from 2 to 30 hz for the total respiratory system), Rrs_6 (resistance at 6 hz) and $\bar{X}rs$ (mean reactance).

The rank order of sensitivity or the discriminative power of the different physiologic tests to detect the effect of bronchodilation appeared to depend on the expression of the bronchodilator response. When relative percent changes were considered, Raw, Rrs_6 and $\bar{R}rs$ were the most sensitive tests (but not sGaw), and when absolute changes were considered, FVC, sGaw and Raw were the most sensitive ones. Yet the best discriminating power was not reached by a single variable but by a pair of tests i.e. the greatest roots were obtained by FVC with a resistance parameter (Raw, $\bar{R}rs$, Rrs_6 or sGaw) or by 2 resistance parameters (i.e. Raw-and $\bar{R}rs$) or by FVC with MEF_{75}. For a comparison also the results of a histamine challenge in a group of asthmatics with normal baseline value were analysed [2] (table 2, upper panel), which gave similar results of thresholds, relative changes and rank order of sensitivity. The multiple variable analysis, furthermore, showed that the influence of histamine could be described completely by the relative changes of any one of the following variables: FEV_1, sGaw, Rrs_6 or $\bar{R}rs$ (and that there was no advantage in using pairs of tests in this group).

For clinical practical purposes, spirometry and resistance measurements thus appear to be almost interchangable and to have very comparable sensitivities. Yet it should be reminded that they have different thresholds.

Conclusion

Quantitatively, the degree of reversibility depends on the type of physiologic tests that are used and on the way of expression of the response. Yet, when strict criteria for thresholds and sensitivity for a positive response are used the spirometric tests and pulmonary mechanics tests are very comparable. Several recent reviews can be recommended for further reading [5, 6].

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The assessment of reversibility; what drugs?

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In obstructive lung disease, it is common to test the influence of drugs on lung function parameters and to take the response in consideration for diagnostic classification of the disease. A number of pharmacological agents have bronchodilator activity when presented to the bronchial tissue from the luminal side when inhaled and from the blood vessels when given systemically by the oral or *i.v.* route.

Beta-adrenergic agonists

After oral intake of plain tablets, the maximum increase in forced expiratory volume (FEV) is seen after 1.5-2 h and a highly significant correlation has been found between the percentage increase in FEV_1 and serum concentration of terbutaline. After *i.v.*, *i.m.*, or s.c. administration the onset of action is seen within a few minutes and the maximum bronchodilation seen after 30-60 min.

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Systemic treatment with beta-adrenergic agonists is limited by side effects and it seems possible to achieve additional bronchodilation from an inhaled dose. The superior ratio for the inhaled route between bronchodilation and side effects makes this the preferred form for administration. Also for the inhaled route, beta-adrenergic agonists show a dose response relationship. Individual factors seem to determine the dose at which maximum bronchodilation is achieved but little benefit is unusual from single doses of more than 1-2 mg terbutaline/salbutamol or equivalent. When higher doses are given this results in a prolonged action but also in an increased incidence of side effects. The newly developed longer acting beta-2 agonists for inhaled use seems to achieve this prolonged action without a proportional increase in side effects.

Methylxanthines

Methylxanthines are widely used as bronchodilators in the treatment of obstructive lung diseases. The drug does not seem to reveal a reversibility in airways

obstruction not uncovered by a test with inhaled beta-adrenergic agonists, although one study has pointed to individual differences in the dose-response to oral theophylline and beta-2-agonist (terbutaline).

Anticholinergic drugs

In obstructive lung disease, inhaled ipratropium and oxitropium gives a bronchodilation. When tested in patients in "stable" condition the maximum effect is seen from 40 mg ipratropium. In allergic bronchial asthma, the bronchodilation from inhaled anticholinergic drugs seem inferior to the effect from an inhaled beta-agonist but in older, non-atopic patients the bronchodilations from an anticholinergic have been found equal or superior to inhaled beta-agonists.

Oral antihistamines

Antihistamines can improve resting lung function in a dose dependent manner. This effect has not been used systematically as a test for reversible airways obstruction.

Corticosteroids

Oral and inhaled corticosteroids may in some patients with airway obstruction improve dynamic and static lung volumes 3-9 h after dosing and it has been possible to show that this effect is dose dependent. This has been called the acute effect of corticosteroid.

Several days of corticosteroid treatment may be necessary to achieve an improvement in lung function as the effect is slow in onset and also longer lasting than the action of bronchodilators. Most patients respond during the first week of treatment. No correlation seem to exist between the immediate responsiveness to an inhaled beta-2-adrenergic agonist and the response to corticosteroids.

Bronchodilation can be achieved from drugs with different mechanism of action. The underlying disease mechanism may determine the responsiveness to the pharmacological agent applied. Several drugs often have to be tested to determine their role in a patient and as the acute response to a bronchodilator does not exactly predict a therapeutic response in long term treatment the clinical benefit from a treatment should always be determined. The response to single doses of a bronchodilator does not seem to define disease entities but simple shows the ability of the substance to influence airway calibre at that particular moment.

The assessment of reversibility: short-term

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The objectives for short-term assessments are to prove the efficacy of drugs:

- in acute stages, *e.g.* acute severe asthma,
- after short-term application, mainly after a single dose or a few applications and repeated measurements of the parameters of airways obstruction within some hours,
- in an acute model.

For the clinician, most important information comes from the comparison of pharmacodynamic effects of different drugs. For such purposes the differences between baseline values at different days and the minimal improvement, which has to be achieved with a standard drug has to be defined prospectively, *e.g.* $R_t \geq 25\%$, $FEV_1 \geq 15\%$.

In an acute trial the efficacy may be described as follows:

- onset of action,
- maximum efficacy,
- duration of the plateau,
- duration of a clinical relevant effect, *e.g.* $FEV_1 \geq 15\%$.
- $AUEC_{limit}$ which may be defined as $FEV_1 \geq 15\%$.

There are many different questions to be proved in an acute trial:

- single dose studies of different drugs,
- different doses of one drug (dose-finding-study),
- cumulative dose of one drug to find out the maximum efficacy,
- repeated doses of one drug in different time intervals to compare the different formulations, *e.g.* for theophylline preparations.

Looking at the bronchospasmolytic effect of a new compound we obtain information which is clinically relevant: this does not apply to the provocation test model. Nevertheless such tests are often used because this model can nicely be standardized.

It may be applied in different modifications:

- the protective effect of different doses of one drug or of different drugs to a constant stimulus is compared,
- threshold doses are evaluated.

The test may be performed after a single application (when the efficacy is expected to be maximum) or under steady state conditions.

The assessment of drugs is mainly concerned with their protective effect but the challenge may be used to look at the reversibility of bronchoconstriction induced by different stimuli such as allergens, mediators, drugs, exercise, cold air or SO_2.

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