arrhythmia[1-3].

In case of the orthopedic problems, an appropriate degree of exercise to induce airway contraction is likely not to be performed. 12-Lead electrocardiogram recorded during the last year should be checked in patients aged 60 or more[2].

4. Interpretations

FEV_1 is the primary variables for reactive evaluations, and spirometry test to measure these should be proceeded in the sitting position continuously before and after exercise[1-3].

Appropriately measured values should be obtained for each test times at least 2 times or 3 times if possible, and difference between the highest and second highest FEV_1 should be within 0.2 L. The highest value of the valid FEV_1 is selected as a representative value of each test time[2].

Expiratory time should be limited to 2–3 seconds; it is very important to lead very aggressively the patients to breathe in as deeply as possible in all cases[2].

EIB is determined by converting the measured FEV_1 at each time after exercise to % of baseline FEV_1 before exercise, and the case that is reduced to 90% of the baseline FEV_1 is regarded as the general abnormal response[1,2]. The decrease of FEV_1 by 15% and more is considered a more diagnostic value to the EIB, especially the exercise provocation test is performed outdoors[2,28].

Conclusion

Nonspecific bronchoprovocation test is an important test for diagnosing asthma by measuring the airway hyperresponsiveness, and includes direct (methacholine) and indirect (mannitol, exercise) bronchoprovocation test. The tests need descriptions of specific measurement conditions, such as the selection of subjects, the choice of the stimulus, the method of measurement of bronchoconstriction, and technical or medical precautions. In addition, it has become evident that challenge tests with each of the various bronchoconstrictors stimuli require distinct protocols. Therefore, it is important to understand the most commonly used bronchoprovocation tests with direct stimuli and indirect stimuli when we perform the tests and interpret the results.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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