Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD

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ABSTRACT: It has been shown that patients with chronic obstructive pulmonary disease (COPD) develop dynamic hyperinflation (DH), which contributes to dyspnoea and exercise intolerance. Formoterol, salmeterol and oxitropium have been recommended for maintenance therapy in COPD patients, but their effect on DH has only been assessed for salmeterol.

The aim of the present study was to compare the acute effect of four inhaled bronchodilators (salbutamol, formoterol, salmeterol and oxitropium) and placebo on forced expiratory volume in one second, inspiratory capacity, forced vital capacity and dyspnoea in COPD patients. A cross-over, randomised, double-blind, placebo-controlled study was carried out on 20 COPD patients.

Patients underwent pulmonary function testing and dyspnoea evaluation, in basal condition and 5, 15, 30, 60 and 120 min after bronchodilator or placebo administration.

The results indicate that in chronic obstructive pulmonary disease patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnoea sensation at rest. For all bronchodilators used, inspiratory capacity reversibility should be tested at 30 min following the bronchodilator. On average, formoterol elicited the greatest increase in inspiratory capacity than the other bronchodilators used, though the difference was significant only with salmeterol and oxitropium. The potential advantage of formoterol needs to be tested in a larger patient population.
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In patients with chronic obstructive pulmonary disease (COPD), bronchodilator reversibility testing is used routinely to exclude a significant asthmatic component. International guidelines recommend that bronchodilator responsiveness be evaluated by the change in forced expiratory volume in one second (FEV1) greater than a cut-off level, calculated in different ways [1, 2]. However, in COPD patients, exercise tolerance and dyspnoea are poorly correlated with FEV1 [3–5]. Recently, it has been shown that in COPD patients, indices related to dynamic hyperinflation (DH), such as inspiratory capacity (IC), are both reproducible [6] and more closely related to exercise tolerance and dyspnoea than FEV1 and forced vital capacity (FVC) [3, 6–11]. PELLEGRINO et al. [11] demonstrated that changes in FEV1 frequently fail to detect significant functional responses to bronchodilators in patients with chronic airflow obstruction. Furthermore, an increase in IC after bronchodilator administration implies a reduction in DH, which is the main cause of reduced exercise capacity and dyspnoea [7–12]. Accordingly, an increase in IC should represent the main target for bronchodilator therapy.

The effect of bronchodilator administration on IC and other ventilatory variables in COPD patients has been described in several publications [8, 10, 13–18]. However, bronchodilator-induced changes in IC were correlated with the concurrent changes in dyspnoea sensation in COPD patients at rest in only one study [14]. Surprisingly, the changes in IC (ΔIC) correlated poorly with those in dyspnoea. In contrast, the latter correlated well with the forced inspiratory volume in one second. However, the poor correlation between ΔIC and improvement of dyspnoea is probably due to the fact that patients were not separated into those with and without baseline DH; only the latter exhibits a significant reduction of DH after bronchodilator administration, reflected by decreased functional residual capacity (FRC) and increased IC [19].

The purpose of the present study was to evaluate the acute effect of four inhaled bronchodilators (salbutamol, formoterol, salmeterol and oxitropium) and placebo on IC, FEV1, FVC, FEV1/FVC and dyspnoea at rest in COPD patients, and to assess the correlation between the changes in these variables. The patients were separated into two groups, those with normal and those with reduced IC (<80%

predicted), because the effect of bronchodilators on IC should be more pronounced in the latter group [19]. Long-acting bronchodilators were included because present international guidelines on COPD management [20] suggest treatment with long-acting bronchodilators, such as long-acting β_2-agonists (formoterol and salmeterol) or anticholinergic drugs (oxitropium).

Methods

Subjects

Twenty consecutive COPD outpatients (14 males) were enrolled. Inclusion criteria were: >35 yrs of age, current or former smoker (>10 pack-yrs) and a diagnosis of COPD as defined by the American Thoracic Society (ATS) [21], an $FEV1/FVC$ ratio of <70%, and a baseline severity of breathlessness of at least grade 1 (short of breath when hurrying on a level or walking up a slight hill) according to the modified Medical Research Council (MRC) dyspnoea scale [22]. Exclusion criteria included: unstable respiratory status within the previous 4 weeks, a known history of asthma or chronic respiratory disease other than COPD, any clinically significant concurrent disease, and a change in medication for COPD within the 4 weeks prior to the screening visit. Patients′ anthropometric characteristics and lung function data are given in table 1. Each patient gave informed consent and the study protocol was approved by the local ethics committee.

Study design

A cross-over, randomised, double-blind, placebo-controlled study was carried out on 20 consecutive patients with stable COPD. On 5 separate days (within a span of no more than 10 days between the first and the last study day), patients underwent pulmonary function testing and dyspnoea evaluation, under basal conditions and after bronchodilator administration. Standard drug dosage, as suggested by international guidelines for COPD management [20], was used: two salbutamol inhalations (200 µg); one formoterol fumarate inhalation (12 µg) plus one placebo inhalation; two salmeterol xinafoate inhalations (50 µg); two oxitropium bromide inhalations (200 µg); and two placebo inhalations.

The drugs were administered randomly. In addition, the placebo study was performed simultaneously with formoterol in all patients. Drugs were administered by metered-dose inhaler using a blind holding chamber (Fluspacer®; Menarini srl, Florence, Italy) with a mouthpiece.

Methods

In the basal condition and 5, 15, 30, 60 and 120 min after bronchodilator administration, FEV1, IC, FVC and dyspnoea were assessed. The patients were investigated in the morning in a sitting position. None had received inhaled short-acting β_2-agonists for 8 h, or long-acting β_2-agonists or oxitropium bromide for 24 h, before the study. None of the patients were receiving oral β_2-agonists, theophylline or systemic corticosteroids. Spirometric measurements

Table 1. – Anthropometric characteristics and baseline respiratory data of chronic obstructive pulmonary disease patients

	All patients	Patients with basal IC <80% pred	Patients with basal IC >80% pred	p-value
Patients n	20	12	8	
Sex M/F	14/6	9/3	5/3	0.92
IC % pred	74±3	64±2	89±2	<0.001
Age yrs	65±2	66±2	64±3	0.57
Height cm	166±2	167±2	164±3	0.39
Weight kg	73±2	72±3	74±4	0.68
BMI kg·m^{-2}	26.5±1.1	27.4±1.2	25.3±2.3	0.39
FEV1 % pred	52±3	46±3	60±4	0.01
FVC % pred	79±4	76±5	83±7	0.41
FEV1/FVC % pred	44±3	41±3	49±4	0.12
FRC % pred	134±3	145±8	118±9	0.04
TLC % pred	110±4	115±4	103±6	0.10
Pa,O$_2$ mmHg	74±2	72±2	77±2	0.04
Pa,CO$_2$ mmHg	40±2	41±1	38±2	0.16
MRC dyspnoea score	1.9±0.3	2.3±0.3	1.5±0.3	0.04
Baseline VAS score % (range)	31±4 (10–61)	38±4 (10–61)	21±3 (11–44)	0.03
Current smoker n	9	5	4	0.92
Pack-yrs	46±7	53±6	37±3	0.04

Data are presented as mean±SEM unless otherwise stated. p-Values pertain to differences between subjects with basal inspiratory capacity (IC) higher and lower than 80% predicted. M: male; F: female; BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced expiratory capacity; FRC: functional residual capacity; TLC: total lung capacity; Pa,O$_2$: arterial oxygen tension; Pa,CO$_2$: arterial carbon dioxide tension; MRC: Medical Research Council; VAS: visual analogue scale (standard version).

were performed using a constant volume/pressure body plethysmograph (Elite DL; MedGraphics®, St Paul, MN, USA), while mouth and box flow were measured through a pneumotachograph (Elite DL; MedGraphics®). Volume was obtained by integrating the flow signal. IC was determined by a slow manoeuvre (slow inspiration until maximum volume after regular tidal breathing), while FRC was determined by asking patients to pant at a frequency of <1 Hz against a closed shutter [23]. This manoeuvre was followed by a slow manoeuvre to obtain total lung capacity (TLC) and residual volume. Reference values from the European Community for Steel and Coal [24] were used. For IC, predicted values were calculated as the difference between predicted TLC and predicted FRC. For analysis, the highest FEV1 and the highest FVC were selected from three acceptable expiratory manoeuvres, according to the ATS guidelines [2].

The patients were classified as responders and nonresponders to bronchodilators according to a change in FEV1 of more or less than 10% of the predicted value, as recommended by the European Respiratory Society (ERS) consensus statement [1]. Changes in perception of dyspnoea were assessed with the visual analogue scale (VAS) method (bipolar transitional version), previously used to determine the effects of salbutamol on dyspnoea in COPD patients at rest [14, 25]. The VAS used was a 20-cm long horizontal line labelled "very much worse" at the left end and "very much better" at the right end, and "no change" in the middle. Care was taken that the patients understood the scale, i.e. the three possibilities of improvement, no change and worsening of breathlessness. All subjects were instructed to mark the VAS line at any point they felt appropriate. Ratings (ΔVAS %) were expressed as the percentage of the distance between zero and +100% (very much better), and zero and -100% (very much worse). Patients were instructed to rate only breathlessness, ignoring other sensations such as cough and chest tightness. The standard VAS was used to assess the baseline dyspnoea before bronchodilator administration (range 0–100%).

Statistical analysis

Data are presented as mean±SEM. Data analysis was carried out on the whole group of patients, and in subjects stratified with and without basal IC reduction (80% pred as cut-off point). Analysis of variance was used for repeated measures and t-test with Bonferroni correction for multiple comparison. The ΔVAS scores were analysed both before and after correction for placebo score. The corrected values represented the iso-time difference between ΔVAS (%) after drug administration and ΔVAS (%) after placebo inhalation. The ΔVAS (%) dyspnoea scores were tested nonparametrically (Friedman test) to minimise assumptions about distribution of data. Correlations were established using the least squares method. As the correlation coefficient (r) increases towards unity, error constitutes a smaller portion of the observed

value: r<0.4 indicates poor reliability, r of 0.4–0.75 fair to good reliability, and r>0.75 excellent reliability [26]. This analysis was carried out using the ΔVAS scores as dependent variables; the possible independent variables included FEV1, IC, FVC and FEV1/FVC. The effect of different drugs on giving significant bronchodilation in terms of changes in FEV1, IC, FVC and FEV1/FVC was compared by means of the Chi-squared test for categorical variables with Yates' correction. A p-value of <0.05 was considered significant.

Results

Table 1 shows the anthropometric and lung function characteristics of the patients (all patients stratified into two groups: with or without a baseline reduction in IC with cut-off at 80% pred). The 12 patients with baseline IC reduction showed a greater exposure to smoke (pack-yrs) and disease severity (lower arterial oxygen tension (P_{a,O_2}) and FEV1 and higher FRC; p<0.05). Moreover, patients with basal IC reduction reported a greater chronic MRC dyspnoea score (p=0.04) and baseline VAS score (p=0.03). According to ERS criteria (ΔFEV1 >10% pred with salbutamol), only six patients were responders.

The changes in FEV1 % pred, IC % pred and ΔVAS score (%) after bronchodilator and placebo administration are depicted in figures 1, 2 and 3. There was no significant difference in baseline FEV1 and IC in the 5 different study days. Overall, while placebo had no effect on FEV1 and IC, all bronchodilators used caused significant increases in the variables within 5 min of administration, except for salmeterol and oxitropium, which caused a significant increase of IC, 15 and 30 min after drug administration, respectively (figs. 1 and 2). After 30 min, all bronchodilators reached a maximum increase in FEV1 and IC (with no further significant improvement by 60 and 120 min), as shown in figures 1 and 2. In terms of FEV1, 5 and 15 min after inhalation, formoterol showed a greater improvement than salmeterol and oxitropium but not salbutamol. After 30, 60 and 120 min, all β2-agonists led to changes in FEV1 significantly greater than oxitropium; formoterol was more effective than salmeterol at 30 min (p=0.01). In terms of IC, the overall patient analysis showed that formoterol elicited changes significantly higher than oxitropium, both 15 and 30 min after bronchodilator inhalation, and higher than salmeterol after 30 min.

Tables 2 and 3 show the changes in IC and FEV1 (expressed as L, % pred and % control) after 30 min in all patients and two subgroups (patients with and without a basal IC reduction). There was essentially no difference if data were expressed in absolute terms (L) or as % pred or % control. While there was little or no difference in FEV1 response between the two subgroups of patients, the increase in IC was greater with all bronchodilators in the patients with reduced baseline IC. However, the difference was only significant for formoterol. In patients with reduced
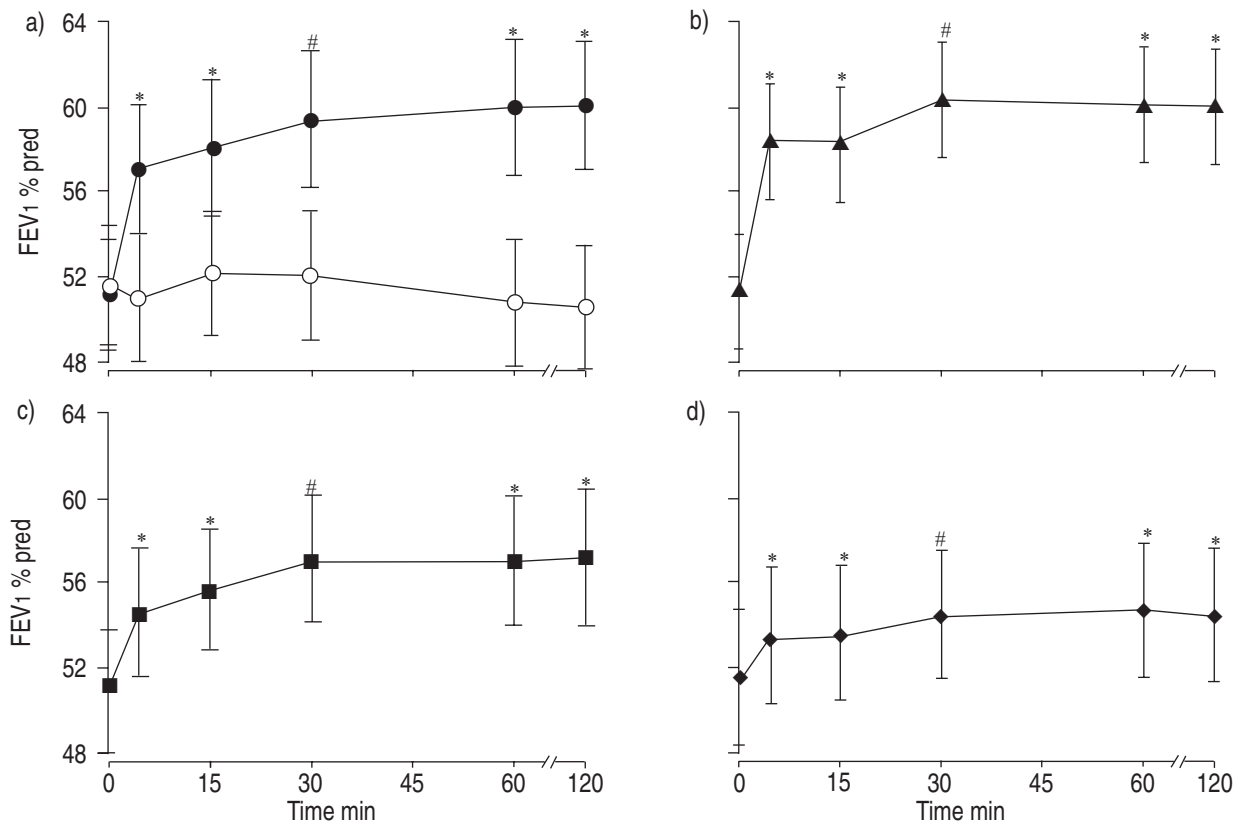
Fig. 1. – Mean±SEM change in forced expiratory volume in one second (FEV1) % predicted after administration of a) salbutamol (●) and placebo (○), b) formoterol (▲), c) salmeterol (■) and d) oxitropium (◆). *: p<0.05 compared with baseline. #: time at which plateau was reached, i.e. no further significant change.

baseline IC, formoterol also elicited a more marked increase in IC than the other bronchodilators. In fact, the difference with both salmeterol and oxitropium was significant (p<0.05). This was not the case in terms of FEV1 response. By 30 min after drug administration, a plateau response was reached for ΔFVC and maintained for another 90 min. Table 4 shows the changes in FVC 30 min after bronchodilator administration. Salbutamol, formoterol and salmeterol elicited ΔFVC values significantly higher (p<0.05) than oxitropium in all patient analysis and in both subgroups. There was little or no difference in FVC response between the two subgroups of patients. The FEV1/FVC ratio was not significantly changed after either placebo or any bronchodilator used.

After 30 min of drug administration, 12 patients had a ΔFEV1 of >10% pred with one or more of the bronchodilators used. Half of these patients had a baseline IC of <80% pred, while the other 50% had a baseline IC of >80% pred. In contrast, only two of 12 patients who had a ΔIC of >12% control [19] had a baseline IC of <80% pred.

On average, there was no significant difference in baseline (prebronchodilators) VAS score (standard VAS) between the values obtained on the 5 days in which measurements were made. There was, however, some intrasubject variation that was taken into account when assessing the effects of the four different

bronchodilators through use of the bipolar transitional VAS [20, 22]. The changes in bipolar transitional VAS score are shown in figure 3; maximal ΔVAS (%) score reduction was achieved 60 min after bronchodilator and placebo intake. In the 5 different study days, there was no significant difference in basal VAS score (standard version) evaluated before bronchodilator administration. All drugs tested induced a dyspnoea improvement significantly higher than placebo. After 30 min of bronchodilator administration, ΔVAS (%) was higher (through not significantly) for salbutamol and formoterol than salmeterol and oxitropium. On average, in the patients with reduced baseline IC, the decrease of dyspnoea was more marked (though not significantly) than in the patients with basal IC within the normal limits.

As shown in figure 4, 30 min after bronchodilator administration there was a low (r=0.52) correlation between the improvement in dyspnoea (ΔVAS score with placebo correction) and ΔFEV1 only in patients with a basal IC of <80% pred. In these patients there was a close correlation (r=0.70) between the improvement in dyspnoea and ΔIC (fig. 5). In contrast, in the patients with basal IC within the normal limits, this correlation, though significant, was poor. After administration of all bronchodilators the changes of FVC and FEV1/FVC were not correlated significantly to the concurrent changes in ΔVAS scores.
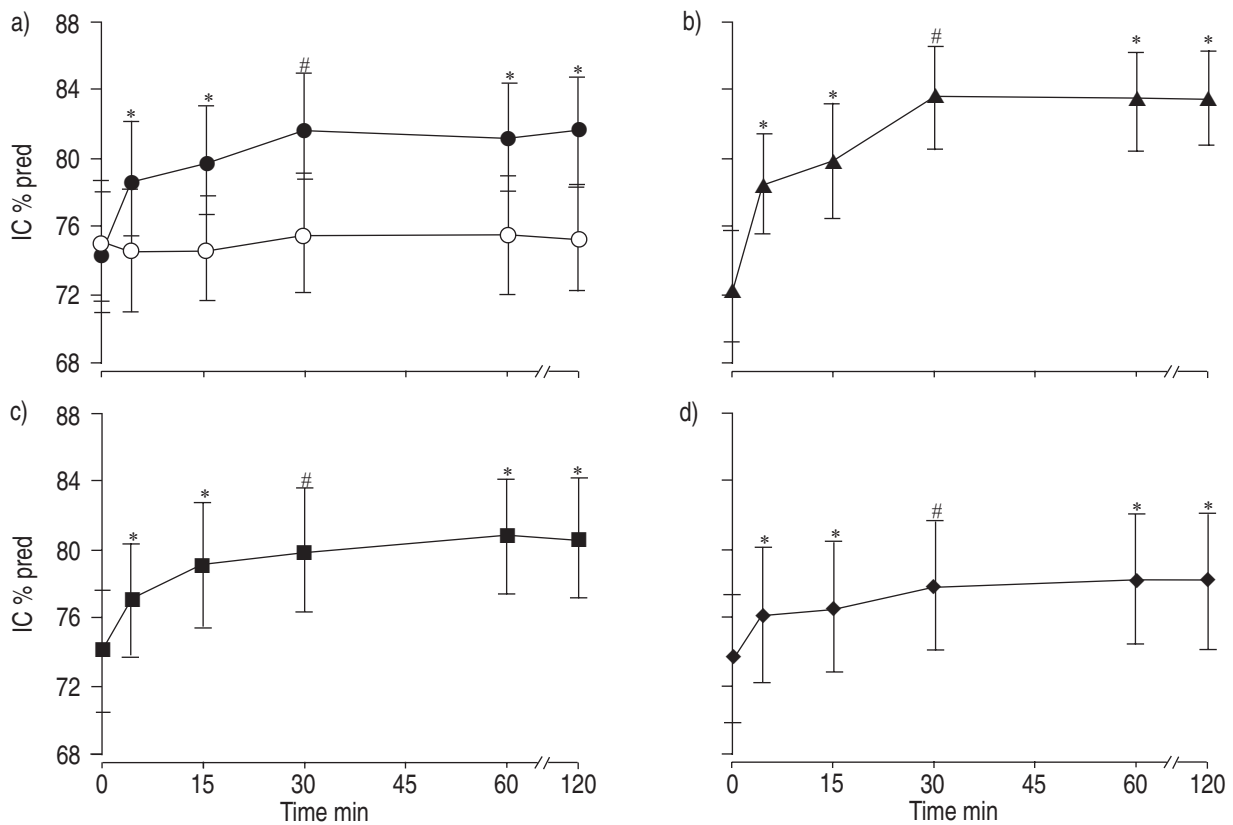
Fig. 2. – Mean±SEM change in inspiratory capacity (IC) % predicted after administration of a) salbutamol (●) and placebo (○), b) formoterol (▲), c) salmeterol (■) and d) oxitropium (◆). *: p<0.05 compared with baseline. #: time at which plateau was reached, *i.e.* no further significant change.

Discussion

The main new findings of the present investigation are that in COPD patients with decreased baseline IC there was: 1) a much greater increase of IC after bronchodilator administration, which correlated closely with the improvement of dyspnoea sensation at rest; 2) IC changes reached a plateau 30 min after drugs inhalation, and thus, for all bronchodilators used, IC reversibility should be tested 30 minutes following administration; and 3) at standard recommended dosage, formoterol elicited the greatest average increase in IC among the four bronchodilators used.

In line with a previous report [3], patients with a reduced baseline IC had a significantly lower $P\mathrm{a,O_2}$ and higher FRC than patients with baseline IC within the normal limits (p=0.04). Moreover, these patients also had a higher MRC dyspnoea score (p=0.04) and a higher baseline VAS score (p=0.03) (table 1).

TANTUCCI et al. [19] assessed the effect of salbutamol on IC and FRC in COPD patients stratified into two groups, namely with and without tidal expiratory flow limitation (EFL) measured using the negative expiratory pressure method. They reasoned that DH was more likely to be present in patients with tidal EFL, who should accordingly exhibit a greater improvement of DH after bronchodilator administration than patients without EFL. In line with this prediction,

they found that EFL patients exhibited a significant increase in IC and decrease in FRC (p<0.01), while this was not the case in the non-EFL patients. In the present study, the authors stratified the patients according to reduced or normal IC, based on the observation that in patients with tidal EFL, the IC is usually reduced below 80% pred [3]. There are, however, some problems inherent in both of the above methods of patient stratification.

Although tidal EFL is the most common cause of DH in COPD patients, its presence does not predict the actual degree of hyperinflation. Indeed, if the available expiratory flows are sufficient to sustain resting ventilation, there is no need for the end-expiratory lung volume to increase even if tidal EFL is present [3]. Furthermore, prediction of the normal values of IC is a problem in elderly individuals; the predicted normal values of IC are presently obtained as difference between predicted TLC and predicted FRC. Nevertheless, in view of the fact that measurement of IC is simple and reliable, it should represent a useful marker as to when important changes in lung volume, associated with improvements in resting breathlessness, are likely to occur after bronchodilation administration [27]. The improvement of IC after bronchodilator administration has been shown to predict the improvement of exertional dyspnoea and exercise tolerance in COPD patients [8, 10]. Recently, in a large population of COPD patients, NEWTON et al.
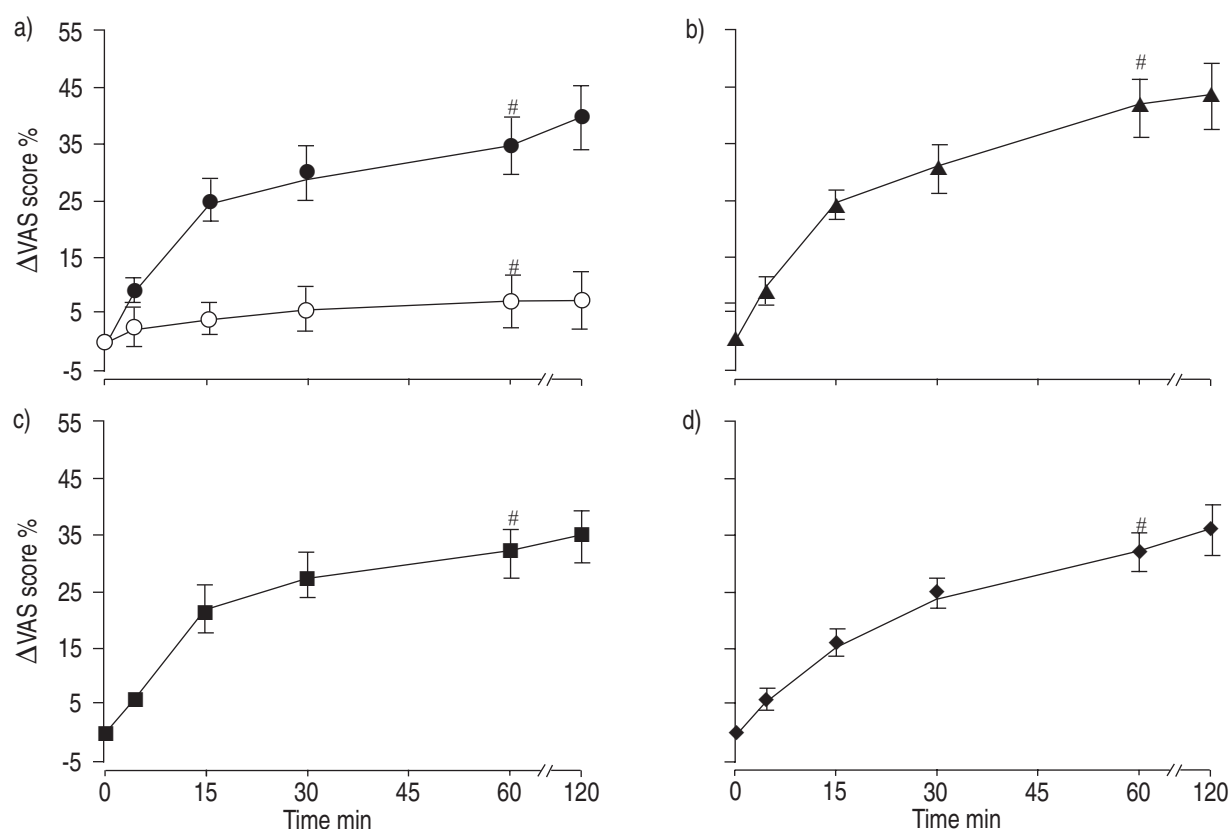
Fig. 3. – Mean±SEM change in visual analogue scale (VAS) % after administration of a) salbutamol (●) and placebo (○), b) formoterol (▲), c) salmeterol (■) and d) oxitropium (◆). #: time at which plateau was reached, *i.e.* no further significant change.

[17] found that the increase of IC after salbutamol administration (200 μg) was more pronounced in subjects with more severe hyperinflation. Surprisingly, however, they used TLC as a marker of hyperinflation rather than, more appropriately, FRC or IC.

The above studies, together with other reports [8, 12, 15–18], have clearly shown that standard measurement of ΔFEV_1 after bronchodilator administration does not uncover significant volume responses that may be more relevant in terms of bronchodilator therapy of COPD patients.

In the present study, it was found that the increase of IC after bronchodilator administration correlated more closely with the improvement of dyspnoea sensation in patients with reduced baseline IC (r=0.70) than in subjects with baseline IC within normal limits (r=0.38; fig. 5). In fact, in patients with reduced baseline IC, the bronchodilators elicited a greater increase of IC than in the patients with baseline IC within normal limits. In a study of 61 COPD patients, TAUBE *et al.* [14] found that the correlation coefficient between ΔVAS (%) and ΔIC

Table 2. – Increases in forced expiratory volume in one second (FEV1) and inspiratory capacity (IC) 30 min after drug inhalation

	Bronchodilator	All patients	Patients with basal IC <80% pred	Patients with basal IC >80% pred	p-value
Subjects			12	8	
ΔFEV_1	Salbutamol	8.2±1.0 (0.20±0.02)	7.0±0.8[#] (0.18±0.02)	10.1±1.3[#] (0.24±0.02)	0.14 (0.20)
	Formoterol	9.1±0.9 (0.24±0.03)	8.6±0.9[#] (0.23±0.02)	9.8±1.1[#] (0.27±0.04)	0.54 (0.56)
	Salmeterol	6.2±0.8 (0.17±0.02)	6.3±0.9 (0.18±0.02)	6.0±0.6 (0.16±0.02)	0.83 (0.65)
	Oxitropium	2.8±0.6 (0.07±0.02)	3.2±0.7 (0.09±0.02)	2.3±0.5 (0.05±0.01)	0.49 (0.29)
ΔIC	Salbutamol	7.4±2.1 (0.22±0.06)	10.1±2.1 (0.29±0.06)	3.3±1.8 (0.10±0.05)	0.10 (0.13)
	Formoterol	11.0±1.7 (0.33±0.05)	14.0±1.8[¶] (0.42±0.06)	6.4±0.8 (0.18±0.03)	0.02* (0.03)
	Salmeterol	5.9±1.9 (0.17±0.06)	8.2±2.2 (0.25±0.07)	2.5±1 (0.06±0.03)	0.15 (0.12)
	Oxitropium	4.3±1.6 (0.14±0.05)	6.2±1.7 (0.20±0.05)	1.3±1.3 (0.04±0.04)	0.14 (0.13)

Data are presented as mean±SEM % predicted (L). *: p<0.05 relative to patients with basal IC >80%. #: significant difference of salbutamol and formoterol to oxitropium in both subgroups of patients (p<0.05). ¶: formoterol shows values significantly higher (p<0.05) than salmeterol and oxitropium only in patients with basal IC <80% pred.

Table 3. – Increases in forced expiratory volume in one second (FEV1) and inspiratory capacity (IC) 30 min after drug inhalation

	Bronchodilator	All patients	Patients with basal IC <80% pred	Patients with basal IC >80% pred	p-value
Subjects			12	8	
ΔFEV1	Salbutamol	16.0±1.8[#]	15.2±1.7[#]	17.0±1.9[#]	0.62
	Formoterol	18.4±2.1[#]	19.0±2.2[#]	17.4±2.1[#]	0.72
	Salmeterol	13.3±2.3	15.4±2.7	10.1±1.0	0.26
	Oxitropium	6.7±1.7	8.5±2.0	3.8±0.7	0.18
ΔIC	Salbutamol	11.4±3.3	16.1±4.7	4.2±2.1	0.07
	Formoterol	16.5±3.0[¶]	22.5±4.1[¶]	7.5±0.9	0.01*
	Salmeterol	9.0±3.2	13.3±4.8	2.4±1.2	0.09
	Oxitropium	6.5±2.4	10.0±3.4	1.2±1.4	0.07

Values are means±SEM % control. *: $p < 0.05$ relative to patients with basal IC >80%. [#]: significant difference of salbutamol and formoterol to oxitropium in overall patient analysis and in both subgroups ($p < 0.05$). In overall patient analysis, formoterol was more effective than salmeterol ($p < 0.05$). [¶]: formoterol shows values significantly higher ($p < 0.05$) than salmeterol and oxitropium in overall patient analysis and in patients with basal IC <80% predicted, but not in patients with basal IC >80% pred.

Table 4. – Changes in forced vital capacity (FVC) 30 min after drug inhalation

	Bronchodilator	All patients	Patients with basal IC <80% pred	Patients with basal IC >80% pred	p-value
Subjects			12	8	
ΔFVC	Salbutamol	9.1±0.6[#] (0.30±0.02)	8.7±0.6[#] (0.28±0.02)	9.8±0.7[#] (0.32±0.02)	0.42 (0.41)
	Formoterol	10.3±0.8[#] (0.34±0.03)	10.2±0.8[#] (0.33±0.03)	10.5±1.0[#] (0.34±0.03)	0.85 (0.91)
	Salmeterol	8.0±0.7[#] (0.26±0.02)	8.3±0.8[#] (0.27±0.03)	7.4±0.5[#] (0.25±0.02)	0.51 (0.65)
	Oxitropium	4.1±0.8 (0.13±0.03)	4.9±0.8 (0.16±0.03)	2.8±0.5 (0.09±0.02)	0.19 (0.22)

Data are presented as mean±SEM % predicted (L); [#]: salbutamol, formoterol and salmeterol show values significantly higher ($p < 0.05$) than oxitropium in overall patient analysis and in both subgroups. p-Value relative to patients with basal IC >80%.

(% control) was low (r=0.25, p<0.05). However, they did not stratify their patients according to severity of baseline DH. In fact, the result of the present study shows that such stratification is fundamental because only patients with reduced baseline IC exhibited a good correlation between changes in dyspnoea and ΔIC (fig. 5).

The changes in dyspnoea after bronchodilator use also correlated significantly with ΔFEV1 in the patients with reduced baseline IC (fig. 4), but the correlation coefficient was lower than that with ΔIC (0.52 versus 0.70). No significant correlation was found in the changes in dyspnoea to ΔFVC and Δ(FEV1/FVC).

In the present study, the authors assessed the effect of bronchodilators only on dyspnoea at rest. In a recent study, Boni et al.[8] showed that in COPD patients during exercise (33% of the maximal predicted workload) the changes in dyspnoea (conventional Borg scale) and ΔIC (% pred) are significantly correlated (r=0.69; p<0.05).

In line with previous reports [8, 9, 13, 14], it is likely that the improvement of dyspnoea sensation after bronchodilator administration in COPD is due to reduced DH with a concurrent decrease in the inspiratory threshold loading (reduced intrinsic positive end-expiratory pressure and inspiratory flow resistance), and improved mechanical advantage of the inspiratory muscles. Hatipoglu et al. [27] tested the hypothesis that in COPD patients the decrease in dyspnoea after salbutamol inhalation might be due in part to increased diaphragmatic contractility, but concluded that the reduction of dyspnoea occurred more as a result of improvement of the length/tension relationship of the diaphragm rather than increased contractility per se.

The present results indicate that, on average, formoterol induced the greatest increase of IC among the four bronchodilators studied, though at 30 min the difference was significant (p<0.05) only with salmeterol and oxitropium. It should be stressed that these experiments were limited to 120 min after bronchodilator administration, and in previous studies in COPD patients, it was found that early bronchodilator reversibility in terms of ΔFEV1 does not always predict long-term response [28, 29]. Ayers et al. [13] investigated the effectiveness of salmeterol and ipratropium bromide on exertional dyspnoea and IC at 1 and 6 h after drug inhalation, and found that at 1 h the changes in IC were similar with salmeterol and ipratropium bromide, while after 6 h, ΔIC was significantly higher with salmeterol than ipratropium (+19 and +9% of control, respectively). In the present study, salmeterol elicited the highest increase in IC at 1 h (10% of control).

In the present study, all four bronchodilators elicited a significant increase of FEV1 after 5 min of administration and a peak response was achieved by
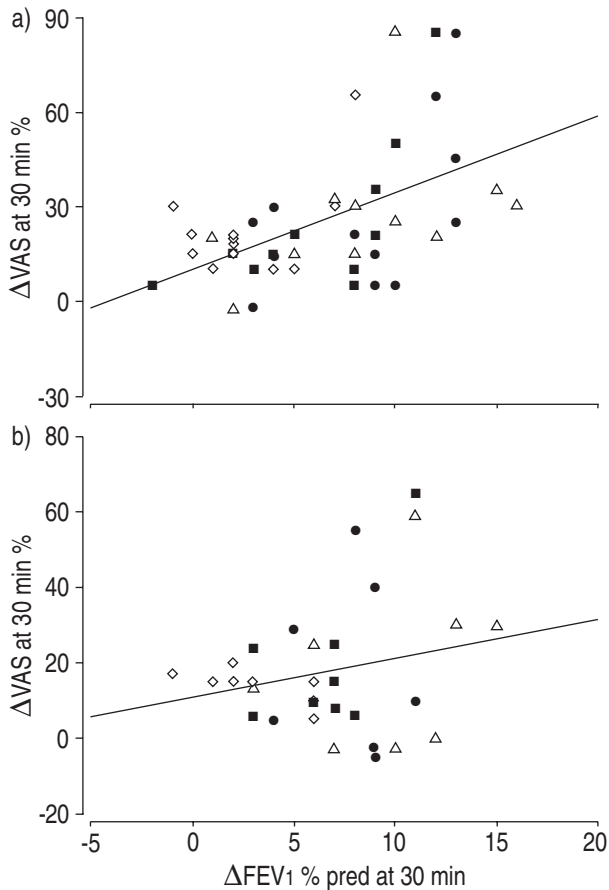
Fig. 4. – Relationship of changes in visual analogue scale (VAS) with placebo correction (%) with changes in forced expiratory volume in one second (FEV1) 30 min after bronchodilation in patients with baseline inspiratory capacity a) lower (r=0.52; r^2=0.27; p<0.001), and b) higher (r=0.21; r^2=0.05; p=0.26) than 80% predicted. ●: salbutamol; △: formoterol; ■: salmeterol; ◇: oxitropium.

Fig. 5. – Relationship of changes in visual analogue scale (VAS) with placebo correction (%) with changes in inspiratory capacity (IC) 30 min after bronchodilation in patients with baseline IC a) lower (r=0.70; r^2=0.48; p<0.001), and b) higher (r=0.38; r^2=0.15; p<0.05) than 80% predicted. ●: salbutamol; △: formoterol; ■: salmeterol; ◇: oxitropium.

30 min (fig. 1). In contrast, salbutamol and formoterol elicited a significant increase of IC 5 min after administration, while salmeterol and oxitropium showed a significant IC increase only after 15 and 30 min, respectively. In terms of FEV1, a faster onset of action has been reported for salbutamol and formoterol than salmeterol and oxitropium in COPD patients [30]. In line with previous results [17], these data show that there is a dichotomy in the time course of changes in FEV1 and IC after bronchodilator administration. It should also be noted that the plateau increase of ΔVAS was reached 60 min after bronchodilator administration compared with 30 min for ΔIC and ΔFEV1. This probably reflects a central adaptation to respiratory unloading due to reduced DH.

In conclusion, the present results indicate that in chronic obstructive pulmonary disease patients with decreased baseline IC there was a greater increase of inspiratory capacity (reduced dynamic hyperinflation) after bronchodilator administration than in patients with inspiratory capacity within normal limits, which closely correlated with the improvement in dyspnoea sensation at rest. In contrast, the response in terms of
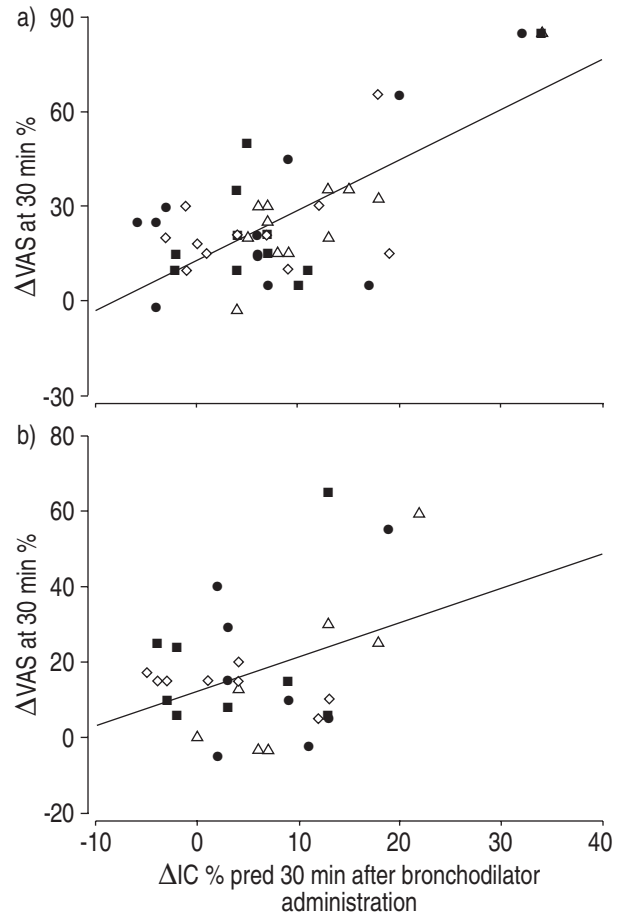
change in forced expiratory volume in one second and forced vital capacity was similar between the two groups of patients. Although the initial rate of change of inspiratory capacity was faster with salbutamol and formoterol than salmeterol and oxitropium, 30 min after drug administration a plateau response was achieved with all four drugs tested and was maintained for another 90 min; inspiratory capacity reversibility for all bronchodilators used should be tested 30 min following the drug. At standard recommended dosage, formoterol elicited a greater average increase in inspiratory capacity than the other bronchodilators used, although the difference was only significant with salmeterol and oxitropium. The potential advantage of formoterol over the other drugs tested needs to be further evaluated in a larger patient population.

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