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A comparison of six different ways of expressing the bronchodilating response in asthma and COPD; reproducibility and dependence of prebronchodilator FEV_1

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A comparison of six different ways of expressing the bronchodilating response in asthma and COPD: reproducibility and dependence of prebronchodilator FEV_1. E. Dompeling, C.P. van Schayck, J. Molema, R. Akkermans, H. Folgering, P.M. van Grunsven, C. van Weel.

ABSTRACT: Various indices are used to express the bronchodilating response. It is unclear, however, which index is most informative. The aim of this study was to compare six expressions of the bronchodilating response and to examine: 1) the independence of the prebronchodilator forced expiratory volume in one second (FEV_1); and 2) the reproducibility of the bronchodilating response.

Bronchodilating responses (increases in FEV_1 60 min after salbutamol 400 μg and ipratropium bromide 80 μg) on six test occasions, during two years, of 183 patients (72 asthma, 111 chronic obstructive pulmonary disease (COPD)) from a large bronchodilator intervention study were used. The dependence of the prebronchodilator FEV_1 was investigated both between patients (cross-sectional analysis) and within patients (longitudinal analysis) by means of linear regression analysis. The reproducibility of the bronchodilating response was calculated by means of the coefficients of variation (CVs) of the six bronchodilating responses during two years. The CVs of the six expression indices were compared by analysis of variance (ANOVA).

No index was independent of the prebronchodilator FEV_1. However, some indices were significantly more dependent on the prebronchodilator lung function and, therefore, less reproducible than others. The "% initial" index (change as a percentage of the prebronchodilator value) was the most dependent on the prebronchodilator lung function and had the worst reproducibility (CV ranged from 50–61%). The "% possible" (change as a percentage of the predicted minus prebronchodilator value) and "% achievable" (change as a percentage of the maximal postbronchodilator minus prebronchodilator value) indices were the least dependent on the prebronchodilator value and had the highest reproducibility (CV ranging from 34–53%).

The way in which bronchodilating responses should be expressed depends on the purpose of the test. It was concluded that the "% initial" index was most dependent on the prebronchodilator FEV_1 and had the worst reproducibility, whereas for the "% possible" or "% achievable" indices the opposite was found. In bronchodilator studies, the latter expression indices increase the possibility of detecting differences in bronchodilating efficacy between different drugs.

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Assessment of the responsiveness to bronchodilators in patients with airway obstruction is a test often used in clinical and experimental situations [1]. The bronchodilating response, mostly assessed by the increase in forced expiratory volume in one second (FEV_1), provides objective information about the degree of reversibility of airway obstruction [2] and the response to different types of drugs [3]. Various indices are used to express the response to bronchodilators: absolute change [4–6] and change as a percentage of the prebronchodilator value [7, 8], of the predicted value [5, 9], of the maximal response [10], of the maximal postbronchodilator minus prebronchodilator value [10, 11] or of the predicted minus prebronchodilator value [12]. It is not clear, however, which method of expressing the bronchodilating response is most informative [1, 13]. Particularly in asthma, marked fluctuations in pulmonary function may occur, both throughout the day and from day-to-day [14, 15]. As a consequence, the bronchodilating response may fluctuate correspondingly, which may lower the comparability of responses, both between and within subjects.

The use of an index independent of the prebronchodilator FEV_1 and with reproducible values may generally be most appropriate [13]. It is not clear which

index (if any) for expressing reversibility has these properties. Two cross-sectional studies on this subject led to contradictory results. POSTMA *et al.* [16] observed that the "% possible" index (change as a percentage of the predicted minus prebronchodilator value) was independent of the prebronchodilator lung function. WEIR and BURGE [13] claimed that not "% possible" but "% predicted" (change as a percentage of the predicted value) was independent of the prebronchodilator lung function. However, these findings were based on a single cross-sectional assessment, in patients with non-asthmatic chronic airway obstruction, in which reversibility of obstruction and fluctuations of pulmonary function are not "characteristic".

In a prospective controlled study, during two years, in both asthma and chronic obstructive pulmonary disease (COPD), we investigated which bronchodilator index was independent of the prebronchodilator FEV_1, and compared the reproducibility of six indices for expressing reversibility. Data on six bronchodilating responses, during two years, of 183 patients participating in a bronchodilator intervention study were used for this purpose [17, 18].

Methods

Patients

An extensive description of patient selection, inclusion and exclusion criteria of the bronchodilator intervention study was given previously [17, 18]. In summary: 29 general practitioners in the catchment area of the University of Nijmegen were asked to select all of their patients aged ≥30 yrs with symptoms of asthma or COPD. Only patients who showed mild to moderate airway obstruction (FEV_1 ≥50% of the predicted value [19]) and/or increased bronchial responsiveness to histamine (provoking concentration producing a 20% fall in FEV_1 (PC_{20}) ≤8 $mg \cdot ml^{-1}$) were included by the investigators.

The diagnosis of asthma or COPD was based on the criteria of the American Thoracic Society (ATS) [14]. Asthma was defined as the combination of [17, 18]: 1) reversible obstruction (increase in FEV_1 one hour after the administration of 400 μg salbutamol and 80 μg ipratropium bromide ≥15% of the prebronchodilator

Table 1. – Clinical characteristics of patients with COPD and asthma

	COPD	Asthma	p-value
Patients n	111	72	
Height m	1.72 (0.09)	1.69 (0.09)	0.049
Age yrs	53 (13)	51 (13)	0.22
Sex M/F	68/43	33/39	0.040
Current smokers +/-	67/44	27/45	0.003
Smoking duration pack yrs	19(17)	13 (16)	0.015
Allergic +/-	20/89	25/46	0.011
FEV_1 *l*	2.44 (0.82)	2.18 (0.77)	0.039
FEV_1 % pred	77 (18)	73 (20)	0.19
FEV_1max *l*#	2.81 (0.83)	2.77 (0.84)	0.80
VC *l*	3.60 (1.03)	3.53 (1.06)	0.66
VC % pred	90 (16)	92 (18)	0.39
VCmax *l*#	3.95 (1.01)	3.95 (1.06)	0.99
Reversibility in FEV_1			
"absolute" *l*	0.26 (0.14)	0.46 (0.27)	0.0001
"% initial"	13 (9)	25 (16)	0.0001
"% predicted"	8 (4)	15 (7)	0.0001
"% maximal"	63 (14)	66 (17)	0.19
"% possible"	34 (19)	44 (23)	0.004
"% achievable"	64 (16)	72 (16)	0.0013
CV-PEFR %	9 (5)	13 (6)	0.0001
PC_{20} $mg \cdot ml^{-1}$ ##	11.3	1.2	0.0001

Data are presented as mean with SD in parentheses. Differences between patients with asthma and those with COPD are tested by means of the Chi-square test (dichotomous variables) or unpaired Student's t-test (continuous variables). #: maximal postbronchodilator value during the two year study period; ##: geometric mean PC_{20} values are given. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; VC: vital capacity; PC_{20}: provoking concentration of histamine producing a 20% fall in FEV_1; CV-PEFR: coefficient of variation of the weekly measured morning peakflow during a 4 week period at the start of the study.

value); 2) bronchial hyperresponsiveness to histamine (PC_{20} ≤8 mg·ml^{-1}); 3) dyspnoea; 4) allergy (at least one positive test out of seven radio-allergosorbent tests (RAST) (Pharmacia®, Sweden: pollen: weeds, grasses, trees; animals: cats and dogs; house dust mite; *Aspergillus fumigatus*)) and/or wheezing. COPD was defined as the combination of [17, 18]: 1) chronic cough or chronic sputum production for at least three months during at least two consecutive years; 2) continuous airway obstruction (FEV_1 <85% of the predicted value).

Thus, separate definition criteria of asthma and COPD were not mutually exclusive (*i.e.* some subjects with asthma had chronic cough, some subjects with COPD had a PC_{20} ≤8 mg·ml^{-1}). However, the combination of features was mutually exclusive: no asthmatics also had a diagnosis of COPD and *vice versa*. Patient characteristics are shown in table 1. The study was approved by the University Ethics Committee. All patients gave informed consent.

Bronchodilator therapy

At the start of the study, all patients were randomly allocated to one of the two treatment regimens: continuous use of a bronchodilator (ipratropium bromide of 160 µg daily or salbutamol of 1,600 µg daily) or inhalation on demand. Within these treatment regimens, a crossover comparison was applied between ipratropium bromide and salbutamol. All patients used ipratropium bromide during one year and salbutamol during the other. The sequence of salbutamol and ipratropium bromide was determined by random allocation. No corticosteroids, cromoglycate or bronchodilators other than the medication mentioned above (ipratropium bromide or salbutamol) were permitted.

Spirometry and bronchodilator testing

At the start of the study and after 6, 12, 13, 18 and 24 months, respectively, assessments were made by two trained laboratory technicians during an exacerbation-free period. Patients were requested to abstain from bronchodilating medication for at least 8 h prior to the lung function tests. Smoking or exercise just before or during the experiments was not permitted. The FEV_1 and the forced vital capacity (FVC) were assessed three times by means of the Microspiro HI-298 (Chest Corp., Japan) [20]. The data from the flow-volume curve with the highest sum of FVC and FEV_1 were used for calculations. The FEV_1 was measured before and one hour after the inhalation of 400 µg salbutamol and 80 µg ipratropium bromide (both metered dose aerosols). The bronchodilating response of each patient on every test occasion was expressed in six different ways:

1) Absolute change ("absolute") [4–6]:

$$FEV_1\text{post-}FEV_1\text{pre}$$

2) Change as a percentage of prebronchodilator value ("% initial") [7, 8]:

$$\frac{FEV_1\text{post-}FEV_1\text{pre}}{FEV_1\text{pre}} \cdot 100$$

3) Change as a percentage of predicted value ("% predicted") [5, 9]:

$$\frac{FEV_1\text{post-}FEV_1\text{pre}}{FEV_1\text{pred}} \cdot 100$$

4) Change as a percentage of the maximal absolute response ever recorded during the two year study period ("% maximal") [10]:

$$\frac{FEV_1\text{post-}FEV_1\text{pre}}{\Delta FEV_1\text{max}} \cdot 100$$

5) Change as a percentage of predicted value minus prebronchodilator value ("% possible") [12]:

$$\frac{FEV_1\text{post-}FEV_1\text{pre}}{FEV_1\text{pred-}FEV_1\text{pre}} \cdot 100$$

6) Change as a percentage of the highest postbronchodilator value ever recorded during the two year study period minus prebronchodilator value ("% achievable") [10, 11]:

$$\frac{FEV_1\text{post-}FEV_1\text{pre}}{FEV_1\text{max-}FEV_1\text{pre}} \cdot 100$$

Analysis

Cross-sectional analysis. In order to investigate the dependence of the six indices for expressing reversibility of the prebronchodilator FEV_1, linear regression analysis of the bronchodilating response (dependent variable) on the prebronchodilator FEV_1 (independent variable) was applied on six different test occasions (fig. 1). The Pearson correlation coefficient (r) was taken as a measure for the extent of the relationship [21].

Longitudinal analysis. The reproducibility of the bronchodilating response was determined by calculating the coefficient of variation (CV=SD/mean×100) [22, 23] of the six assessments. A low CV implies a high reproducibility and vice versa. The dependence of the six indices of the prebronchodilator FEV_1 was also determined within subjects. For this purpose, the six bronchodilating tests of an individual were incorporated in a linear regression analysis of the bronchodilating response (dependent variable) on the prebronchodilator lung function (independent variable). The r-square (% of explained variance) was taken as a measure for the extent of the relationship [21]. Individual r-squares were averaged to get the mean r-square of that index in asthma or COPD. The mean CVs and mean r-square of the six indices were statistically compared with each other by means of ANOVA.

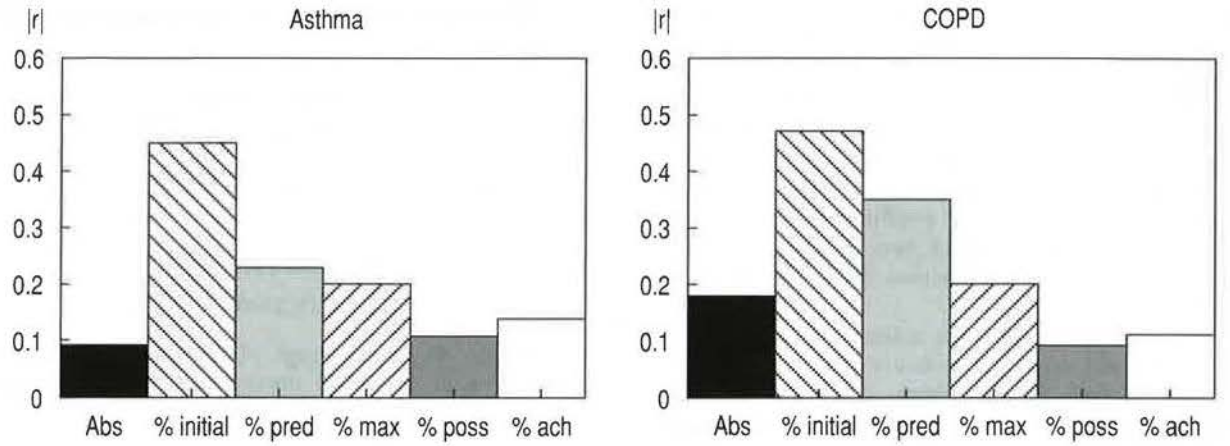

Fig. 1. – The correlation between bronchodilating response and prebonchodilator FEV_1 (cross-sectional analysis) of six different expression indices. The absolute Pearson correlation coefficients (mean of six different tests) are given for asthma and COPD separately. FEV_1: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease; Abs: Absolute; pred: predicted; max: maximal; poss: possible; ach: achievable.

Table 2. – Results of the cross sectional analyses

	Bronchodilator test						
Index	1	2	3	4	5	6	Mean
Asthma							
"absolute"	-0.06	-0.07	+0.10	-0.03	+0.04	-0.22	0.09
"% initial"	-0.39†	-0.47††	-0.32**	-0.46††	-0.51††	-0.53††	0.45
"% predicted"	-0.24*	-0.26*	-0.05	-0.21	-0.21	-0.39***	0.23
"% maximal"	-0.28*	-0.22	+0.07	-0.18	-0.05	-0.39†	0.20
"% possible"	-0.22	-0.10	-0.04	+0.11	-0.10	-0.09	0.11
"% achievable"	-0.16	+0.04	+0.26*	+0.08	+0.26*	+0.05	0.14
COPD							
"absolute"	-0.19*	-0.16	-0.09	-0.11	-0.25**	-0.27***	0.18
"% initial"	-0.45††	-0.48††	-0.48††	-0.39††	-0.51††	-0.49††	0.47
"% predicted"	-0.35††	-0.35†	-0.30***	-0.26**	-0.40††	-0.42††	0.35
"% maximal"	-0.28***	-0.22*	-0.08	-0.07	-0.23*	-0.31***	0.20
"% possible"	-0.09	+0.01	-0.10	+0.15	+0.04	+0.12	0.09
"% achievable"	-0.13	-0.19	+0.04	-0.03	-0.08	-0.16	0.11

The Pearson correlation coefficients of the relationship between the bronchodilating response and the prebronchodilator FEV_1 are calculated at six different cross-sectional assessments for six indices of reversibility (between-subject analysis). The statistical significance of the correlations are also presented. *: $p<0.05$; **: $p<0.01$; ***: $p<0.005$; †: $p<0.001$; ††: $p<0.0001$. FEV_1: forced expiratory volume in one second.

Results

Cross-sectional analysis. In table 2, the Pearson correlation coefficient of the relationship between the bronchodilating response and the prebronchodilator FEV_1 at cross-sectional assessments are represented for six different indices of reversibility. The Pearson correlation coefficients of a particular index of reversibility varied substantially between the different cross-sectional assessments (table 2). In asthma, the "absolute change" and "% possible" indices had no statistically significant correlations with the prebronchodilator FEV_1 on any test occasion. In COPD, only the "% possible" and "% achievable" indices had no significant correlations at any test moment. In both asthma and COPD, the average Pearson correlation coefficient was low (<0.20) for the "absolute change", "% possible" and "% achievable" indices but high (≥0.45) for the "% initial" index.

Longitudinal analysis. The results of the longitudinal analysis are shown in table 3. All indices of reversibility demonstrated a pronounced relationship between the bronchodilating response and the prebronchodilator FEV_1, as represented by the high r-square. The reproducibility of the bronchodilating response was low: the CVs ranged from 34–50% in asthma to 46–61% in COPD. "% possible" and "% achievable" appeared to be the indices with the lowest r-square and CV in both asthma and COPD.

Table 3. – The results of the longitudinal analyses

	Asthma		COPD	
Index	CV	$r^2 \times 100\%$	CV	$r^2 \times 100\%$
"absolute"	43 (24)	54 (34)	57 (29)	47 (32)
"% initial"	50 (25)	63 (33)	61 (30)	51 (33)
"% predicted"	43 (24)	54 (34)	57 (29)	47 (32)
"% maximal"	43 (24)	54 (34)	57 (29)	47 (32)
"% possible"	34 (23)**	49 (34)*	46 (24)**	45 (33)
"% achievable"	36 (21)**	40 (32)***	53 (27)*	38 (33)**

The CVs of bronchodilating responses of six indices of reversibility. Moreover, the r-square (% of explained variance) of the relationship between the bronchodilator response and the prebronchodilator lung function are also presented (within-subject analysis). The CVs and r-square of "% initial" were statistically compared with the other indices by ANOVA. *: $p<0.05$; **: $p<0.001$; ***: $p<0.0001$. CV: coefficient of variation; ANOVA: analysis of variance; COPD: chronic obstructive pulmonary disease.

Table 4. – The influence of the treatment regimen during two years (continuous bronchodilator therapy *versus* treatment on demand) on the reproducibility of the bronchodilating response of six different expression indices

	Asthma		COPD	
Index	Continuous	On demand	Continuous	On demand
"absolute"	47 (22)	49 (25)	58 (31)	61 (27)
"% initial"	55 (22)	58 (30)	66 (36)	64 (28)
"% predicted"	47 (22)	49 (25)	58 (31)	61 (27)
"% maximal"	43 (24)	54 (34)	57 (29)	47 (32)
"% possible"	52 (55)	38 (29)	50 (32)	58 (35)
"% achievable"	41 (24)	39 (22)	46 (22)*	62 (28)

Differences in CV between the continuous treatment and on demand treatment group were tested by the unpaired Student's t-test. *: $p<0.005$. For abbreviations see legend to table 3.

The influence of the bronchodilator treatment regimen. During the 2 yr study period, there was a decline in the baseline FEV_1 of 85 (SEM 16) $ml \cdot yr^{-1}$ during continuous bronchodilator treatment, but of only 39 (SEM 16) $ml \cdot yr^{-1}$ during treatment on demand (unpaired Student's t-test, $p<0.05$). The influence of the treatment regimen on the reproducibility of the bronchodilating response is given in table 4 for the six different expression indices. It appeared that, in general, no differences existed in CV between patients with asthma or COPD treated continuously or on demand, with only one exception. In COPD, the CV of "% achievable" was higher in patients treated on demand (62%) than in patients treated continuously (46%) ($p<0.005$).

Discussion

Nowadays, a number of indices to express the bronchodilating response are used, all of them with specific advantages and drawbacks. It is difficult to give general statements about the way bronchodilating responses should be expressed, because the method of expression depends on the purpose of the bronchodilating test [1]. Is the test used to separate asthmatics from subjects with COPD? Is it used to evaluate the bronchodilating efficacy of drugs or to predict the decline in lung function? It is not likely that only one index is most appropriate for answering all these different questions and indeed our study does not suggest "one optimal index".

Two general aspects of expressing the bronchodilating response were investigated in our study: the dependence of the prebronchodilator FEV_1 and the reproducibility of the bronchodilating response. In general, the use of an index independent of the prebronchodilator FEV_1 will increase the comparability of bronchodilating responses between different subjects and of repeated tests within the same subjects. Moreover, an index that gives more reproducible values will increase the validity of the test result. Therefore, an index least dependent on the prebronchodilator FEV_1 and with most reproducible values has many advantages.

Our study demonstrated that every index of expressing the bronchodilating response was to some extent dependent on the prebronchodilator FEV_1, in contrast to previous claims [13, 16]. However, some were clearly more dependent and, therefore, less

reproducible than others. The most common way to express the bronchodilating response ("% initial") was most dependent on the prebronchodilator FEV_1 and had the worst reproducibility. On the contrary, the "% possible" and "% achievable" indices were least dependent on the prebronchodilator FEV_1 and were most reproducible. This does not imply that bronchodilating responses should always be expressed as "% possible" or "% achievable". For instance, when the bronchodilating test is used to separate asthma from COPD, the data of our study and those of others [5] suggest that these indices might not give an optimal separation between the two disease categories and are, therefore, not appropriate for this purpose. In our study, the "absolute", "% initial" and "% predicted" indices gave an optimal separation between asthmatics and subjects with COPD. MESLIER *et al.* [6] and ELIASSON and DEGRAFF [5] found that the "% predicted" index was most useful in this respect.

When the bronchodilator test is used to evaluate the bronchodilating efficacy of a certain drug, the "% possible" or "% achievable" indices might be more useful than the other indices because of the higher reproducibility. Based on our results, the standard error of a single bronchodilator test can be estimated at 34–61%, dependent on the expression index. This indicates that at an individual level the value of a single bronchodilator test is limited. As the standard error generally decreases with the square root of the number of assessments [21], about 14 tests will bring the standard error of the mean within the 15% limit, when expressed as "% initial" in asthma. With the "% possible" and "% achievable" indices, however, just seven assessments will give the same accuracy. Therefore, in bronchodilator trials, comparing the bronchodilating efficacy of different drugs within asthma or COPD, the "% possible" or "% achievable" indices might increase the possibility of detecting differences in bronchodilating efficacy between different drugs.

The index widely used is the one that expresses the absolute improvement in FEV_1 as a percentage of the prebronchodilator value. An advantage of this index is that it is easy to use and to calculate. A drawback is the strong dependence on the prebronchodilator FEV_1. Small absolute changes become large percentage changes in patients with a low FEV_1, so that the patients with the greatest impairment of lung function usually appear to have the greatest reversibility [5, 13]. In this study, the low reproducibility appeared to be another drawback of this index. Expressing the bronchodilating response as an absolute change is also very easy, but this index is dependent on sex and height: tall male patients are more likely to demonstrate a certain degree of reversibility than small female patients [1]. Moreover, we found that the "absolute change" index was also dependent on the prebronchodilator value, although to a smaller extent than the "% initial" index.

A recent cross-sectional study in non-asthmatic patients claimed that the "% predicted" index was the only index independent of the prebronchodilator FEV_1 [13]. However, our study clearly demonstrated that this index is also dependent on the prebronchodilator FEV_1, both between and within subjects. The Pearson correlations of the relation between the bronchodilator response and the prebronchodilator lung function varied substantially between different cross-sectional assessments in our study. Therefore, only one cross-sectional measurement of the bronchodilating response, as in the studies of WEIR and BURGE [13] and POSTMA *et al.* [16], is not sufficient to compare different indices of reversibility.

The "% maximal" index (absolute change as a percentage of the maximal absolute response ever recorded) is not often used and appeared to have no specific advantages in this study. Data from our study showed that it is of no value in separating asthmatics from patients with COPD.

The "% possible" and "% achievable" indices are difficult to calculate, because predicted or maximal postbronchodilator values are necessary. In patients with little ventilatory impairment, bronchodilating responses expressed as "% possible" may be exaggerated because the prebronchodilator FEV_1 may reach the predicted value of the FEV_1. The "% achievable" index does not have this drawback but repeated tests are necessary to determine the individual maximal postbronchodilator value. These limitations make this index useless in clinical practice.

The patients in this study were selected from 29 general practices and were representative of the adult population aged ≥30 yrs with asthma or COPD [17, 18]. The FEV_1 varied widely between the patients in our study. It ranged from 50–130% at the start to 22–140% at the end of the two year study period.

In our study, high dosages of both an adrenergic and an anticholinergic agent were given. It is possible that the reproducibility of bronchodilating responses is worse when only one drug is given, when lower dosages are used, or when the bronchodilating responses are handled as an "all-or-nothing" phenomenon (no response or a clear response) [24]. From the study of LINDGREN *et al.* [10] in five asthmatic patients, it could be inferred that the reproducibility of the bronchodilating response decreased (the CV increased by 6–22%), when instead of 2.25 mg, 0.25 mg terbutaline sulphate was administered.

The bronchodilator treatment regimen (continuous bronchodilator therapy or on demand) appeared to have no influence on the reproducibility of the bronchodilating response. The only significant difference in CV between COPD patients treated continuously and those treated on demand (the CV of "% achievable") was probably an artefact. The reversibility at the start of the study appeared to be slightly higher in the on demand treated COPD patients than in the COPD patients treated continuously. However, the baseline or prebronchodilator FEV_1 declined more rapidly during continuous bronchodilator treatment than during treatment on demand. This may have been the consequence of an increased exposure to allergens,

cigarette smoke or other environmental triggers during continuous bronchodilator treatment [17, 18]. As a consequence of the decline in prebronchodilator lung function, the bronchodilating response increased in the course of time when expressed as "absolute", "% initial", "% predicted" or "% maximal", but it did not change when expressed as "% possible" or "% achievable". This might indicate that the "% possible" or "% achievable" indices are more useful in following the degree of reversibility in the course of time than the other indices.

The method in which bronchodilating responses should be expressed depends on the purpose of the test. From this study, it was concluded that the most common method of expressing bronchodilating responses ("% initial") appeared to be most dependent on the prebronchodilator FEV_1 and had the lowest reproducibility of the bronchodilating response. The "% possible" (change as a percentage of the predicted minus the prebronchodilator value) and "% achievable" (change as a percentage of the maximal postbronchodilator minus prebronchodilator value) indices were least dependent on the prebronchodilator FEV_1 and had the best reproducibility of the bronchodilating response. In bronchodilator studies, the latter expression indices increase the possibility of detecting differences in bronchodilating efficacy of different bronchodilator drugs.

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