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Salbutamol delivery during non-invasive mechanical ventilation in patients with chronic obstructive pulmonary disease: a randomized, controlled study

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Abstract *Objective*: We investigated the clinical response to equivalent doses of salbutamol delivered, via metered dose inhaler (MDI) during non-invasive mechanical ventilation (NIMV-MDI), during spontaneous breathing using a spacer (MDI-Spacer), and also during intermittent positive pressure breathing (IPPB).
Setting: A respiratory intensive care unit.
Design: Prospective, randomized, and placebo-controlled study.
Patients: Eighteen stable patients with chronic obstructive pulmonary disease (mean FEV_1 = 38.5 ± 8.8 % predicted).
Results: Overall salbutamol administration induced, compared to placebo, a significant improvement in FEV_1, irrespective of the mode of administration (+7.9 ± 7.1 % or +108 ± 91 ml for IPPB, +9.6 ± 8.8 % or 112 ± 67 ml for MDI-NIMV (inspiratory pressure = 14.3 ± 1.8 cmH_2O; expiratory pressure = none), and +10.8 ± 11.4 % or 119 ± 114 ml for MDI-Spacer, respectively). ΔFVC significantly increased from placebo only in MDI-NIMV (+214 ± 182 ml $P = 0.02$). A second set of experiments performed in eight patients to ascertain the possible effect of NIMV on pulmonary function tests, showed a significant improvement from baseline values in FVC both after the delivering of placebo or salbutamol via NIMV-MDI (+206 ± 147 ml and 208 ± 145, respectively). FEV_1 significantly increased only after salbutamol. No changes in gas exchange were observed after bronchodilator delivery.
Conclusions: We show that delivery of bronchodilators via MDI with a spacer chamber during NIMV is feasible and induces a significant bronchodilator effect compared to placebo, even though it may be slightly less effective than the classical delivery system (MDI-Spacer).

Keywords Non-invasive ventilation · COPD · Salbutamol

Introduction

When acute respiratory failure occurs in patients with exacerbations of chronic obstructive pulmonary disease (COPD), or a severe acute asthma attack, the use of therapeutic aerosols is usually attempted before instituting mechanical ventilation [1, 2]. Even if mechanical ventilation cannot be avoided, medical treatment should not be stopped, since it has repeatedly been shown, for example in patients affected by COPD, that bronchodilators can significantly reduce airway obstruction and hyperinflation, thereby diminishing the mechanical load imposed on the respiratory muscles [3, 4, 5]. Non-invasive mechanical ventilation (NIMV) is also a widely used technique to treat episodes of acute hypercapnic respiratory failure in several clinical contexts [6]. The scenario of bronchodilator use during NIMV may differ from that in intubated patients, since the use

of an "open circuit" may interfere with drug delivery to the patient. Indeed, while in most of the studies dealing with intubated patients, drug delivery was performed during volume controlled ventilation, this mode is seldom used during NIMV. The feasibility of delivering beta-adrenergic agents aerosol during NIMV was assessed only in patients with acute asthma using, as a measure of bronchodilation, the peak flow rate [7] which may be more dependent on the patient's effort than the standard pulmonary function test [8].

A randomized placebo-controlled trial of bronchodilator delivery during NIMV is very difficult to perform in an acute setting, partly because there might be difficulty in returning to baseline between trials, and especially because in the first few hours of an episode of acute respiratory failure, not all subjects may be co-operative enough to perform the pulmonary function tests adequately. We therefore designed a prospective, randomized study in severe, but stable, COPD to compare the feasibility and efficacy of salbutamol delivery during NIMV, with the response achieved, during spontaneous breathing, by aerosol delivery via MDI or by nebulized solution delivered with intermittent positive pressure breathing (IPPB).

Indeed, since the cooperation of the patients is likely to be different when in stable conditions or during an episode of acute respiratory failure, we used the so called volume assured pressure support (VAPS) as the ventilatory modality [9]. This ensures a "fixed" tidal volume even during a pressure-assisted ventilation and thus may minimize the potential differences encountered between acute and stable patients.

Material and methods

Twenty-one clinically stable in-patients with COPD [10] were enrolled in the first set of experiments and eight in the second set. Criteria for enrollment were: age < 75 years, $FEV_1/FVC < 60\,\%$, $FEV_1 < 1.5$ l or 50 % predicted. The patients' characteristics pertinent to the study are given in Table 1. All the patients received a short- or long-acting β2-agonist as a part of their chronic therapy. Patients gave written informed consent to their participation in the study which was approved by our Ethics Committee.

Arterial blood from the radial artery was measured using an automatic analyzer (ABL Radiometer, Copenhagen, Denmark).

Pulmonary function tests (PFT) were performed using a water sealed spirometer (Biomedin, Padova, Italy). The best of three consecutive measurements was considered for data analysis.

Systemic blood pressure and heart rate were recorded with the patient sitting.

First set of experiments

All the medications except oxygen were suspended at least 24 h prior to the study. Over five consecutive days, after having carried out preliminary pulmonary function tests, including a standard reversibility test with salbutamol 200 μg on day one, the methods of delivery were randomized, using a computer-generated sequence afterwards enclosed in opaque sealed envelopes, so that on four consecutive days at the same time of day the patient received: 1) placebo via MDI with spacer chamber (Volumatic, Allen & Hanburys, Greenford, UK) using an empty canister; 2) a global 400 μg dose of salbutamol via MDI with spacer during spontaneous breathing (MDI-Spacer) (two breaths were allowed within each puff); 3) a global dose of 400 μg of salbutamol via MDI (four puffs) with spacer chamber (Volumatic: Allen & Hanburys, Greenford, UK, modified) fitted into the inspiratory limb of the circuit, immediately after the Y of the circuit, during NIMV (MDI-NIMV); and 4) 5 ml of saline solution with 5 mg of salbutamol delivered by the IPPB device.

Table 1 Clinical characteristics of the patients enrolled for the two sets of experiments. No statistically significant differences were observed between the two groups of patients

Variables	First experiment (18 patients)	Second experiment (8 patients)
Age (years)	67.7 ± 4.9	61.4 ± 7.3
Male/female	13/5	6/2
FEV_1 (% predicted)	38.5 ± 8.8	33.1 ± 9.7
FEV_1 (ml)	1,083 ± 94	887 ± 94
FVC (% predicted)	66.8 ± 7.4	63.9 ± 8.6
FVC (ml)	2,082.3 ± 121.2	1,933.5 ± 135.5
FEV_1/FVC	50.3 ± 5.8	45.2 ± 7.1
pH	7.41 ± 0.02	7.39 ± 0.03
PaO_2 (mmHg)	55.8 ± 7.6	52.3 ± 9.4
$PaCO_2$ (mmHg)	49.9 ± 6.3	50.8 ± 8.2

Both responders and non-responders to the standard reversibility test with salbutamol 200 μg were included in the study, because some recent studies have shown that a subset of non-responders (in terms of FEV_1,) may nevertheless obtain a significant improvement in vital capacity after bronchodilator delivery (i.e., volume responders), as an indirect sign of a decreased degree of hyperinflation [11, 12].

The patients' clinical stability was checked by measuring FEV_1 prior to the test. If the $\Delta FEV_1 > 5\,\%$ from the one recorded the day before, the patient was removed from the study; this occurred in only three patients, so that a total of 18 patients finished the protocol.

During NIMV, to ensure a "minimal" tidal volume during an assisted mode of ventilation, we used volume-assured pressure support (Helia, Saime, Savigny Le Temple, France), with dried, unwarmed gas. The following settings were used: pressure support 14.3 ± 1.8 cmH_2O, V_T guarantee: 10 ml/kg; inspiratory trigger:–0.5 cmH_2O. All the patients were breathing air. NIMV was delivered by full-face mask (Gibeck Respiration, Upplands-Vasby, Sweden) and maximal care was taken to avoid air leaks by comparison of the inspired and expired tidal volumes on the display of ventilator [13]. The patients were taught by a respiratory therapist to breath through their mouths.

During IPPB the patient was connected through a rigid mouthpiece to a Bennet IPPB device driven by air with a pressure of 15 cmH_2O, a flow rate of 50 l/m and no oxygen supplementation (PR II Respiratory Unit, Puritan Bennett, USA). The total time of nebulization was ≈ 10 min. IPPB was used as an aerosol delivery method since it is possible to standardize the pressure of nebulization and the inspiratory flow, giving at the same time similar clinical results to those achieved by "standard nebulizers" [14].

All the measurements were recorded 10 min before aerosol administration and these measurements were repeated 15 min and 30 min after aerosol administration.

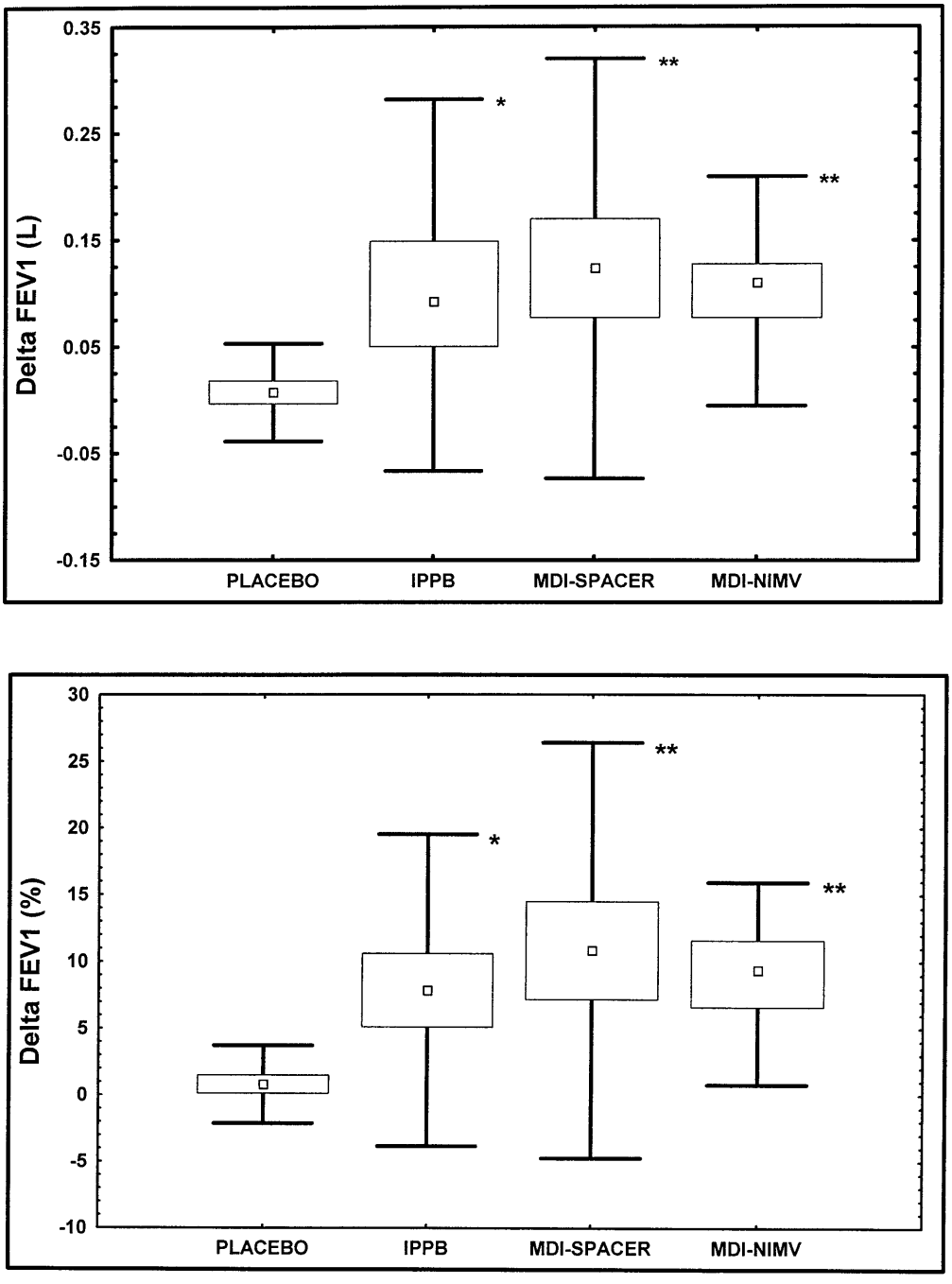

Fig. 1 *(Upper)* Box-whisker plot of changes in FEV_1 (l) after placebo or salbutamol delivery by intermittent positive pressure breathing (IPPB), metered-dose inhaler and spacer (MDI-Spacer), and metered dose inhaler during non-invasive ventilation (MDI-NIMV) in all patients (* $P = < 0.05$, ** $P = 0.01$ vs placebo). *(Lower)* Changes in FEV_1 (%) after placebo or salbutamol delivery by IPPB, MDI-Spacer, and MDI-NIMV in all patients (* $P = 0.05$, ** $P = 0.01$, vs placebo). *Small square* mean, *large square* ± 1 SD, *vertical line* ± 1.96 SD

Second set of experiments

To ascertain the changes in pulmonary function due to possible direct effects of NIMV, an additional group of eight patients were studied. The criteria of enrollment into the study were identical to those of the patients enrolled for the first set of experiments. On two different days the patients were randomized to receive: 1) 400 μg of salbutamol via MDI with spacer chamber during NIMV delivered with the same setting as described above; or 2) placebo via an empty canister placed in the inspiratory limb of the ventilator, during NIMV.

Data analysis

Results are expressed as mean ± standard deviation. The analysis of variance for repeated measurements was used to determine the difference between baseline measurements and the difference between the changes in the recorded variables according to the different method of the bronchodilator delivery. Comparison of individual pairs of groups was done using Newman-Keuls' post hoc method. Results after each delivery method were compared with those of the preceding baseline using the paired Student's *t*-test. The tolerance scores reported for the different methods of delivery were

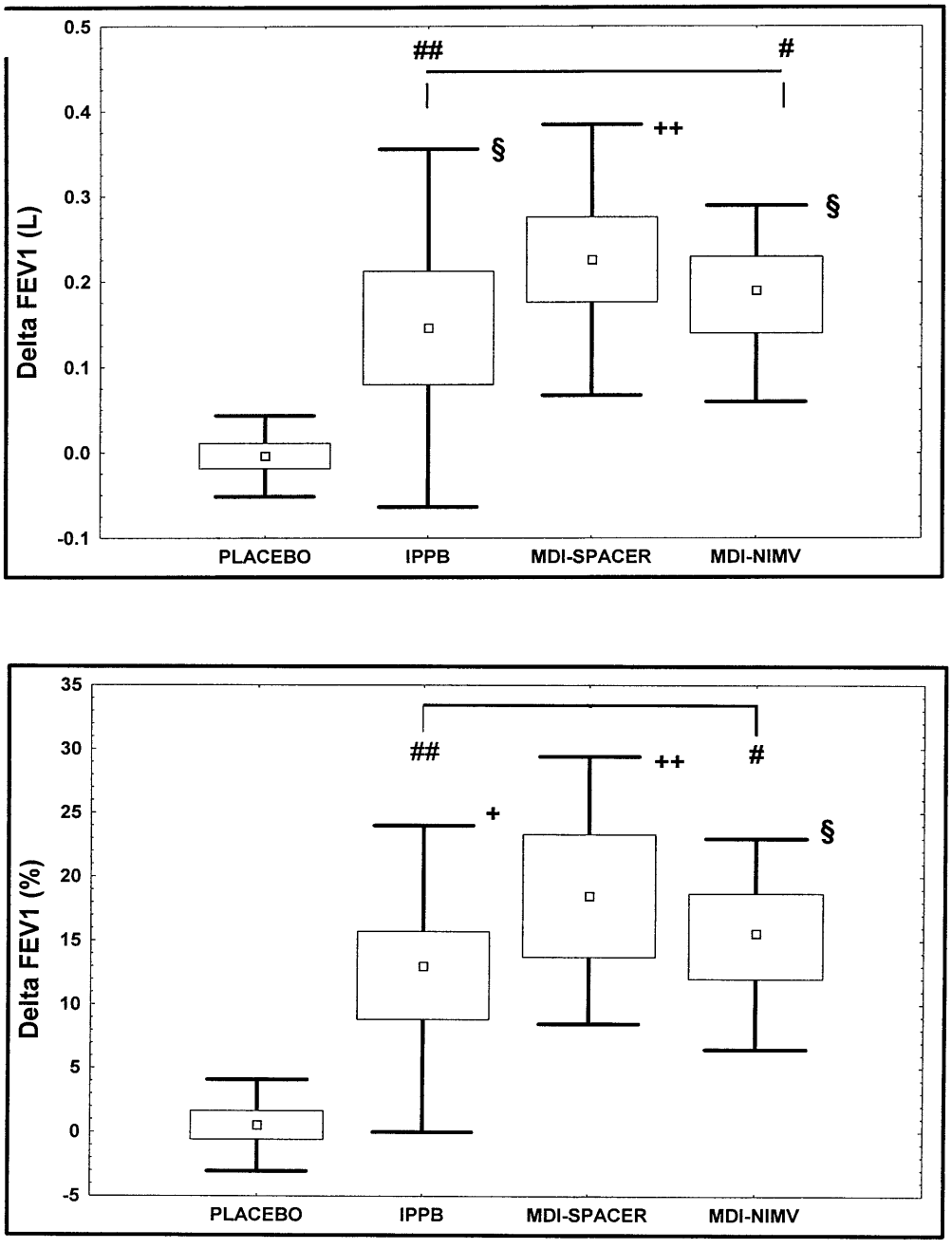

Fig. 2 *(Upper)* Box-whisker plot of changes in FEV_1 (l) after placebo or salbutamol delivery by IPPB, MDI-Spacer, and MDI-NIMV in the subgroup ($n = 9$) of responders (+ $P < 0.01$, ++ $P < 0.001$, § 0.005 vs placebo, # $P < 0.05$ MDI-Spacer vs MDI-NIMV, ## $P < 0.01$ IPPB vs MDI-Spacer). *(Lower)* Changes in FEV_1 (%) after placebo or salbutamol delivery by IPPB, MDI-Spacer, and MDI-NIMV in the subgroup ($n = 9$) of responders. Symbols as for the upper panel. *Small square* mean, *large square* ± 1 SD, vertical line ± 1.96 SD

compared using the Friedman-ANOVA test. Statistical significance was defined as a two-tailed P-value < 0.05.

Results

Eighteen of 21 patients completed the first set of experiments, and 8/8 the second experimental procedure. None had any adverse clinical effects such as desaturations or bronchoconstriction.

Baseline FEV_1 and forced vital capacity (FVC) were constant throughout the experiment. During the preliminary PFT, at enrollment in the study, 9/18 patients did not respond significantly to inhaled salbutamol ($\Delta FEV_1 \leq 12\%$ and ≤ 200 ml), so that they were classified as non-responders [10]. This different response was thereafter confirmed in all patients, irrespective of the method of bronchodilator delivery.

The data reported are those obtained after 15 min of salbutamol delivery, since no significant variations

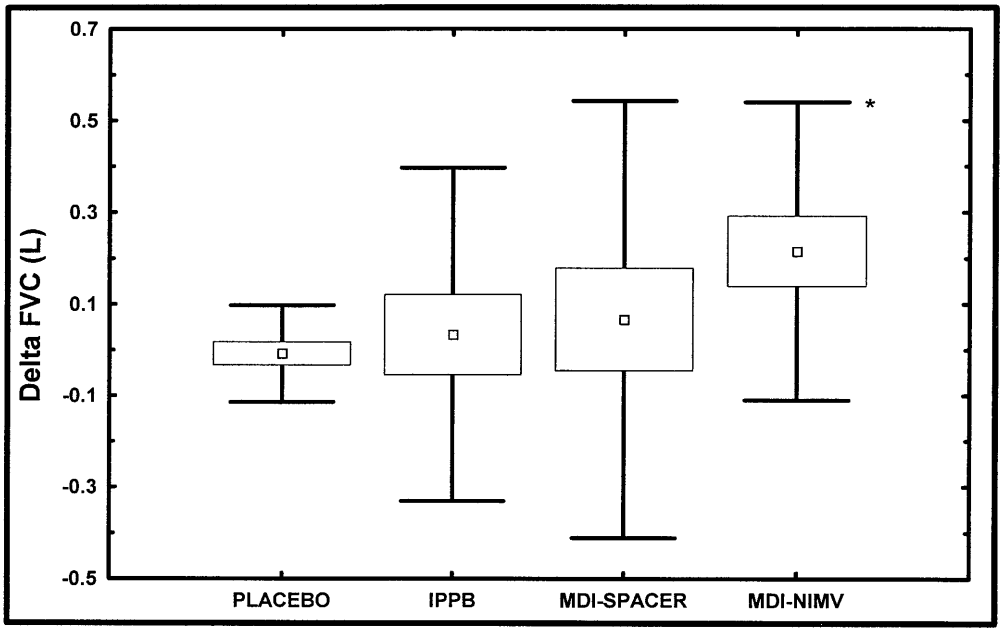

Fig. 3 Box-whisker plot of changes in FVC after placebo or salbutamol delivery by IPPB, MDI-Spacer, and MDI-NIMV in all the patients (* $P = 0.02$ vs placebo). *Small square* mean, *large square* ± 1 SD, *vertical line* ± 1.96 SD

were observed between these measurements and those after 30 min.

Figure 1 is a box-whisker plot, illustrating ΔFEV_1 changes, expressed as absolute values and percentage, with the different methods of delivery. Overall, salbutamol administration induced a significant improvement in FEV_1, irrespective of the mode of administration. The effect of the drug vs placebo was however more pronounced ($P < 0.01$) when the salbutamol was delivered via an MDI-Spacer (+10.8 ± 11.4 % or 119 ± 114 ml) and during MDI-NIMV (+9.6 ± 8.8 % or 112 ± 67 ml) than IPPB (+7.9 ± 7.1 % or +108 ± 91 ml $P < 0.05$), but no statistical difference was observed within the different methods of delivery. The elimination of the non-responders (50 % of the patients) from data analysis clearly increased the effect of the bronchodilators, as illustrated in Fig. 2. In this subgroup of patients both the absolute and percent changes in FEV_1 were statistically higher using the MDI-Spacer than using the other two methods ($P < 0.05$ vs MDI-NIMV and $P < 0.01$ vs IPPB).

Figure 3 is a box-whisker plot for ΔFVC, expressed both as absolute values and percentage. Only MDI-NIMV induced a small but statistically significant ($P < 0.05$) improvement vs placebo; this finding was eliminated when the analysis was restricted to the responders. Figures 4 and 5 show the individual absolute changes in FEV_1 and FVC in the additional group of patients studied to ascertain the potential direct effects of NIMV on pulmonary function. FEV_1 significantly increased only when salbutamol was administered (+144 ± 108 ml $P < 0.01$), while FVC increased from baseline both with placebo or the drug (+206 ± 147 ml and 208 ± 145, respectively). Table 2 shows the effect of the bronchodilator, delivered by each of the described delivery methods, on arterial blood gases, heart rate, and blood pressure. No statistical difference was observed in arterial blood gases and systemic blood pressure between placebo and all delivery modes of the bronchodilator. Heart rate rose following salbutamol administration, irrespective of the mode of delivery, but this increase did not achieve statistical significance

Table 2 Effect of the bronchodilator delivered by each of the described delivery methods on arterial blood gases, heart rate, and systemic blood pressure. No significant improvement was observed in any variable after any delivery mode

	Placebo	IPPB	MDI-Spacer	MDI-NIMV
pH	7.41 ± 0.02	7.42 ± 0.03	7.41 ± 0.02	7.42 ± 0.02
PaO_2 (mmHg)	55.8 ± 7.6	54.4 ± 8.9	56.7 ± 9.1	56.5 ± 6.5
$PaCO_2$ (mmHg)	49.9 ± 6.3	48.6 ± 7.7	50.1 ± 8.3	48.1 ± 6.8
HR (b/m)	82.7 ± 11.1	88.6 ± 14.1	87.4 ± 15.8	86.7 ± 14.8
Systolic BP (mmHg)	126.2 ± 12.6	128.2 ± 11.1	127.5 ± 12.4	126.7 ± 11.3
Diastolic BP (mmHg)	85.4 ± 8.6	87.4 ± 9.0	86.6 ± 7.3	87.4 ± 7.2

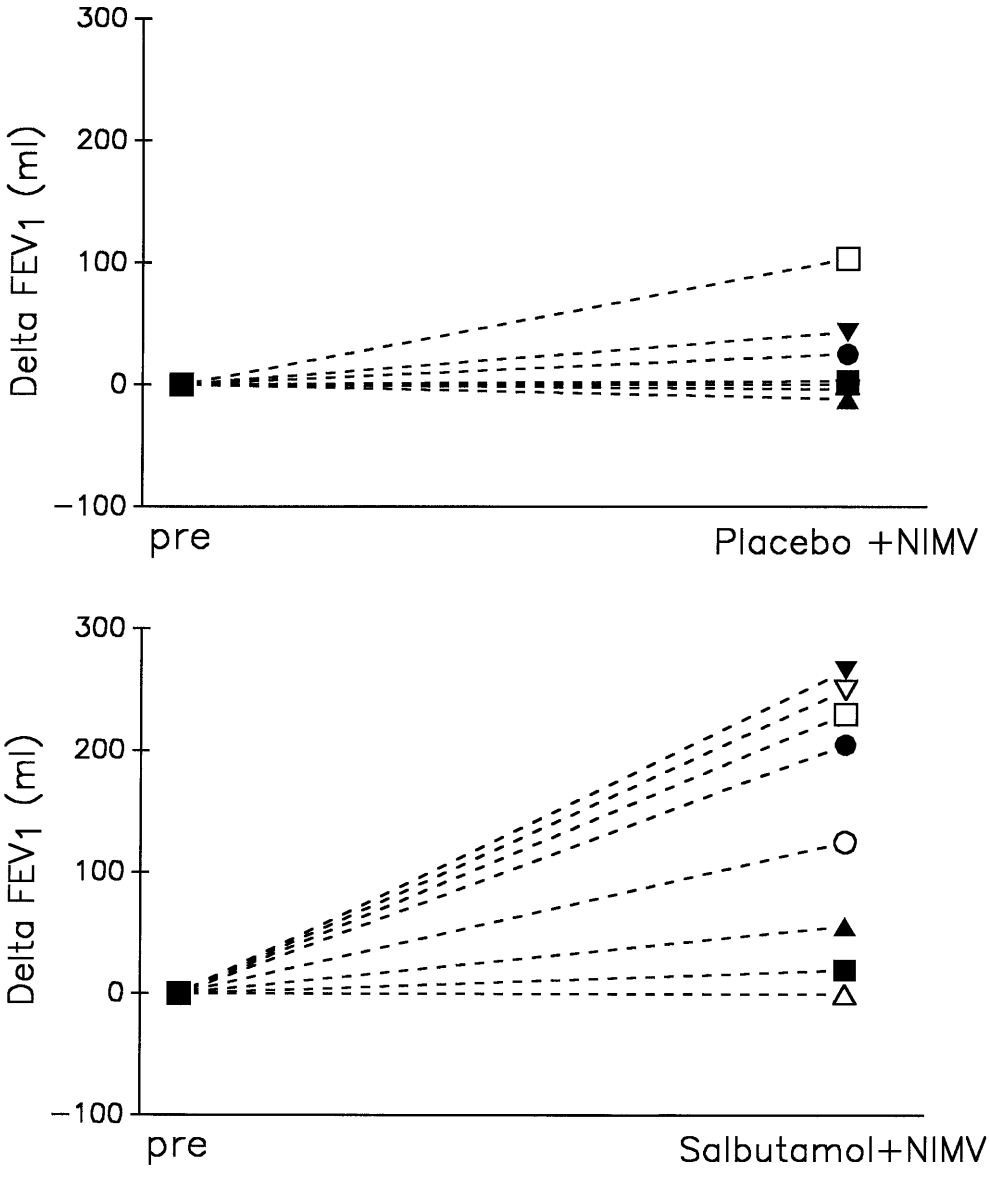

Fig. 4 Individual percent changes from baseline in FEV_1 after NIMV+placebo *(upper)* or NIMV+salbutamol *(lower)* in the eight patients who were randomly administered placebo or salbutamol during NIMV

($P = 0.052$ for MDI-Spacer, 0.058 for IPPB, and 0.071 for MDI-NIMV).

Discussion

In this study, performed in patients with severe, stable COPD, we have shown that inhalation therapy with bronchodilators may be safely and effectively given during NIMV. In the subgroup of responders in terms of FEV_1, the clinical response to salbutamol delivered by MDI placed in the proximal inspiratory limb of the ventilator was slightly smaller than that achieved using the gold standard, i.e., MDI with a spacer during spontaneous breathing, but was significantly better than after placebo. This study was, however, only aimed at assessing the feasibility of bronchodilator delivery during NIMV and was not designed to demonstrate the optimal setting of delivery (i.e., the ventilatory mode) and the dose-response curve of bronchodilators. Indeed, our findings may bear little relation to delivery in the acute setting, in which the interaction between patients and ventilator is likely to be different from that achieved with a cooperative patient.

NIMV may be considered, when endotracheal intubation is not mandatory, as first-line treatment for an episode of severe hypercapnic respiratory failure in COPD patients, since medical therapy alone works in only about 30 % of the patients admitted to an intensive care unit [6]. As bronchodilators are a primary compo-

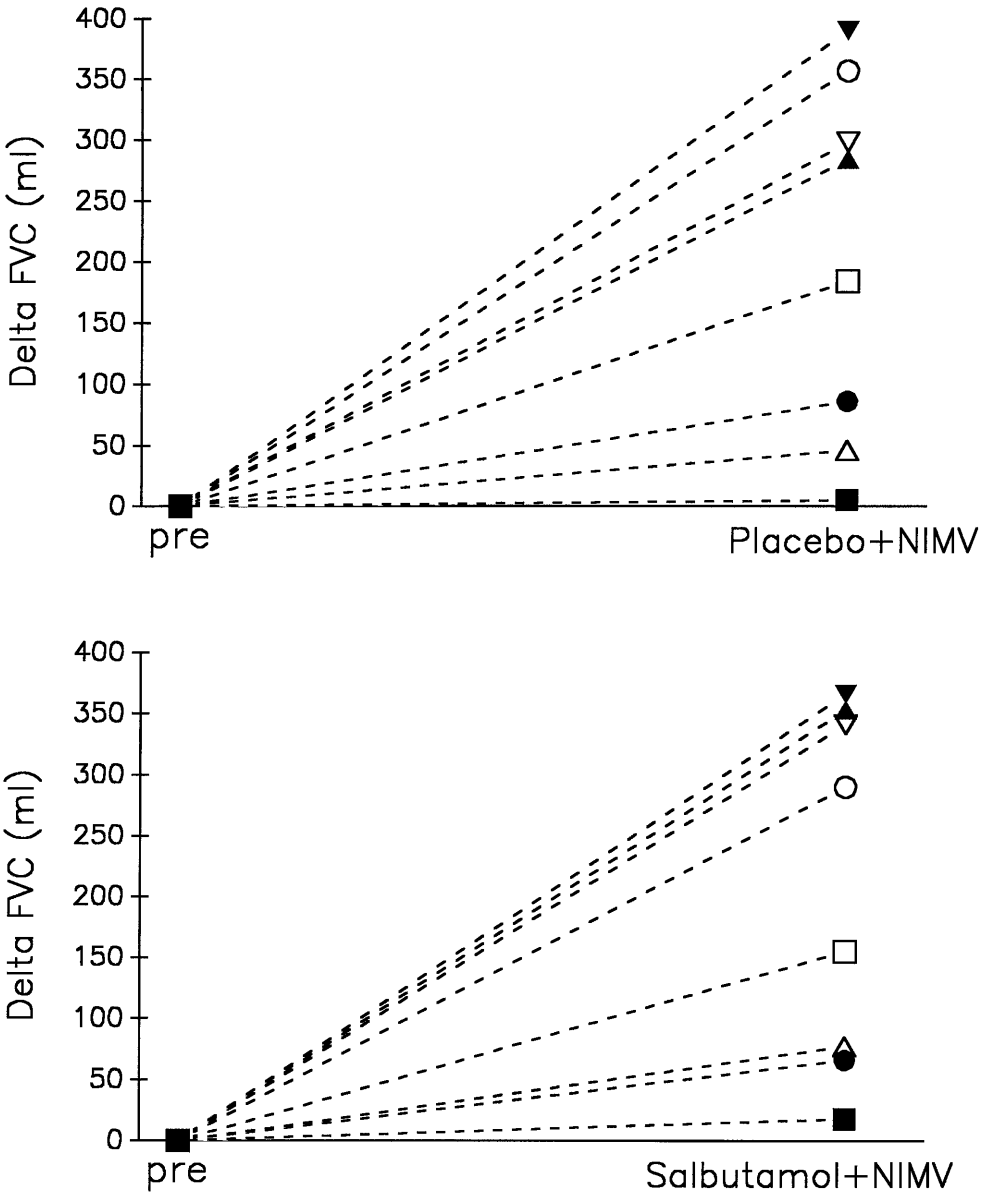

Fig. 5 Individual percent changes from baseline in FVC after NIMV+placebo *(upper)* or NIMV+salbutamol *(lower)* in the eight patients who were randomly administered placebo or salbutamol during NIMV

nent of the treatment of COPD exacerbations [15], they should not be discontinued once NIMV is initiated. Several studies have shown that the use of inhaled bronchodilators may reduce airway resistance and intrinsic positive end-expiratory pressure (PEEPi) by 20–25% in intubated COPD patients [3, 4, 5, 16]. It is therefore important that not only "pumping" (i.e., ventilation), but also "emptying" (i.e., bronchodilation) should be considered a major goal to achieve in these severely obstructed patients [17].

This is the first study showing that bronchodilator delivery via MDI is feasible during NIMV. Parkers et al. [18] investigated aerosol kinetics and bronchodilator efficacy during non-invasive CPAP ventilation which, being the only totally spontaneous ventilatory mode, is seldom employed during an episode of acute hypercapnic respiratory failure. Indeed salbutamol was delivered in that study by a small volume nebulizer, while we used MDI which has several advantages over nebulizers during invasive mechanical ventilation, including ease of administration, decreased cost, reliability of dosing, and freedom from contamination, making it more appealing in the critical care setting. Parkers and coworkers [18] showed, in the first in vitro part of their study, that the total aerosol delivery was reduced from 6.85% to 1.3% during CPAP. The clinical part of their study, however, showed that there was no significant difference between bronchodilator response to β_2-agonists

delivered by conventional nebulization or nebulization during CPAP in patients with chronic stable asthma, so that they suggested that the efficacy of the nebulized bronchodilator was maintained during CPAP. Our study was carried out exclusively in vivo, since we were actually interested in testing the clinical feasibility of bronchodilator delivery during NIMV.

Overall we did not observe a significantly different bronchodilator response to the drug administered by any of the three methods of delivery, but when compared to placebo the FEV_1 increase was statistically more "important" using MDI with the spacer during spontaneous breathing. Indeed these results were even more striking when the subgroups of patients (i.e., responders and non-responders) were analyzed alone. This could suggest that the efficacy of salbutamol delivered by MDI during NIMV and during IPPB may be partly reduced in the former because of the impact of aerosol particles with the circuit or the interface, and in the latter because of evaporation of the drug, since the high rates of gas flow may lead to cooling and hypertonicity of the droplets which may induce paradoxical bronchoconstriction [19]. Despite these potential biases the clinical response was very similar using MDI-Spacer or MDI-NIMV.

We found a small but significantly greater mean improvement in FVC only during NIMV, while this effect "paradoxically" disappeared when only the responders in terms of FEV_1 were considered. To ascertain the possible direct effect of NIMV on pulmonary function, in an additional set of experiments we studied eight patients to whom we administered placebo or salbutamol during NIMV. While FEV_1 improvement was related only to the delivery of salbutamol, FVC increase was observed after both placebo and active drug. Although there is the theoretical possibility of more evenly distributed drug delivery into the lungs during NIMV, the increase in FVC may have been due to an improvement in pulmonary compliance resulting from reversal of small airway closure and microactelectasis because of the direct effect of NIMV on pulmonary mechanics [20].

Some technical details and study limitations need to be addressed.

Since only a small fraction of the inhaled bronchodilator reaches the pulmonary receptors during spontaneous breathing and especially during mechanical ventilation, great care must be taken over the ventilator settings. A critical factor for increasing lung deposition of bronchodilators in vitro is to provide an adequate inspired tidal volume [21]. The VAPS mode gave us the unique opportunity to guarantee, using a pressure supported mode, a minimal V_T, set in this study at about 10 ml/kg, so that drug delivery was optimized. Other variables such as respiratory rate and ventilatory modes, flow pattern, and flow rate were not fully controlled. While all these factors were considered important determinants of aerosol delivery during in vitro investigations [21], more recent studies clearly showed that this may be not the case in vivo [22, 23, 24].

The dose of salbutamol used in this study was 400 μg since Dhand et al. [25] showed, in COPD patients, that four puffs of albuterol (90 μg each) can produce the same decrease in airway resistance and PEEPi as 28 puffs of albuterol, while at the same time avoiding a dangerous increase in the heart rate. This observation may, however, not be applicable to our study because of the different settings and conditions.

In conclusion, we have shown in this randomized, placebo-controlled study performed in stable COPD patients, that delivery of a bronchodilator via MDI with a collapsible spacer chamber during NIMV was safe and feasible and induced a significant clinical response, albeit slightly lower than that achieved with the standard delivery systems used in spontaneously breathing patients (i.e., MDI-Spacer). Great attention should, however, be given to setting the ventilator and the apparatus. Whether or not these findings can be extrapolated to patients with acute respiratory failure should be addressed by future investigations, although the design of randomized, controlled studies in the acute setting will be fraught with difficulties.

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