

## How to express the reversibility of bronchial obstruction?

A. Harf\*

Since the original description of the "épreuve de bronchodilatation par aérosols adrénaliniques" [1], testing the reversibility of bronchial obstruction has become one of the most common measurements in the pulmonary function laboratory. It is performed for clinical assessments as well as for fundamental investigations. However there are still many questions and controversies on the technical aspects of the tests, the type of analysis and the clinical relevance of the results.

One of the most common ways of expressing the bronchodilating response is to quantify the change in forced expiratory volume in one second ( $FEV_1$ ) as a percentage of the basal obstruction (prebronchodilator or initial  $FEV_1$ ). In recent years, this mode of analysis has been challenged as reviewed by MESLIER and RACINEUX [2] for the following reasons: 1) this expression implies that the variation is related to the initial value, which has been shown to be false for  $FEV_1$ ; 2) it gives an unjustified advantage to low initial values; and 3) it is affected by the error related to the tendency of any result to regress towards the mean. Most of these criticisms also apply to the index recommended by the Societas Europaea Physiologiae Clinicae Respiratoriae (SEPCR) in 1983 [3] where the change in  $FEV_1$  is expressed as a percentage of the mean between the initial and the final values of  $FEV_1$ . A number of studies [4-7] have supported these criticisms through the analysis of the bronchodilator response of patients with asthma and chronic obstructive pulmonary disease (COPD).

For several years, there has been a tendency to substitute this index of bronchodilation (change in  $FEV_1$  as a percentage of the initial  $FEV_1$ ) with another expression of bronchodilation: the change in  $FEV_1$  as a percentage of the predicted value of  $FEV_1$ . ELIASSON and DEGRAFF [4], in a large review of published data, and MESLIER and co-workers [2, 5] have shown that this index could be used to distinguish between patients with asthma and those with COPD and that it was not significantly correlated to initial  $FEV_1$ . However, one must keep in mind the possibility that, at least in some patient groups, there may be a real negative correlation between response and baseline spirometry.

In this issue of the Journal, DOMPELING *et al.* [8] have reassessed the problem of expressing the bronchodilator response. They have followed a cohort of nearly 200 patients over two years and evaluated the bronchodilator response every six months. The analysis was performed by looking for a relationship between the index of reversibility and the prebronchodilator  $FEV_1$ , firstly at each period (equivalent to a cross-sectional study), but also by examining the responses of each subject along the six evaluations (longitudinal study): once more the improvement of  $FEV_1$  expressed as % of initial value was shown to be highly dependent on the prebronchodilator value, both in the COPD patients and in the asthmatics. However, the disappointing observation was that the improvement of  $FEV_1$ , expressed as % of predicted value, was also dependent on the prebronchodilator value; this was especially marked in the patients with COPD for whom this index was nearly as dependent on the initial  $FEV_1$  as the conventional method (% of initial value). The reasons for this discrepancy are not clear: among the differences with previous studies, one can note that the bronchodilator challenge consisted of the combination of salbutamol and ipratropium bromide, both at a higher dosage than usual for bronchodilator challenges; the assessment of bronchodilation was also performed one hour after the administration of the bronchodilators, a strategy which, for practical reasons, is difficult to recommend in the routine of lung function laboratories. On the other hand, the large number of subjects studied by DOMPELING *et al.* [8] may have been a determinant factor in bringing to light the relationship between the change in  $FEV_1$  expressed as % of predicted value, and the initial  $FEV_1$ .

Of the numerous indices that have been analysed by DOMPELING *et al.* [8], the ratio of the change in  $FEV_1$  to the difference between the predicted value and the initial value was found: 1) to have one of the best reproducibilities; and 2) to be independent of the initial  $FEV_1$ . This finding may explain some of the differences in results between this study and previous ones regarding the index "% of predicted  $FEV_1$ ". Table 1 shows a theoretical computation of different indices of bronchodilation for different initial  $FEV_1$  values; considering a constant value for the proposed index "% of predicted minus initial  $FEV_1$ ", the index "% of predicted  $FEV_1$ " shows little variation, whereas, the index "% of initial  $FEV_1$ " varies considerably.

\*Département de Physiologie and INSERM U296, Hôpital Henri Mondor, 94010 Créteil, France.

Table 1. - Theoretical computation of different indices of bronchodilation for different initial FEV<sub>1</sub> values

	Initial FEV <sub>1</sub> , % pred		
	50	60	70
Change in FEV <sub>1</sub> as			
% pred - initial	30	30	30
% pred	15	12	9
% initial	30	20	13

For a constant value of index "% of predicted minus initial FEV<sub>1</sub>", the index "% of predicted FEV<sub>1</sub>" decreases as the initial FEV<sub>1</sub> increases, however, with much less variation than the index "% of initial FEV<sub>1</sub>". FEV<sub>1</sub>: forced expiratory volume in one second; pred: predicted.

Therefore, the absence of statistical correlation between the change in FEV<sub>1</sub> as % of predicted FEV<sub>1</sub> and the value of the initial FEV<sub>1</sub> may be ascribed to statistical problems (type II or beta error), whereas, the change in FEV<sub>1</sub> as % of initial FEV<sub>1</sub> is so strongly dependent on the initial FEV<sub>1</sub> that it appears clearly even in a small number of subjects. The study of DOMPELING *et al.* [8] demonstrates that this index "% of predicted minus initial FEV<sub>1</sub>" can be used both to evaluate and to follow-up patients in terms of reversibility of obstruction.

It can be predicted that a number of further studies will be performed on the assessment of reversibility of bronchial obstruction: it can also be predicted that no single solution will be found for this difficult problem and that the question to be answered (test for drug trial in asthma [9], follow-up of COPD patients...) will be a determinant factor in selecting the most useful index. Among the basic recommendations, it has to be stressed that it is important to control as many of the possible variables that affect bronchodilator response, such as the type and dose of the bronchodilator used, method and quality of delivery, bronchodilator use before the test, time of day,

subject performance *etc.* Considering the number of bronchodilator tests performed daily in Europe, and the miracles accomplished by computers, it can be suggested, if it is considered that this problem is worth solving, that the European Respiratory Society might organize a large data base, which could help to reach a consensus on how to assess reversibility.

#### References

1. Tiffeneau R, Beauvallet M. - Epreuve de bronchoconstriction et de bronchodilatation par aérosols. Emploi pour le dépistage, la mesure et le contrôle des insuffisances respiratoires chroniques. *Bull Acad Med (Paris)*, 1945; 129: 165-168.
2. Meslier N, Racineux JL. - Tests of reversibility of airway obstruction. *Eur Respir Rev*, 1991; 1: 34-40.
3. Cotes JE, Peslin R, Yernault JC. - Dynamic lung volumes and forced ventilatory flow rates. *Bull Eur Physiopathol Respir*, 1983; 19 (Suppl. 5): 22-27.
4. Eliasson O, Degraff AC. - The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. *Am Rev Respir Dis*, 1985; 132: 858-864.
5. Meslier N, Racineux J, Six P, Lockhart A. - Diagnostic value of reversibility of airway obstruction to separate asthma from chronic bronchitis. *Eur Respir J*, 1989; 2: 497-505.
6. Tweedale PM, Alexander F, McHardy GJR. - Short-term variability in FEV<sub>1</sub> and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax*, 1987; 42: 487-490.
7. Weir DC, Burge PS. - Measures of reversibility in response to bronchodilators in chronic airflow obstruction: relation to airway caliber. *Thorax*, 1991; 46: 43-45.
8. Dompeling E, Van Schayck CP, Molena J, *et al.* - A comparison of 6 different ways of expressing the bronchodilating response in asthma and COPD: reproducibility and dependence on prebronchodilator FEV<sub>1</sub>. *Eur Respir J*, 1992, 5: 945-952.
9. Vermeire P. - Basic principles of drug trials in asthma. *Eur Respir Rev*, 1991; 1: 12-18.