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Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of tidal volume

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Abstract *Objective*: The delivery of bronchodilator drugs with metered-dose inhaler (MDI) and a spacer in mechanically ventilated patients has become a widespread practice. However, the various ventilator settings that influence the efficacy of MDI are not well established. The tidal volume (V_T) during drug delivery has been suggested as one of the factors that might increase the effectiveness of this therapy. To test this, the effect of two different V_T on the bronchodilation induced by β_2-agonists administered with MDI and a spacer in a group of mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) was examined.
Methods: Nine patients with COPD, mechanically ventilated on volume-controlled mode, were prospectively randomised to receive six puffs of salbutamol (S, 100 µg/puff) either with a V_T of 8 ml/kg (normal V_T, 582 ± 85) or with a V_T of 12 ml/kg (high V_T, 912 ± 137). With both modes inspiratory flow was identical. S was administered with an MDI adapted to the inspiratory limb of the ventilator circuit using an aerosol cloud enhancer spacer. After a 6-h washout, patients were crossed-over to receive S by the alternative mode of administration. Static and dynamic airway pressures, minimum (Rint) and maximum (Rrs) inspiratory resistance, the difference between Rrs and Rint (ΔR), static end-inspiratory respiratory system compliance (Cst,rs), intrinsic positive end-expiratory pressure (PEEPi) and heart rate (HR) were measured before and at 15, 30 and 60 min after S.
Results: S caused a significant decrease in dynamic and static airway pressures, PEEPi, Rint and Rrs. These changes were not influenced by V_T and were evident at 15, 30 and 60 min after S. With normal and high V_T, Cst,rs, ΔR and HR did not change after S.
Conclusions: We conclude that S delivered with an MDI and a spacer device induces significant bronchodilation in mechanically ventilated patients with COPD, the magnitude of which is not affected by at least a 50% increase in V_T. These results do not support the V_T manipulations when bronchodilators are administered in adequate doses during controlled mechanical ventilation.

Key words Airway resistance · Respiratory system mechanics · Salbutamol

Introduction

The delivery of bronchodilator drugs with metered-dose inhalers (MDIs) in mechanically ventilated patients has attracted considerable interest in recent years [1–5]. It has been shown that MDIs adapted to the inspiratory line of the ventilator using a spacer device are as effective as nebulizers, despite a significantly lower dose of bronchodilator being given by the MDI [1–5]. A spacer device is thought to be fundamental in order to demon-

Table 1 Patient characteristics and baseline ventilator settings. Values are mean ± SD (*FIO_2* fractional inspired oxygen, *V_T* tidal volume, *Fr* breathing frequency, $\dot{V}_I$ constant inspiratory flow, *T_I/TOT duty cycle*, $\dot{V}_E$ minute ventilation)

Age (years)	FIO_2 (%)	V_T (l)	Fr (breaths/min)	$\dot{V}_I$ (l/s)	T_I/T_{TOT}	$\dot{V}_E$ (l/min)
71.8 ± 7.3	0.39 ± 0.08	0.58 ± 0.09	11.4 ± 1.3	0.60 ± 0.02	0.21 ± 0.03	6.63 ± 1.1

strate the efficacy of bronchodilatory therapy given by MDI [1–5]. Studies in which bronchodilators with MDI were delivered directly into the endotracheal tube failed to demonstrate any beneficial effect even after high doses were given [6]. The use of MDIs has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing and lower risk of contamination [7–10].

The technique of administration of bronchodilators in mechanically ventilated patients using an MDI and a spacer is an important factor that determines the efficacy of this therapy. Proper timing of drug delivery, tidal volumes > 500 ml, low inspiratory flows and application of end-inspiratory pause (breath-hold) are some of the variables that have been suggested to enhance drug delivery to target sites and, thus, bronchodilation [4, 5, 11]. These suggestions, however, are based on in vitro studies with models of mechanical ventilation. Indeed, we recently demonstrated that in mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) application of an end-inspiratory pause time of 5 s when adequate doses of bronchodilators were administered did not have any additional bronchodilator effect [12]. This study raises the issue that under certain circumstances (i.e. adequate dose of the drug) ventilator settings may not be a critical factor for the bronchodilation. We undertook the present study in order to investigate further the influence of ventilator settings on drug-induced bronchodilation. Specifically, the purpose of the present study was to examine the effect of increasing the tidal volume on the bronchodilation induced by β_2-agonists administered with an MDI and a spacer, in a homogeneous group of mechanically ventilated patients with COPD.

Patients and methods

Nine patients (eight men and one woman) with COPD, requiring mechanical ventilation to manage acute respiratory failure due to an acute exacerbation of chronic airflow obstruction, were studied. All patients had a previous diagnosis of COPD and met established criteria for this diagnosis [13]. Patients with a diagnosis of bronchial asthma were excluded. The study was approved by the Hospital Ethics Committee and informed consent was obtained from the patients or their families.

The patients were studied in a semirecumbent position during a period of clinical stability, 2–3 days after the onset of mechanical

ventilation. All patients were intubated with endotracheal tube, 8–9 mm internal diameter, heavily sedated (propofol and fentanyl) and ventilated on volume controlled mode using Servo 300 (Siemens, Germany) ventilators. The absence of respiratory muscle activity was based on specific criteria, including absence of negative deflection of airway pressure (Paw), stabilisation of Paw waveform, constancy of peak inspiratory pressure from breath to breath and exponential decline of expiratory flow [14]. The ventilator was set to deliver a specific tidal volume (V_T) (8 ml/kg) with a square wave flow-time profile. Inspiratory flow was set between 0.55 and 0.65 l/s and no end-inspiratory pause was applied. Minute ventilation was adjusted in each individual by the attending physician in order to maintain normal arterial pH and remained constant throughout the study. Extrinsic positive end-expiratory pressure (PEEP) was set to zero. The patients' physical characteristics and baseline ventilator settings are shown in Table 1.

Flow at the airway opening was measured with a heated pneumotachograph (Hans-Rudolf 3700, Kansas, USA) and differential pressure transducers (Micro-Switch 140PC, Honeywell, Ontario, Canada) placed between the endotracheal tube and the ventilator. Flow was electronically integrated to provide volume. Airway pressures (Micro-Switch 140PC, Honeywell, Ontario, Canada) were measured from a side port between the pneumotachograph and the endotracheal tube. All signals were sampled at 50 Hz (Windaq Instruments, Ohio, USA) and stored on a computer disk for later analysis.

Patients were prospectively randomised to receive six puffs of salbutamol (100 μg/puff given by an MDI canister, Aerolin inhaler, Glaxo Wellcome) either with a V_T identical to that selected previously (8 ml/kg, normal V_T, mean 582 ± 85 ml, range 450–660 ml) or with a V_T of 12–13 ml/kg (high V_T, mean 912 ± 137 ml, range 700–1100 ml). In all cases, the high V_T was at least 50% higher than normal V_T (range 50–67%, 280–440 ml). After a 6 h washout, patients were crossed-over to receive the drug by the alternative mode of administration. Inspiratory flow during drug administration was kept constant to baseline values and no end-inspiratory pause was applied. When the drug was administered with a high V_T, this caused a proportional increase in inspiratory time (T_I) and duty cycle (T_I/T_{TOT}). With high V_T, T_I and T_I/T_{TOT} were 1.7 ± 0.3 s and 0.33 ± 0.05 s, respectively, considerably higher than the corresponding values with normal V_T (Table 1). The MDI canister was adapted to the inspiratory limb of the ventilator circuit using an aerosol cloud enhancer spacer (ACE, Diemolding Healthcare Division, USA), whereby the MDI flumenn is directed away from the patient (Fig. 1). The spacer was placed just before the Y-ventilator connector. The canister was shaken before each series of puffs. Each actuation was performed at 20 to 30 s intervals, immediately before initiation of airflow by the ventilator. Between the intervals the patients were ventilated at baseline ventilator settings. All bronchodilators were withheld at least 6 h before the study. All but one patient received corticosteroids (240 mg methylprednisolone/day) and this regimen was not modified during the study. All patients were on regular treatment with short-term β_2-agonists (salbutamol). None of the patients was on theophylline. In our intensive care unit, this ther-
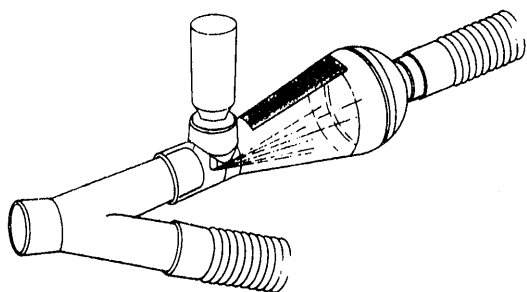
Fig. 1 Schematic representation of the MDI adapted to the spacer device in the inspiratory limb of the ventilator circuit

apy is the standard treatment for acute exacerbations of COPD. Arterial blood gases were measured before drug administration. Saturation of hemoglobin (SaO_2) was measured continuously using a pulse oximeter (Critikon, Tampa, Fla,. USA).

Respiratory system mechanics and heart rate (HR) were assessed before (baseline) and at 15, 30 and 60 min after each series of puffs. The mechanical properties of the respiratory system were determined while the patient was ventilated at baseline ventilator settings shown in Table 1. Respiratory system mechanics were measured using the occlusion technique [15, 16]. In brief, the airways were occluded at end-inspiration for 5 s and there was an immediate drop in airway pressure from a peak to a lower value, followed by a gradual decay to a plateau. In each patient, at least five breaths with satisfactory plateau were analysed and the mean values were reported. Intrinsic PEEP (PPEPi) was measured by occluding the airways at the end of a tidal expiration for 5 s and observing the airway pressure. Again, five breaths were analysed. Respiratory system static inflation end-inspiratory compliance (Cst,rs) and minimum (Rint) and maximum (Rrs) respiratory system resistance were computed according to standard formulas [15, 16]. The difference between Rrs and Rint (ΔR), caused by time-constant inequalities and/or viscoelastic behaviour (stress relaxation), was also calculated. Rint and Rrs were corrected for the finite occlusion time of the occlusion valve of the ventilator [17]. The endotracheal tube resistance was not taken into account, because each patient served as his or her own control. Nevertheless,

values of Rint and Rrs after subtraction of endotracheal tube resistance ($Rint_{cor}$, Rrs_{cor}), calculated as suggested by Rossi et al. [18], were also reported.

Data were analysed by paired t-test and two-way analysis of variance for repeated measurements (ANOVA), where appropriate. When the F value was significant, Tukey's test was used to identify significant differences. A value of $p < 0.05$ was considered statistically significant. Data are expressed as mean ± SD.

Results

Baseline respiratory system mechanics and HR before the administration of each series of puffs of salbutamol are shown in Table 2. As a group there was no significant difference in any of these variables between the two methods of drug delivery (ANOVA). Furthermore, baseline arterial blood gases did not differ significantly between the two modes (paired t-test). When salbutamol was given with normal V_T, baseline arterial oxygen tension (PaO_2) and arterial carbon dioxide tension were 73.1 ± 11.2 and 59.9 ± 6.8 mmHg, respectively, while the corresponding values with a high V_T were 74.2 ± 9.2 and 57.4 ± 5.4 mmHg (paired t-test, $p > 0.05$). Similarly, baseline (before salbutamol administration) respiratory system mechanics and arterial blood gasses did not differ during the six hours of observation (paired t-test, $p > 0.05$). In the first part of the study, baseline Rint and Rrs were 17.7 ± 3.1 and 22.5 ± 4.6 cmH$_2$O/l/s, respectively, while the corresponding values after 6 h were 17.3 ± 2.7 and 21.7 ± 3.7 cmH$_2$O/l/s, indicating that factors other than salbutamol did not appreciably affect lung function.

The effects of salbutamol, administered with normal and high V_T, on respiratory system mechanics and HR are shown in Table 2 and Figs. 2, 3 and 4. With both modes of administration, six puffs of salb-

Table 2 Airway pressures, respiratory system mechanics and heart rate before and after salbutamol administration with normal and high V_T. Values are mean ± SD (*B* baseline, *Ppk, P$_l$, Pp* dynamic and static airway pressures at end-inspiration, *Rrs, Rint* maximum and minimum airflow resistance, *ΔR* difference between Rrs and Rint, *Rrs$_{cor}$, Rint$_{cor}$* maximum and minimum airflow resistance after subtraction of calculated endotracheal tube resistance, *Cst, rs* respiratory system static inflation end-inspiratory compliance, *PEEPi* intrinsic PEEP, *HR* heart rate

	With normal V_T				With high V_T			
	B	15 min	30 min	60 min	B	15 min	30 min	60 min
Ppk (cmH$_2$O)	32.7 ± 7.0	29.9 ± 6.0*	29.6 ± 6.4*	29.6 ± 5.8*	31.3 ± 5.5	28.4 ± 4.7*	28.5 ± 5.0*	28.1 ± 5.1*
P$_1$ (cmH$_2$O)	21.7 ± 5.6	21.0 ± 5.4	21.0 ± 5.6	20.8 ± 4.9*	21.2 ± 4.8	19.9 ± 4.6*	20.0 ± 4.7*	19.5 ± 4.3*
Pp (cmH$_2$O)	19.0 ± 4.8	18.0 ± 4.8*	18.1 ± 4.9*	17.8 ± 4.0*	18.5 ± 4.3	16.9 ± 4.1*	16.9 ± 4.0*	16.9 ± 4.0*
Rrs (cmH$_2$O/l per s)	22.7 ± 4.3	19.9 ± 2.60*	19.1 ± 2.9*	19.7 ± 3.7*	21.4 ± 3.4	19.1 ± 2.4*	19.3 ± 2.6*	18.8 ± 3.0*
Rint (cmH$_2$O/l per s)	18.2 ± 3.2	14.9 ± 2.2*	14.4 ± 2.1*	14.7 ± 2.6*	16.8 ± 2.1	14.1 ± 2.0*	14.2 ± 2.0*	14.5 ± 2.7*
ΔR (cmH$_2$O/l per s)	4.5 ± 1.9	5.0 ± 1.6	4.8 ± 1.8	5.0 ± 1.8	4.6 ± 1.8	5.0 ± 1.6	5.1 ± 1.9	4.3 ± 1.2
Rrs$_{cor}$ (cmH$_2$O/l per s)	20.3 ± 4.6	17.4 ± 2.7*	16.7 ± 3.1*	17.2 ± 3.9*	19.0 ± 3.7	16.7 ± 2.5*	16.8 ± 2.8*	16.4 ± 3.2*
Rint$_{cor}$ (cmH$_2$O/l per s)	15.8 ± 3.3	12.4 ± 2.3*	11.9 ± 2.3*	12.3 ± 2.8*	14.3 ± 2.2	11.7 ± 2.1*	11.7 ± 2.2*	12.0 ± 2.9*
Cst, rs (ml/cmH$_2$O)	45.4 ± 11.1	46.2 ± 11.7	44.9 ± 13.2	43.8 ± 9.9	45.3 ± 10.3	46.7 ± 9.8	46.5 ± 10.4	45.6 ± 10.8
PEEPi (cmH$_2$O)	6.1 ± 3.2	5.3 ± 3.0*	4.8 ± 3.0*	4.6 ± 3.0*	5.7 ± 3.3	4.6 ± 3.1*	4.5 ± 2.3*	4.1 ± 2.9*
HR (beats/min)	88.7 ± 12.5	90.9 ± 11.3	92.6 ± 10.9	92.3 ± 9.8	86.0 ± 12.2	88.7 ± 13.1	88.2 ± 13.1	91.2 ± 12.6

* Significantly different from baseline values ($p < 0.05$, two-way ANOVA)

Fig. 2 Individual values of Rint **A** and Rrs **B** before and after salbutamol administration. *Open bars* with normal V_T. *Closed bars* with high V_T. For a given patient and mode of drug administration, the four bars represent Rint and Rrs at time 0 (before salbutamol administration, baseline) and at 15, 30 and 60 min after salbutamol administration
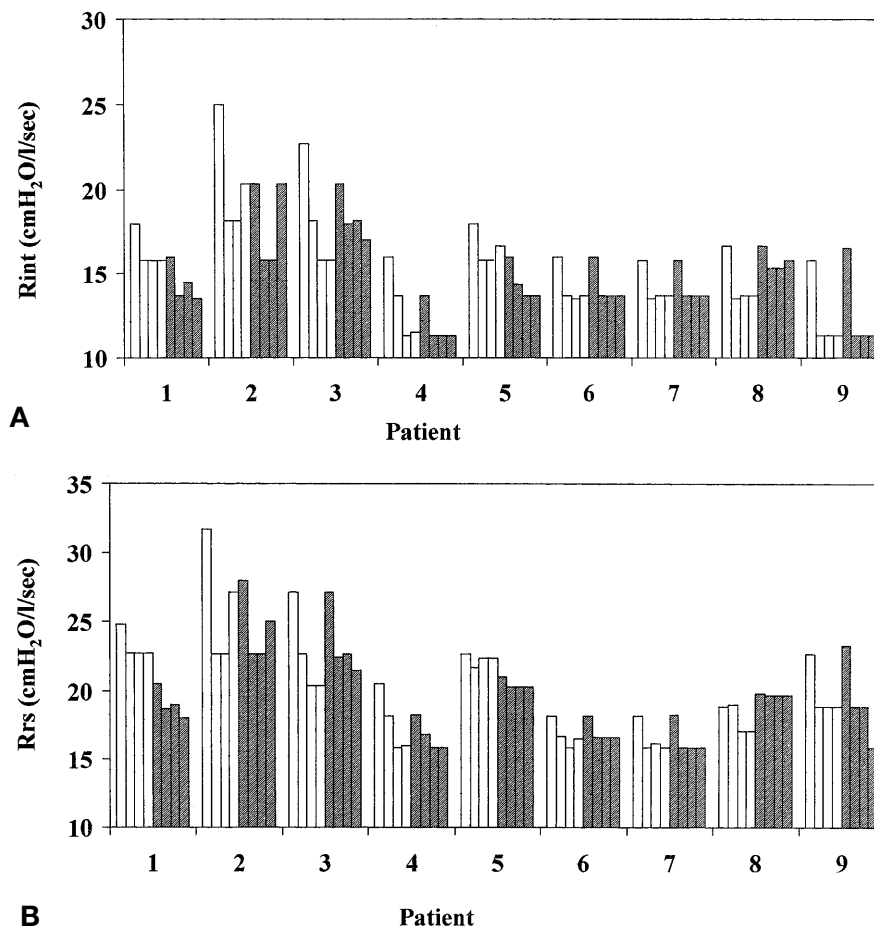
utamol caused a significant decrease in dynamic and static airway pressures, Rint, Rrs and PEEPi (ANOVA). These effects were evident at 15 min after drug delivery and remained relatively constant for at least 60 min. $Rint_{cor}$ and Rrs_{cor} behaved similarly (Table 2). However, $Rint_{cor}$ and Rrs_{cor} should overestimate by an unknown amount the true Rint and Rrs because the calculation of endotracheal tube resistance was based on in vitro data [18]. Indeed, it has been shown that in vivo endotracheal tube resistance is higher than that measured in vitro, perhaps because of secretions, head or neck positions and tube deformation [19]. With normal and high V_T changes in ΔR, Cst,rs and HR values were not significant at any time interval after salbutamol administration. SaO_2 remained constant throughout the study, indicating that clinically significant changes in PaO_2 as a result of salbutamol administration did not occur.

V_T did not have any significant effect on salbutamol induced bronchodilation. With normal V_T salbutamol decreased Rint by 18.1 ± 5.8, 20.7 ± 7.4 and $19.0 \pm 7.7\%$ from baseline at 15, 30 and 60 min, respectively, after administration. The corresponding values with high V_T were 15.7 ± 6.8, 15.5 ± 6.9 and $14.1 \pm 8.1\%$. Similarly, with normal V_T salbutamol decreased Rrs by $11.6 \pm 8.3\%$, $15.0 \pm 8.6\%$ and $13.1 \pm 7.2\%$ from baseline, at 15, 30 and 60 min, respectively, after drug delivery, while the corresponding values with high V_T were 10 ± 7.2, 9.3 ± 8.3 and $11.5 \pm 9.9\%$. There was a significant linear relationship ($r = 0.54$, $p < 0.05$) between the response of Rint to salbutamol with normal and high V_T. This indicates that within patients the response to salbutamol was quite consistent and independent on the mode of drug administration.

Discussion

Our work reconfirmed previous studies showing that in mechanically ventilated patients with COPD β_2-agonists delivered by MDI and a spacer produced a significant and sustained decrease in inspiratory resistances (Rint and Rrs) [1–3]. Although in our study expiratory resistance was not measured, this most likely was decreased by salbutamol, as indicated by the significant reduction in PEEPi and end-inspiratory static plateau

Fig. 3 Individual values of Ppk **A** and Pp **B** before and after salbutamol administration. Symbols as in Fig. 2
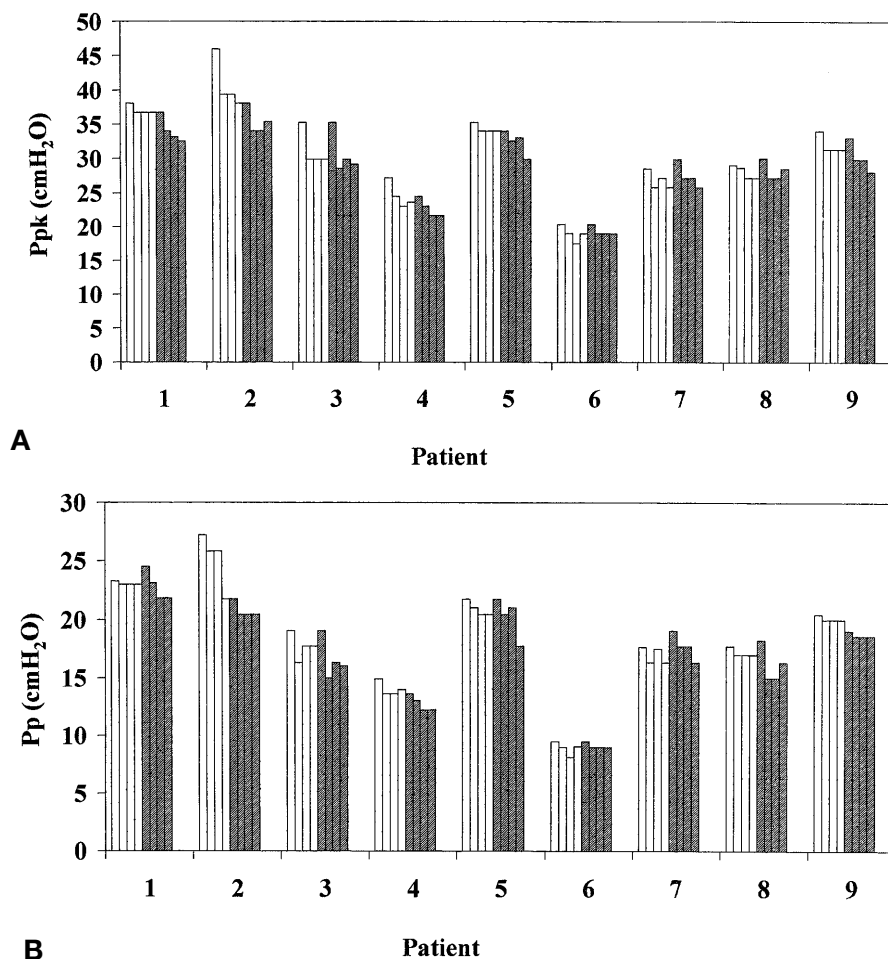
pressure, indirect indices of dynamic hyperinflation. Furthermore, we demonstrated that increasing the V_T by at least 50 % during drug delivery did not enhance salbutamol-induced bronchodilation.

All but one patient were on corticosteroids and this regimen remained unaltered during the study. We do not believe that the administration of corticosteroids influenced the results. The patients were on corticosteroids for at least 24 h before being studied (most of them > 48 h). It has been shown that administration of corticosteroids during acute exacerbations of COPD induces significant bronchodilation that reaches near maximum by 24 h [20]. This is also supported by the fact that baseline (before salbutamol) respiratory system mechanics and blood gasses were stable during the 6 h of observation. Therefore, in these patients lung function during the study period was not significantly affected by factors other than salbutamol.

In mechanically ventilated patients, the optimal ventilatory pattern during bronchodilator delivery with MDI and a spacer is not known. The use of low inspiratory flow, a V_T of at least 500 ml, high T_I/T_{TOT} and 3–5-s end-inspiratory pause has been suggested to increase the effectiveness of MDI therapy [4, 5, 11]. However, these recommendations are based mainly on aerosol delivery data [11, 21], which may not reflect bronchodilator drug effect. Indeed, in a recent study we showed that application of a 5-s end-inspiratory pause, which likely enhanced drug delivery, did not increase the bronchodilator effect of six puffs of salbutamol [12]. In the current study, we demonstrated that at a constant inspiratory flow rate, increasing the V_T (and T_I/T_{TOT}) by at least 50 % did not have any beneficial effect on salbutamol induced bronchodilation by MDI and a spacer. These two studies do not support alterations in ventilator settings when bronchodilator drugs are administered.

By increasing the V_T at a constant inspiratory flow rate, inspiratory time is also increased proportionally. It has been shown that both manipulations (increases in V_T and inspiratory time) are associated with significant increases in bronchodilator delivery to the lower respiratory tract [11, 21]. Although we did not measure drug delivery to the lower respiratory tract, it is likely that

Fig. 4 Individual values of PE-EPi **A** and Cst,rs **B** before and after salbutamol administration. Symbols as in Fig. 2
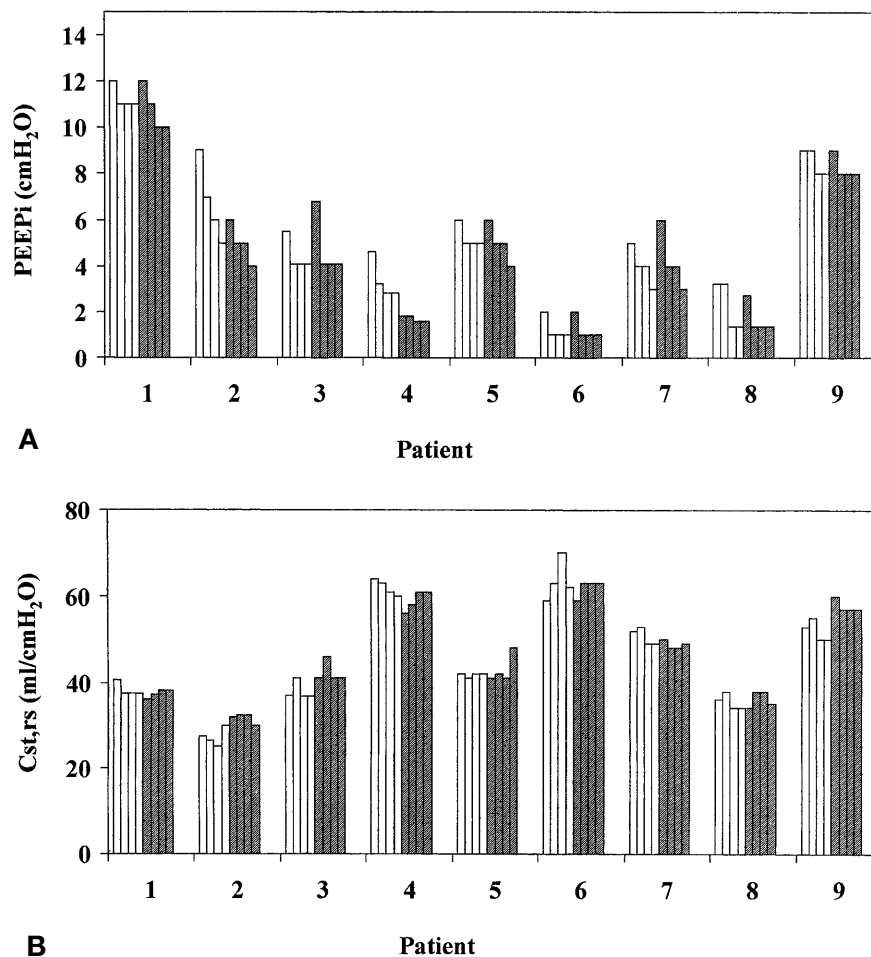
salbutamol with high a V_T and an increased T_I/T_{TOT} should enhance drug deposition to the target sites [11, 21]. The reasons why this enhancement was not associated with additional bronchodilation are not entirely clear. Maximal or near maximal bronchodilation may be achieved in patients receiving controlled mechanical ventilation when relatively high doses of salbutamol are administered with a high volume spacer, a square wave inspiratory flow profile, a V_T of approximately 500 ml and MDI actuation synchronised with inspiratory flow. It is likely that under these circumstances V_T and T_I/T_{TOT} do not represent critical factors for bronchodilation. Although the design of the study does not permit further clarification of the possible factors involved in the response, we believe that the dose of salbutamol may play a primary role. Indeed, Dhand et al. [3] have shown, in mechanically ventilated patients with COPD, that the decrease in airway resistance with four puffs of albuterol (90 μg/puff) was comparable to that observed with cumulative doses of 28 puffs. Thus, it is possible that six puffs of salbutamol, as used in the current study, by producing a plateau in the bronchodi-

latory response masked any beneficial effect of increasing V_T and T_I/T_{TOT}.

It is not known if a V_T lower than 8 ml/kg could affect the response to bronchodilators. It has been shown using an in vitro model of drug delivery that on continous positive airway pressure mode, aerosol delivery with a V_T of 300 ml was 30 % lower than with a V_T of 500 ml [21]. Under such circumstances, the total dose of salbutamol reaching the target sites may be less than the minimum dose able to achieve a plateau in the response, thus resulting in less bronchodilation. Further studies are needed to clarify this issue.

In summary, this study demonstrated in mechanically ventilated patients with an acute exacerbation of COPD that six puffs of salbutamol given by an MDI and a spacer device induced significant bronchodilation that lasted for at least 60 min. Increasing the V_T by at least 50 % did not have any additional bronchodilatory effect; significant bronchodilation may be achieved with the commonly used V_T of 8 ml/kg. Thus, these results do not favour an increase in V_T when bronchodilators are administered in passively ventilated patients with ob-

structive pulmonary disease. Provided that the dose of the bronchodilator drug is adequate and the technique of administration is appropriate (use of spacer with high volume, actuation at the beginning of inspiration), the response to bronchodilators may reach a plateau without the need to modify commonly used ventilator settings.

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