Eur Respir J 1999; 13: 1103–1108
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

Effects of formoterol in apparently poorly reversible chronic obstructive pulmonary disease

B.L.P. Maesen, C.J.J. Westermann, V.A.M. Duurkens, J.M.M. van den Bosch

Effects of formoterol in apparently poorly reversible chronic obstructive pulmonary disease. B.L.P. Maesen, C.J.J. Westermann, V.A.M. Duurkens, J.M.M. van den Bosch. ©ERS Journals Ltd 1999.

ABSTRACT: This randomized, double-blind, placebo-controlled, crossover study was designed to investigate the effects of the long-acting β_2-adrenoreceptor agonist formoterol fumarate in 12 current or exsmokers having chronic obstructive pulmonary disease, with a mean forced expiratory volume in one second (FEV_1) 47% of predicted, poorly reversible (5.1% pred) after terbutaline sulphate inhalation.

After inhaling a single dose of formoterol (6 or 24 μg), or placebo *via* Turbuhaler®, FEV_1 and pulmonary function parameters measured during quiet breathing (work of breathing (WoB) and airway resistance (R_{aw})) were recorded over 12 h on three test days.

Immediate changes in FEV_1 were modest, although each dose of formoterol caused a response >12% pred within 10 min in one subject. Compared to placebo, both doses of formoterol induced a clinically and statistically relevant improvement in WoB (>25%) and R_{aw} (>20%), which occurred within 10 min and lasted over a period of 12 h ($p \leq 0.02$, analysis of variance).

Thus, inhaled formoterol causes long-lasting lung functional improvements in apparently poorly reversible chronic obstructive pulmonary disease. Additional lung function measurements during quiet breathing after forced expiration tests may be useful in such patients to assess beneficial effects of bronchodilators.

Eur Respir J 1999; 13: 1103–1108.

Dept of Pulmonology, St Antonius Hospital, Koekoekslaan, Nieuwegein, The Netherlands.

Correspondence: C.J.J. Westermann
Dept of Pulmonology
St Antonius Hospital
Koekoekslaan 1
3435 CM Nieuwegein
The Netherlands
Fax: 31 306052001

Keywords: Airway resistance
bronchodilators
chronic obstructive pulmonary disease
forced expiratory volume
formoterol
work of breathing

Received: January 15 1998
Accepted after revision January 30 1999

Supported by Astra Pharmaceutica BV.

Formoterol is a potent and selective β_2-adrenoceptor agonist causing immediate symptom relief with a duration of action of 12 h in adult asthmatic subjects [1]. Long-term efficacy is confirmed without signs of clinically relevant tachyphylaxis [2]. In patients with chronic obstructive pulmonary disease (COPD), treatment with long-acting β_2-agonists is less well investigated. The few studies performed have been mainly in patients with airways obstruction reversible to short-acting β_2-agonists and have shown comparable beneficial short-term effects with the long-acting drugs [3, 4]. Long-term evaluation of these effects, however, is lacking. Studies with long-acting β_2-agonists in patients who poorly respond to routine airways obstruction reversibility tests with forced expiratory manoeuvres, such as forced expiratory volume in one second (FEV_1), are scarce. Such studies, however, seem to show favourable effects on clinical and functional parameters [5] that include work of breathing (WoB) [6]. This may explain the subjective improvements and changes in quality of life with long-acting β_2-agonists in patients with COPD [7]. The lack of effect on forced expiration tests may be due to early airway collapse and subsequent airflow decline causing underestimation of the existing bronchodilatory effects located more peripherally in the respiratory tract [8], where the major site of resistance is located in obstructive lung disease [9]. Because of the reduced expiratory transpulmonary pressures in non-forced pulmonary function tests, dynamic airway compression is smaller and airflow can be measured more sensitively [10, 11].

The present study was designed to investigate the effects of two doses (6 and 24 μg) of formoterol fumarate (Oxis®; Astra Draco, Lund, Sweden) inhaled by Turbuhaler® (Astra) in patients with poorly reversible, moderate-to-severe COPD. During a period of 12 h after inhalation, effects on airflow limitation were evaluated. The effects measured with methods using quiet breathing were compared with the changes induced in FEV_1, which is the parameter used to test bronchodilatory effects according to the European Respiratory Society (ERS) consensus statements [12, 13].

Methods

Subjects

Twelve ex- or current smokers, aged 40–70 yrs, with a clinical diagnosis of moderate-to-severe COPD (FEV_1 30–60% of the predicted value, but >1,000 mL) were recruited if they showed only poor reversibility. The diagnosis of COPD and reversibility was made according to ERS criteria [12, 13]. "Poor reversibility" was defined as an increase in FEV_1 of <9% pred following inhalation of 1 mg terbutaline sulphate *via* a Turbuhaler. Patients with a history suggesting respiratory diseases other than COPD,

or diseases likely to interfere with the conduct or results of the study, were excluded. No pregnant or breast-feeding females, or those with child-bearing potential were included. Patients were of both sexes and had a smoking history of >10 pack-yrs. All subjects gave written informed consent to be included in the study, which was approved by the local Medical Ethics Committee.

Study design

The study was of a randomized, double-blind, placebo-controlled, crossover design. Initially, baseline lung function was assessed and reversibility in FEV1 was measured 15 min after administration of a single dose of 1 mg terbutaline.

Thereafter, on three test days (separated by 1–7 days), a Latin square was used to randomize the patients to the three treatments: a single dose of formoterol, 6 or 24 μg metered dose, or placebo inhaled *via* a Turbuhaler. Correct inhalation technique was checked on each test day using a placebo Turbuhaler, connected to a Turbuhaler Usage Trainer. All Turbuhalers were primed before use. Subjects were not allowed to use other bronchodilatory drugs continuously or for symptom relief during the study periods. Oral and systemic theophylline and β_2-agonists were withheld throughout the study. Prior to the test days, short-acting β_2-agonists and anticholinergics were withheld for at least 8 h, long-acting β_2-agonists for 72 h and antihistamines for 24 h. The use of a stable steroid dose during the study period was allowed. Smoking was not permitted from 2 h before and during the assessments.

On the test days, investigations started at 08:00 h. During a 12-h period, WoB, airway resistance (Raw) and spirometry values were measured at 10 min before, and 10, 30, 60, 120, 180, 360, 540 and 720 min after inhalation of the study medication.

Study measurements

At the first visit, spirometry was performed in triplicate and the highest FEV1 value, at body temperature and ambient pressure, and saturated with water vapour (BTPS), was recorded both before and 15 min after inhaling terbutaline.

At least 30 min before inhalation of the test dose, a disposable oesophageal balloon (according to the guidelines of the European Community for Coal and Steel [14]) was inserted through the nose under local anaesthesia. The balloon was positioned at 40 cm from the nares and calibrated, after which the oesophageal pressure was recorded with a pressure transducer. The dynamic compliance was calculated from functional residual capacity (FRC), which was measured during inhalation and expiration, as the mean slope (of three curves) between FRC and FRC + 0.5 L. Oesophageal pressure and lung volume were measured in triplicate and plotted using an X–Y-recorder. Volume-corrected viscous WoB was defined by the area enclosed by the volume–oesophageal pressure curve and expressed per unit of tidal volume.

Raw was assessed at FRC using a pressure-compensated integrated flow plethysmograph (SensorMedics 6200; SensorMedics Corporation, Yorba Linda, CA, USA). The rate of airflow measured at the mouth and plethysmograph pressures were simultaneously plotted by an X–Y-recorder during gentle panting. The Raw values were obtained at 0.5 $L \cdot s^{-1}$ of inspiratory and expiratory flows at a respiratory rate of 0.5 Hz. Means of three measurements are reported. The specific airway conductance (sGaw) was calculated on the basis of these values.

Data evaluation

WoB and Raw were analysed as change from baseline (10 min prior to administration) values. Over the 12-h study period, the area under the time curve (AUC) was calculated by a trapezoidal method. FEV1 was assessed as percentage change of the predicted value, because the severity and change of this parameter is best expressed in relation to the reference values in moderate-to-severe COPD [12, 13, 15]. WoB and Raw were expressed as percentage change from baseline, because reliable reference values do not exist. On the basis of several studies a 10% increase in FEV1, 25% decrease in WoB, and 20% decrease in Raw was considered to be of clinical relevance [6, 16, 17]. No formal power calculation was performed before the study, but pilot experiments indicated that 12 patients would be needed for statistical significance. Absolute changes in parameters at 10 min and the AUC values were analysed by two-way analysis of variance (ANOVA). When significant overall treatment effects were found in ANOVA, the Student′s t-test for paired variables was performed for the three comparisons, correcting for multiplicity in the manner of Bonferroni; a significant difference was stated as $p<0.017$. The effects at 12 h were not formally assessed.

Results

The 12 patients enrolled all completed the study. The treatments and assessments were well tolerated, although in one patient codeine was given to prevent irritation and displacement of the oesophagus balloon. Half of the patients were current smokers. The group displayed clinical, radiological and physiological signs of emphysema (data not shown). There was clear-cut exertional dyspnoea and little sputum production. The anthropometric characteristics of all individual patients are shown in table 1. The mean baseline FEV1 value was 1.39 L, or 46.9% pred, and the reversibility in FEV1 after inhalation of terbutaline was 5.1% pred.

Baseline lung function data were comparable on the three test days. Inhalation of 6 or 24 μg of formoterol induced a rapid, though modest increase in FEV1. After 10 min, the mean increase was comparable to the response after reversibility testing with terbutaline inhalation (measured 15 min post dose). This increase in FEV1 was below the margin of reversibility (3.4 and 6.8% pred for 6 and 24 μg, respectively; table 2), although the highest dose of formoterol caused a statistically significant improvement compared to both the 6 μg dose and placebo ($p=0.002$). On the individual basis, the presumed clinically relevant response (>10% pred in FEV1) was observed in one patient after a dose of 6 μg formoterol and in two patients

Table 1. – Patient characteristics

Patient No.	Sex M/F	Age yrs	Height m	Weight kg	Baseline FEV1		FEV1/FVC %	Reversibility*		
					mL	% pred		mL	% pred	% baseline
1	F	48	1.65	80	1580	58.1	54	220	8.1	13.9
2	F	66	1.59	64	1150	56.6	42	150	7.4	13.0
3	M	69	1.71	73	1380	48.2	56	20	0.7	1.4
4	M	63	1.72	69	1150	37.3	41	200	6.5	17.4
5	M	50	1.79	87	1640	43.7	45	100	2.7	6.1
6	M	61	1.81	94	1430	40.6	32	300	8.5	21.0
7	F	59	1.67	55	1050	41.6	50	40	1.6	3.8
8	F	54	1.59	48	1000	42.9	40	80	3.4	8.0
9	M	70	1.85	69	2000	58.2	46	220	6.4	11.0
10	M	53	1.68	63	1200	37.5	32	70	2.2	5.8
11	M	70	1.72	63	1000	38.2	41	250	8.7	22.7
12	M	66	1.82	80	2050	59.9	53	160	4.7	7.8
Mean		61	1.74	70	1386	46.9	44	151	5.1	11.0

M: male; F: female; FEV1: forced expiratory volume in one second; VC: vital capacity. *: change in FEV1, expressed as absolute value, as % predicted and as % of baseline, 15 min after 1.0 mg terbutaline inhaled *via* Turbuhaler®.

after inhaling the highest test dose (table 3). Improvements reached a maximum of 7.4% (220 mL) and 10.0% (290 mL) after 2 h with a relevant response in two and four subjects for formoterol, 6 and 24 μg, respectively. In contrast, the change after placebo did not exceed 3.6% pred (fig. 1). Compared to placebo, the FEV1 remained (nonsignificantly) higher during the 12 h after formoterol. From the AUC values, a mean increase in FEV1 of 50 mL was calculated for placebo, 120 mL for 6 μg, and 230 mL for 24 μg formoterol over the 12-h interval.

Following placebo administration, WoB steadily increased to 129.2% of the baseline value after 12 h (fig. 2). Formoterol, 6 μg and 24 μg, caused a highly significant reduction in mean WoB 10 min after administration: 29.6% and 27.6% of the initial value, respectively, compared with a 0.6% reduction after placebo (p=0.0007, ANOVA, for the absolute changes, table 2). An improvement of at least 25% in WoB occurred in eight (6 μg) and seven (24 μg) patients at this time point. The maximum reduction was recorded after 60 min (35.1% and 28.0% of baseline values for 6 μg and 24 μg, respectively). Mean WoB remained below the morning values and below placebo values until the last measurement at 12 h. The AUC values for WoB after formoterol were significantly lower than after placebo (p=0.03), but there were no significant differences between the two doses of formoterol.

In addition, both doses of formoterol caused a prompt and highly significant decrease in *R*aw. The reduction was 21.4±13.9% (6 μg) and 25.3±14.5% (24 μg) (table 2) 10 min after inhalation, compared with a 0.4±17.0% change after placebo (p=0.003). By this stage, the presumed clinically important reduction (below the margin of 80% initial value) was recorded in eight (6 μg) and nine (24 μg) of the patients studied. Peak improvement in mean *R*aw was seen after 2 h and reached 25.5% (6 μg) and 30.2% (24 μg) compared with baseline (fig. 3). The differences in AUC values were statistically significant (p=0.01). The FRC levels at which *R*aw was assessed were comparable on the different test days and did not change significantly during the test periods. For this reason, formoterol caused similar changes in *R*aw and s*G*aw within 10 min and for the AUC values.

Table 2. – Changes in parameters 10 min after inhalation of the test medication, and the 12-h average by area under the time curves (AUC) of these parameters

		Placebo	Formoterol 6 μg	Formoterol 24 μg	p-value
Effects after 10 min					
FEV1	L	0.025±0.099	0.100±0.126	0.208±0.138*	0.002
	% pred	0.9±3.4	3.4±4.9	6.8±3.9	NA
WoB	$kPa \cdot L^{-1}$	-0.019±0.066	-0.207±0.131	-0.214±0.180	0.0007
	% baseline	-0.6±11.7	-29.6±13.3	-27.6±16.6	NA
*R*aw	$kPa \cdot L^{-1} \cdot s$	-0.009±0.106	-0.132±0.124	-0.145±0.105	0.003
	% baseline	-0.4±17.0	-21.4±13.9	-25.3±14.5	NA
s*G*aw	$s^{-1} \cdot kPa^{-1}$	-0.01±0.08	0.14±0.11	0.18±0.12	0.0004
	% baseline	0.1±19.4	33.3±21.2	47.3±33.1	NA
AUC values					
FEV1	L·h	0.6±2.51	1.5±1.02	2.68±2.08	NS
WoB	$kPa \cdot L^{-1} \cdot h$	1.21±1.70	-1.33±1.90	-1.34±2.21	0.03
*R*aw	$kPa \cdot L^{-1} \cdot s \cdot h$	0.17±1.26	-1.14±1.53	-1.18±1.18	0.01
s*G*aw	$s^{-1} \cdot kPa^{-1} \cdot h$	-0.15±1.28	1.15±1.18	1.52±1.45	0.02

Data are presented as means±SD. FEV1: forced expiratory volume in one second; WoB: work of breathing; *R*aw: airway resistance; s*G*aw: specific airway conductance; NA: not analysed; NS: not significant. AUC measured as change from baseline *versus* time (in h). *: p=0.002, significantly different from both placebo and 6 μg formoterol.

Table 3. – Individual changes in forced expiratory volume in one second (FEV_1) during the reversibility test (measured 15 min after inhalation of terbutaline 1,000 μg) and at 10 min after inhalation of the test medication

Patient No.	Terbutaline		Placebo		Formoterol 6 μg		Formoterol 24 μg	
	% pred	mL	% pred	mL	% pred	mL	% pred	mL
1	8.1	220	5.5	150	-3.7	-100	11.0	300
2	7.4	150	4.9	100	14.8	300	4.9	100
3	0.7	20	-5.2	-150	-1.7	-50	3.5	100
4	6.5	200	-3.2	-100	4.9	150	6.5	200
5	2.7	100	0.0	0	4.0	150	4.0	150
6	8.5	300	4.3	150	1.4	50	15.6	550
7	1.6	40	-2.0	-50	0.0	0	7.9	200
8	3.4	80	0.0	0	2.1	50	2.1	50
9	6.4	220	2.9	100	8.7	300	8.7	300
10	2.2	70	-1.6	-50	1.6	50	3.1	100
11	8.7	250	5.2	150	3.5	100	5.2	150
12	4.7	160	2.9	100	5.8	200	8.8	300
Mean	5.1	150	0.9	30	3.4	100	6.8	210

Discussion

About one-third of all patients with COPD show no positive "reversibility" in airflow obstruction by spirometry, with FEV_1 measured before and after inhaling a bronchodilator. The observed response is dependent upon several variables, such as the way in which the change in FEV_1 is expressed, the time of assessment after inhalation and the dose and type of bronchodilator used.

The 1995 consensus statement on COPD defined a positive response to medication to be ≥10% of predicted FEV_1 [12]. The 1993 working party additionally described "poorly reversible" COPD as having an increase in FEV_1 of <10% pred after a single high-dose of terbutaline [13]. For the patients included in this study, poorly reversible COPD was defined as a maximal improvement in FEV_1 of 9% pred.

Some patients with COPD and apparently irreversible airway obstruction after acute inhalation of a β_2-agonist will respond over a longer period of time ("period prevalence") [18]. Unfortunately, the ERS statements do not mention a standard time point to test reversibility. In clinical practice, a procedure with a one-time administration of short-acting β_2-sympatheticomimetic with response measurement after 15 min is generally accepted [19, 20].

Although all patients included in the study could be defined as poorly reversible, inhalation of formoterol caused an increase of >12% pred in FEV_1 in one of 12 patients within 10 min. This shows that a small number of apparently poorly responsive patients do not have fixed forced airflows, and fast reversibility can occur when another bronchodilating agent is used. The differences in FEV_1 changes between formoterol and terbutaline are probably due to the higher efficacy of formoterol, in combination with an earlier onset of action [21].

The 1993 guidelines stated that when FEV_1 fails to show an unambiguous bronchodilator response, measurement of R_{aw} may establish a clinical benefit. In contrast, the 1995 COPD statement reported resistance measurements to have no clinical advantage over spirometry. The present study demonstrates immediate, clinically relevant and statistically significant improvements in WoB and R_{aw} in the selected patients with moderate-to-severe airways obstruction. These function tests have an important advantage when compared to forced expiratory reversibility testing in these patients, because it lacks the period prevalence seen in FEV_1.

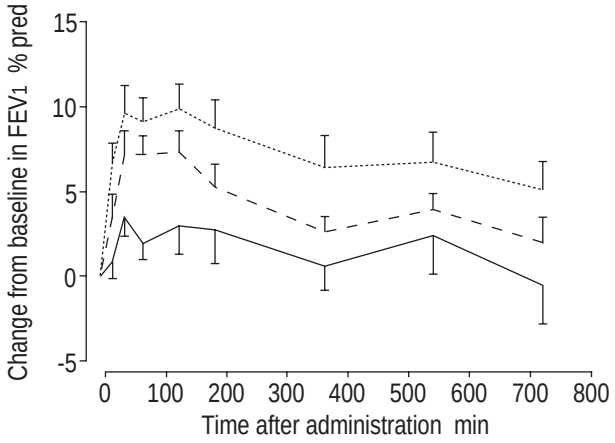

Fig. 1. – Changes in forced expiratory volume in one second (FEV_1) as % predicted after inhalation of 6 μg (– – –) or 24 μg (· · · · ·) formoterol or placebo (——).

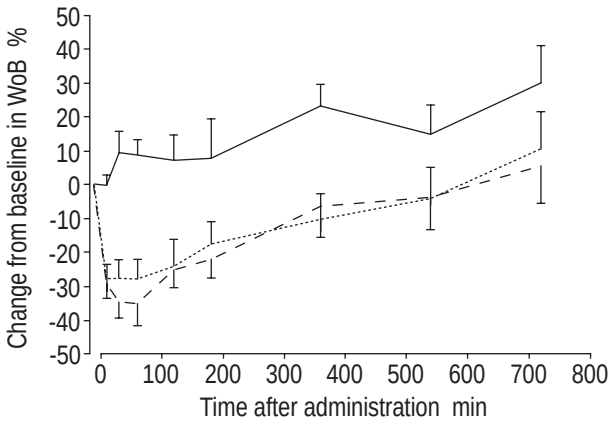

Fig. 2. – Changes in work of breathing (WoB) as % change from baseline after inhalation of 6 μg (– – –) or 24 μg (· · · · ·) formoterol or placebo (——).

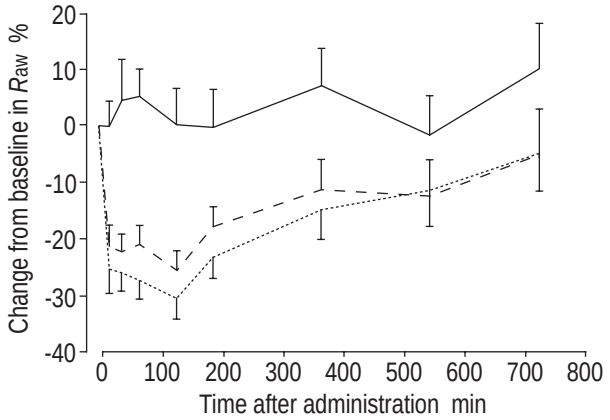

Fig. 3. – Changes in airway resistance (R_{aw}) as % change from baseline after inhalation of 6 μg (– – –) or 24 μg (· · · · ·) formoterol or placebo (——).

A retrospective analysis performed in the author's hospital showed that changes in forced and nonforced tests are correlated [11]. In 505 patients with COPD and loss of lung elasticity, those who tend to have a large reduction in WoB and R_{aw} were likely to have more pronounced bronchodilating effects measured by improvement in FEV_1. However, 52% of these patients showed a lack of response in FEV_1, despite a significant reduction in R_{aw}. Several factors can explain the documented changes in R_{aw} and WoB, despite only limited improvement in FEV_1. Compared to the manoeuvres of forced ventilatory flows, unforced parameters are less effort dependent, and are thus more reliable in subjects who are unable to consistently produce maximal efforts. In addition, dynamic airways collapse or compression pattern due to loss of lung elastic recoil or severe obstruction may mask a beneficial response in R_{aw} to a bronchodilator during forced function testing [22]. Better lung emptying affects small airways calibre, which might reduce the degree of hyperinflation, reducing the inspiratory threshold load imposed by positive end-expiratory pressure, and hence diminish WoB and the perception of breathlessness [23]. The present study could not support this hypothesis in respect to hyperinflation; no significant changes in FRC levels occurred. However, the perception of breathlessness develops particularly during exercise, and while measurements during resting conditions may not detect differences in residual capacities, dynamic hyperinflation can be reduced during exercise after inhaling bronchodilators [24].

Subjective improvements in symptoms and quality of life occur after inhalation of bronchodilators [7]. Although it was not an objective of this study to measure breathlessness, immediate changes in perception of breathlessness were indicated by the patients during pilot-investigations. This is in agreement with the results of an open study by Del Torre *et al.* [6] who demonstrated that nonforced pulmonary function tests were far better correlated with subjective improvement than forced expiration tests.

Bronchodilating drugs are the keystone of pharmacological therapy in dyspnoeic patients with COPD [25]. Documenting reversibility in airway obstruction has important clinical implications, because it can help to predict the prognosis of the disease and is often used as an objective rationale to justify the prescription of bronchodilators [26]. In future, it may also be useful in predicting the response to antiinflammatory medication [27]. Therefore, sensitive methods for assessing response are required to prevent undertreatment of patients. To date, there has been no agreement on which a test or combinations of tests may best identify patients with a reversible component in their COPD. Because of its simplicity and reproducibility, FEV_1 is considered the "gold standard" for assessing the presence of reversible obstruction in the diagnosis of asthma and COPD [28]. However, standardized reversibility tests have limitations in detecting a clinically relevant benefit in a subset of patients with COPD and loss of lung elasticity, and the absence of a response during a single test never justifies withholding bronchodilator therapy. Function tests during normal breathing in addition to forced conditions improve the prediction of reversibility [16]. On the basis of the preset margins (FEV_1 improvement >10%, WoB reduction >25% and R_{aw} reduction >20%) a clinical improvement could be detected 10 min after inhaling 6 μg formoterol in only one patient for FEV_1, while WoB and R_{aw} each showed clinical benefit in eight patients. The high-dose of formoterol (24 μg) had an effect on FEV_1 in two patients when the presumed criteria were applied. Response numbers were nine and seven subjects for WoB and R_{aw} respectively after this dose. Although nonforced tests can detect a considerably larger response to inhalation of bronchodilator drugs, these tests also have a wider variability due to a high within-subject variation. The observed dispersion limits the value of reference values [14]. Because no reliable predicted values exist, it was necessary to express differences in percentage change from baseline. Although this influences the reproducibility, it seems to be the best method to detect changes in nonforced dynamic function tests [16]. For these reasons, margins of reversibility are widened to determine sensitivity to bronchodilators. Several studies concerning this problem confirmed the detection range of 20% and 25% for R_{aw} and WoB respectively, as used in the present study [6, 16, 17].

When the two methods of nonforced measurement studied are available for use in clinical practice, plethysmography is preferred. An obvious advantage of this technique over the volume–oesophageal pressure method is the possibility to measure lung volumes and FRC simultaneously. In this way, spirometry and resistance measurement can be incorporated and information about bronchodilator responses can be gathered without much additional effort and within a reasonable period of time. The plethysmographic tests can be performed even in patients with severe airways obstruction, although it is more difficult to carry out and makes use of more sophisticated equipment than spirometry. The oesophageal balloon method has few clinical indications and cannot be considered a routine test for reversibility due to ethical and technical reasons.

Both doses of formoterol inhaled *via* a Turbuhaler were well tolerated and caused similar maximal changes in WoB and R_{aw} almost instantaneously. With nonforced pulmonary function tests, formoterol was effective within 10 min of administration, and remained below placebo values until the end of the observation period, 12 h after inhalation. For FEV_1, there was a dose-response relationship, although

significant changes could only be shown for the highest dose and the mean changes were below the preset margins of reversibility and clinical relevance. The effectiveness of formoterol administration *via* a Turbuhaler even after a low dose of 6 μg is probably due to the efficient pulmonary deposition of the dry powder inhalation device [29].

Because of the effectiveness and duration of action, long-acting β_2-agonists should be considered an alternative to short-acting bronchodilators in the management of chronic obstructive pulmonary disease [25]. This study provides further evidence that formoterol could have a prominent place in chronic obstructive pulmonary disease, even when reversibility of the airways obstruction seems to be limited or nonexistent.

Acknowledgements: The authors thank Astra Draco for provision of the inhalers, C. Hordijk and H. Poot for their technical expertise, and J.A. van Noord for his critical remarks.

References

1. Bartow RA, Brogden RN. Formoterol, an update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998; 55: 303–322.
2. van der Molen T, Postma DS, Turner MO, *et al*. Effects of the long-acting β-agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1997; 52: 535–539.
3. Cazzola M, Santangelo G, Piccolo A, *et al*. Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease. *Pulm Pharmacol* 1994; 7: 103–107.
4. Boyd G, Morice AH, Pounsford JC, *et al*. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; 10: 815–821.
5. Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single-center randomized, double-blind, placebo-controlled, crossover study. *Thorax* 1995; 50: 750–754.
6. Del Torre L, Melica EV, Del Torre M. Effectiveness of salmeterol in patients with emphysema. *Curr Ther Res* 1992; 52: 888–898.
7. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997; 155: 1283–1289.
8. Gimeno F, Postma DS, van Altena R. Plethysmographic parameters in the assessment of reversibility of airways obstruction in patients with clinical emphysema. *Chest* 1993; 104: 467–470.
9. Hogg JC, Macklem PT, Thurbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968; 278: 1355–1360.
10. Quanjer PH, Hilvering C, Tammeling GJ. The relationship between airway resistance, FEV1 and viscous work of breathing in patients with chronic obstructive lung disease before and after bronchodilatation. *Bull Physiopath Respir* 1971; 7: 539–553.
11. Van Snippenburg R, Duurkens VAM, van den Bosch JMM. Which test best measures bronchodilator drug response in patients with loss of lung elasticity? *Eur Respir J* 1996; 9: Suppl. 23, 310S.
12. Siafakas NM, Vermeire P, Pride NB, *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8: 1398–1420.
13. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Perslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Official statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
14. Quanjer PH, ed. Standardized lung function testing. Report Working Party "Standardization of lung function tests". European Community for Coal and Steel, Luxembourg. *Bull Eur Physiopathol Respir* 1983; 19 (Suppl. 5): 1–95.
15. 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.
16. van Noord JA, Smeets J, Clement J, van de Woestijne KP, Demedts M. Assessment of reversibility of airway obstruction. *Am J Respir Crit Care Med* 1994; 150: 551–554.
17. Hellinckx J, van Noord JA, Gubbelmans HLL, Demedts M. Pitfalls in the interpretation of bronchodilator response. *Am J Respir Crit Care Med* 1997; 155: A599.
18. Cazolla M, Vinciguerra A, Di Perna F, Matera MG. Early reversibility to salbutamol does not always predict bronchodilatation after salmeterol in stable chronic obstructive pulmonary disease. *Respir Med* 1998; 92: 1012–1016.
19. British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. Guidelines Group of the Standards of Care Committee. *Thorax* 1997; 52: S1–S28.
20. Anonymous. Standaard diagnostiek van astma bronchiale en COPD. *Pulmoscript* 1994; 5: 31–46.
21. Wegener T, Hedenström H, Melander B. Rapid onset of action of inhaled flormoterol in asthmatic patients. *Chest* 1992; 102: 535–538.
22. Marini JJ, Lakshminarayan S. The effect of atropine inhalation in "irreversible" chronic bronchitis. *Chest* 1980; 77: 591–596.
23. Hay JG, Stone P, Carter J, *et al*. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992; 5: 659–664.
24. Belman MJ, Botnick CB, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 967–975.
25. Greening A. Pharmacotherapy in COPD. *Eur Respir Rev* 1997; 7: 243–248.
26. Anthonisen NR, Wright EC, Hodgkin JE, *et al*. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
27. Chanez P, Vignola AM, O'Shaugnessy T, *et al*. Corticoid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997; 155: 1529–1534.
28. Berger RB, Smith D. Acute postbronchodilator changes in pulmonary function parameters in patients with chronic airways obstruction. *Chest* 1988; 93: 541–546.
29. Börgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. *Am J Respir Crit Care Med* 1996; 153: 1636–1640.