Table 2. – Indices of airway calibre in children

	Within-subject variability	To be used for the quantification of		
		baseline airway calibre	broncho-constriction	broncho-dilatation
FOT	± 12%	+	+	+
FRC	< 10%	-	-	+
$\Delta Ptco_2$	< 2 mm	-	+	-
PF	± 5%	+	+	+
FEV_1	< 5%	+	+	+
Flow-volume indices	± 12%	+	+	+
sGaw	± 10%	+	+	+

Induced bronchoconstriction can be obtained with histamine, methacholine and cold air from a young age (about 3) and with exercise from the age of about 5. PF measurements can be used, together with symptoms, for daily recordings at home.

The diurnal variability of PF, *i.e.* the difference between the lowest morning or evening value after an inhaled beta-2-agonist, correlates highly with the airway responsiveness to histamine or methacholine in adults [10]. No data exist on children.

Table 2 summarizes the indices which can be used in childhood to measure airway dilatation or obstruction. Reference values have recently been published [11].

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The assessment of reversibility: What physiological tests?

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The assessment of reversibility may be performed for different purposes *e.g.* for population studies or for the evaluation of the individual patient; and it may have different applications *i.e.* diagnostic, prognostic or therapeutic. These differences may determine to some extent the choice of physiological tests and the type of analysis of the measurements.

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Physiological tests

The most often applied tests and variables are those obtained during a forced expiratory manoeuvre after a full inspiration: *i.e.* FEV_1, FVC, PEF, MEFs and

Table 1. – Expression of bronchodilator response

	Case 1 (FEV_1 pred = 51)	Case 2 (FEV_1 pred = 21)
initial value	20%	80%
Postbronchodilator value	30%	90%
Expression		
Relative percent: Δ/initial	+ 50%	+ 0.21
Absolute: Δ in units	+ 0.51	+ 0.21
Absolute percent: Δ/pred	+ 10%	+ 10%
Percent achievable: Δ/ (pred-initial)	+ 12%	+ 50%

Pred: predicted.

FEF_{25-75}. Although the inspiration to TLC may induce a transient increase in bronchomotor tone in most asthmatics, these tests have the advantage that they are very reproducible, are easy to perform and do not require sophisticated equipment.

Tests during quiet breathing mainly consist in the measurement of Raw and sGaw with the body plethysmograph and of total respiratory resistance (Rrs) and reactance (Xrs) with the forced oscillation technique [1, 2]. The advantages of these tests are that almost no cooperation is requested from the subjects and that the percentage changes induced by bronchodilation are larger; yet the reproducibility is less than for the former tests.

For all these reasons, and also because pairs of tests (mainly consisting of spirometry and a resistance measurement) have the best discriminative power for a bronchodilator response, (VAN NOORD *et al.*, unpublished) it seems preferable that for study-purposes the assessment for reversibility is performed with both types of tests. In these instances the quiet breathing test should precede the forced manoeuvre test.

For routine clinical purposes this combination is, however, not necessary since a significant correlation exists between the bronchodilator response measured with most of the physiological tests (VAN NOORD *et al.*, unpublished). However, it should be noted that neither relative changes nor the sensitivity of the different tests are the same.

Expression of bronchodilator response

Many different expressions of response are used, and dependent on these, different categories of responders and non-responders are retained [3, 4], and this is one of the reasons of the controversies and conflicting data in the literature concerning the diagnostic and prognostic value of the assessment of reversibility.

The most often applied routine expression is the "relative percent response" (table 1); this expression tends to select preferentially patients with initially low values as responders. The expression using "absolute" values does not have this drawback, but it favours tall subjects. This size effect is eliminated in the expression using "absolute percent response"; yet this gives no information on the clinical relevance of the response *i.e.* on the postbronchodilator value (in percent predicted). The expression "percent achievable" gives account of the end result but will preferentially select as responders these subjects with initially high values. Although these different expressions may thus favour different categories of patients, the relationship between each of these expressions and other variables such as threshold for positive response, or baseline FEV_1 or decline in FEV_1 with time, is complex and unpredictable [3].

From a theoretical point of view it seems preferable to use the "absolute percent" expression since this is not influenced by the initial value, or alternatively to use 2 complementary expressions *i.e.* "relative percent" and "percent achievable".

Criterium and threshold of positive response

Exact thresholds of a positive response can be calculated using the intra-individual coefficient of variation (CV) of this test. An often used threshold is 1.65 × CV, which corresponds with the 95% probability level. For some purposes, *e.g.* population studies, it may be more appropriate to use the 99.9% probability level (*i.e.* 3 × CV) or even the virtually 100% level (*i.e.* 3.82 × CV). Strictly, two comments which generally are not taken into consideration, should be added to this: 1) the coefficient of variation may change depending on the degree of airways obstruction, and, therefore, also the threshold for positive response can be different depending on the initial value. Indeed, table 2 shows that the mean values of CV are larger in the group of patients with abnormal initial values (lower panel); yet the differences are generally rather small; 2) not only the CV

Table 2. – Effects of bronchodilation and of bronchoconstriction

GROUP I: Asthma with normal baseline: effect of histamine (Van Noord *et al.* ARRD 1989)
n = 53; age = 30±12 yrs; height= 168±8cm

VARIABLE	BASELINE DATA				POSTHISTAMINE DATA	
	Value (±SD)	Intra Coeff. Variation (%)	95% Probab. level (%) CV × 1.65	CV × 1.65 × $\sqrt{2}$	Change (%) (Δ / pre)	Rank order
FEV_1 (% pred)	95±12	2.8	5	7	23±7	3
FVC (% pred)	92±12	2.7	5	7	13±7	4
Raw-Rrs_6-$\overline{Rrs}$* ($cmH_2O.l^{-1}.s$)	1.5±0.5	8 - 9	14	19	40±15	2
sGaw ($cmH_2O^{-1}.s^{-1}$)	0.21±0.07	7.4	12	17	61±14	1

* Mean values of Raw, Rrs_6 and Rrs (Rrs = mean total respiratory resistance between 2 and 30 Hz, and Rrs_6 = the value at 6 Hz)

GROUP II: COPD with abnormal baseline: effect of salbutamol (Van Noord *et al.* unpublished)
n = 125; age = 56±14 yrs; height = 170±7cm

VARIABLE	BASELINE DATA				POST-SALBUTAMOL			
	Value (±SD)	Intra Coeff. Variation (%)	95% Probab. (%) CV × 1.65	CV × 1.65 × $\sqrt{2}$	Relative % change (Δ / pre) Δ	Rank order	Absolute change Δ	Rank order
FEV_1 (*l*)	1.78±0.81	4.6	8	11	19±16	5	0.27±0.21	4
FVC (*l*)	3.05±1.05	3.9	6	8	16±15	4	0.41±0.32	1
PEF ($l.s^{-1}$)	4.89±2.10	8.6	14	20	17±20	8	0.70±0.68	8
MEF_{50} ($l.s^{-1}$)	1.28±1.11	12.9	21	30	22±27	6	0.24±0.36	5
Raw ($cmH_2O.l^{-1}.s$)	3.46±2.04	7.5	12	18	30±21	1	1.13±1.04	3
Rrs_6 ($cmH_2O.l^{-1}.s$)	5.33±1.92	15.2	25	35	21±17	2	1.20±1.18	7
$\overline{Rrs}$ ($cmH_2O.l^{-1}.s$)	4.00±1.17	12.1	20	28	13±15	3	0.54±0.69	6
sGaw ($cmH_2O^{-1}.s^{-1}$)	0.088±0.073	14.9	25	35	72±71	7	0.050±0.053	2

of the initial values but also of the post-bronchodilator values should be taken into consideration: thus, since 2 sets of measurements are compared, the calculation of the threshold should be 2.33 (*i.e.* 1.65 × $\sqrt{2}$) × CV for the 95% level, 4.25 (*i.e.* 3 × $\sqrt{2}$) × CV for the 99.9% level, and 5.4 (*i.e.* 3.82 × $\sqrt{2}$) × CV for the virtually 100% level.

The coefficients of variation and thresholds of positive response are smaller for spirometry tests (FEV_1, FVC) than for pulmonary mechanics tests (Raw, sGaw, Rrs) (table 2). For population studies the exact value of the threshold should be calculated from the CV of the study group itself. For clinical evaluations in individual patients often following threshold values are applied: for FEV_1: 12-15% (of initial value), or 160-200 ml; for FVC: 15% (of initial value) or 300 ml; for FEF_{25-75} and MEF_{50}: 20% (of initial value) or 30% if measured at iso-volumes; for Raw, Rrs or sGaw : 25-40%.

Rank order of sensitivity or discriminative power of different tests

Bronchodilation causes smaller changes in the values of spirometric test than of pulmonary mechanics tests, but also the thresholds for a positive response are smaller in the former (table 2). It is thus a priori not evident which test is most sensitive in this respect.

We investigated this question in 125 COPD patients with light to severe airways obstruction by means of a multiple variable analysis by Fisher's optimal discriminant function (Van Noord *et al.*, unpublished) (table 2, lower panel). This analysis was applied on the complete set of physiological tests before and after bronchodilation in order to detect the most sensitive ones. The forced manoeuvre tests were FEV_1, FVC, PEF, MEF_{75}, MEF_{50}, MEF_{25}; the plethysmographic variables were Raw and sGaw, and the FOT variables were $\overline{Rrs}$ (mean resistance

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