

The Bronchial Provocation Test and Criteria for Positive Reaction

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By bronchial provocation testing (BPT) it is possible to mimic the natural response of the airways to an allergen and to verify whether the tested allergen is a causative factor in eliciting asthma in the patient (1). This test has been used extensively in the diagnostics of asthma over the last 25 years. In recent years, however, the close correlation found between radioallergosorbent test, skin test and provocation test has led to less use of bronchial provocation in routine clinical work. On the other hand, as BPT allows observation of the pathophysiological events in allergic asthma it has become an important tool for such studies.

Bronchial provocation testing is the only way it is possible to establish bronchial reactivity for an allergen or a mediator, and to evaluate the degree of sensitivity for allergen or mediator and thus find a threshold dose. This makes it possible to use BPT for controlling the effect of therapy. By careful observation and analysis of the pulmonary function during and after a bronchial provocation test different patterns of reaction can be discerned, helping in a more precise diagnosis of subgroups of asthma.

If BPT is going to be used for these purposes and not only for a qualitative diagnosis of bronchial allergy, it is of paramount importance to standardize the procedure. A standardization of the BPT has to take into account many factors: the patient, the allergen or mediator, the methods used and the evaluation of reaction.

PATIENT (Table 1)

A prerequisite for reproducibility of the test is that the patient is *free from symptoms* without medication. If the patient is symptomatic the relevance of a positive reaction has to be doubted and cannot be quantified or compared with a reaction under different circumstances. A patient is expected to have a higher reactivity and thus a lower threshold during a symptomatic state than during an asymptomatic state. Furthermore, as the resistance is inversely proportional to the fourth power of the diameter of a tube, a decrease of the bronchial diameter ensued by the BPT gives a larger effect if superimposed upon an already present obstruction than if imposed upon normal patient airways.

The asymptomatic state of the patient can be verified by FEV_1 being *more than 80%* of the predicted normal or of the best FEV_1 previously measured in the same patient.

If the patient is in need of *medication* no test can be

performed. The patient must be able to keep a normal patency of the airways without drugs. The minimum requirements for withdrawal time of drugs usually recommended are shown in Table 1 (2).

Table 1
Standardization of patient

a) asymptomatic	
b) $FEV_1 > 80\%$ of normal	
c) no medication	} for last
beta-2-stimulants	
aminophylline	
cromoglycate	
antihistaminics	
anticholinergics	
d) if repeated provocations	8 h
same time of day and season	12 h
	24 h
	48 h
	8 h
	48 h

Whether steroids could be used during BPT has been debated. One strong argument against steroids is that, if the patient really requires steroids, he is probably in such a labile state that he should not be a candidate for bronchial provocation testing aiming at quantifying the degree of reactivity.

Another condition for standardization regarding the patient is the *time of the day* in which provocation is performed. It has been shown that the bronchial reactivity has a 24-hour rhythm, with larger reactivity late in the evening than in the morning and in the afternoon (7). This stresses the importance of performing BPT always at the same time of the day to increase the reproducibility.

The bronchial obstruction elicited by a BPT usually is of short duration, but late asthmatic responses may occur and sometimes the pulmonary function is not fully restored within 24 hours (5). Thus, to ensure a stable state, the interval after a positive BPT should be at least 48 hours. The possibility of a priming or desensitizing effect of repeated BPT also has to be taken into account although from studies performed so far such an effect has not been noted (4, 9, 11)!

ALLERGEN

Standardization as to allergen follows the same requirements that have already been discussed for allergen extracts in general. For BPT aqueous extracts must be

used, standardized as to content of allergenic component, biologically tested, sterile, non toxic and not containing irritants that can give false positive reactions.

METHOD (Table 2)

The effect of the delivery system must be known as to flow and particle size of the nebulisate. Ideally the particle size should be between 1 and 5 μm . Smaller particles are not retained in the lungs and larger particles are deposited in the mouth and pharynx.

Table 2
Standardization of method

- | |
|----------------------------------|
| a) delivery system — nebulizer |
| b) particle size |
| c) control |
| d) starting dose |
| e) dose increment |
| f) dose interval |
| g) regulated breathing technique |

For establishing a suitable base-line inhalation of a diluent is used as a negative control.

The *allergen concentration* of the initial dose can be assessed from the skin test reaction. It should always be so low as not to elicit a reaction, to allow a determination of the threshold dose which is a prerequisite for evaluation of the degree of sensitivity for the allergen. In this way, too strong reactions are avoided and the safety of the test is increased.

The *increment* in allergen concentration should be in logarithmic dose steps and not larger than *tenfold* but dilutions in between could be used to make the analysis of sensitivity more discriminative.

A time interval between dose steps not exceeding 30 min can be used to obtain a cumulative effect of a steadily increasing dose. It also allows the whole procedure to be performed in one session. Intervals shorter than 30 min involve a risk of overlooking a reaction of the last dose before the next dose is given. Intervals longer than 30 min are unpractical because they prolong the session, which in itself can affect the reaction of the patient. The dose steps chosen must be kept constant during the whole procedure and during repeated tests.

Two main, different *breathing techniques* during inhalation tests have been used:

- (1) tidal volume breathing of a fixed volume, often 1 ml, of a nebulized solution (4, 6),
- (2) a fixed number of breaths either at tidal volume or from FRC to TLC (2, 9).

The rate and depth at which the patient inhales influence the deposition of the aerosol and the nature of the pulmonary reaction elicited (8). It is essential to

choose the kind of breathing technique relevant for the issue.

EVALUATION OF REACTION (Table 3)

A positive bronchial provocation test usually results in obvious clinical signs and symptoms of bronchial obstruction sufficient for clinical diagnosis.

Table 3
Evaluation of reaction

Objective assessment of degree of bronchial obstruction by

- | | |
|--------------------------------|-------------------------------|
| a) peak expiratory flow | PEF |
| b) forced expiratory volume | FEV ₁ |
| c) max. expiratory flow | MEF |
| d) airway resistance | R _{aw} |
| e) specific airway conductance | S _{GAW} |
| f) flow/volume | MEFV |
| g) dynamic compliance | C _{dyn} |
| h) closing volume | CV |
| i) arterial oxygen tension | P _a O ₂ |

Determination of the degree of reaction, however, requires pulmonary function tests. This is particularly important for comparative purposes, for instance for controlling the effect of therapy. Some pulmonary function tests may also be more sensitive than the clinical evaluation and thus allow lower doses of allergen to be used for establishing bronchial sensitivity (4, 6).

CRITERIA FOR POSITIVE REACTION (Table 4)

For only five of the methods enumerated can we today give limits for what we regard as a positive reaction. Those are the ones most widely used in which there is enough experience to establish borders for a significant reaction.

Among these tests the PEF, FEV₁ and MEF are not more sensitive than the clinical evaluation but they give

Table 4
Criteria for positive reaction

- | | | |
|--|-----------------------------|---------------------------------|
| based on the <i>sensitivity of the method</i>
and of the <i>normal variability</i>
within an individual with the same method | | |
| PEF
FEV ₂
MEF | fall > 20% of initial value | |
| R _{aw} | | increase > 50% of initial value |
| S _{GAW} | | fall > 35% of initial value |

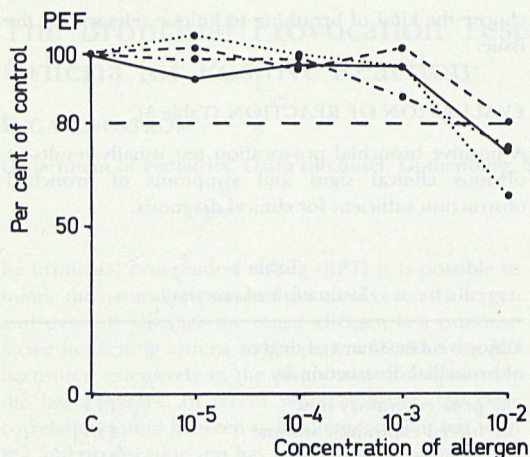


Fig. 1. Dose-response curve.

objective estimation of the degree of bronchial obstruction which can be used in comparative studies.

The airway resistance and its reciprocal the airway conductance are more sensitive methods and can give an indication of a reaction earlier than the clinical evaluation (4, 5, 6, 9, 10).

However, this method requires a pulmonary function laboratory with well trained personnel. Furthermore, the patients have to get used to the measuring equipment before reliable results can be obtained. The normal variability within an individual at different measurements is rather large, which is illustrated by the great increase or fall necessary for a significantly positive reaction.

All these methods measure the resistance of the larger airways and thus the peripheral resistance which might be of particular interest if one wishes to analyse the pattern of reaction in different patients or in the same patient with different inhalation techniques, etc. For such purposes other methods as flow/volume loops, dynamic compliance and closing volume could be used.

When using such sophisticated methods it is necessary to be well acquainted with the method and have a knowledge of its possibilities and limitations.

The reactivity of the patient can thus be assessed using suitable pulmonary function tests and expressed as the dose of allergen that gives a change exceeding a certain pre-set figure for that particular test. This is best illustrated by a dose-response curve (Fig. 1). Such a curve will be more discriminative the more numerous

the points on the curve are. However, the validity of such curves is a function of the precision with which the two axes can be determined, and thus entirely dependent upon a thorough standardization of the whole provocation test procedure.

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