

Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of end-inspiratory pause

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ABSTRACT: The delivery of bronchodilators with a metered-dose inhaler (MDI) and a spacer in mechanically ventilated patients has become widespread practice. However, the various ventilator settings that influence the efficacy of MDI are not well established. Application of an end-inspiratory pause (EIP) 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 EIP 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.

Twelve patients with COPD, mechanically ventilated on volume-controlled mode, were prospectively randomized to receive six puffs of salbutamol ($100 \mu\text{g}\cdot\text{puff}^{-1}$) either with or without EIP of 5 s duration. Salbutamol was administered with an MDI adapted to the inspiratory limb of the ventilator circuit using an aerosol cloud-enhancer spacer. After a 6 h wash-out, patients were crossed over to receive salbutamol by the alternative mode of administration. Static and dynamic airway pressures, minimum (R_{min}) and maximum (R_{max}) airflow resistance, the difference between R_{max} and R_{min} (ΔR), static end-inspiratory respiratory system compliance ($C_{\text{st,rs}}$) and cardiac frequency (f_{C}) were measured before and at 15, 30 and 60 min after salbutamol administration.

Salbutamol caused a significant decrease in dynamic and static airway pressures, R_{min} and R_{max} . These changes were not influenced by application of EIP and were evident at 15, 30 and 60 min after salbutamol. With and without EIP, $C_{\text{st,rs}}$, ΔR and f_{C} did not change after salbutamol.

In conclusion, salbutamol delivered with a metered-dose inhaler and a spacer device induced significant bronchodilation in mechanically ventilated patients with chronic obstructive pulmonary disease, the magnitude of which was not affected by an end-expiratory pause of 5 s. These results do not support the use of end-inspiratory pause when bronchodilators are administered in adequate doses during controlled mechanical ventilation.

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The delivery of bronchodilators with metered-dose inhalers (MDI) in mechanically ventilated patients has received considerable interest in recent years [1–5]. It has been shown that MDI adapted to the inspiratory line of the ventilator using a spacer device are as effective as nebulizers, despite a significantly lower dose of bronchodilator given by the MDI [1–5]. A spacer device is thought to be fundamental in order to demonstrate the efficacy of the bronchodilatory therapy given by MDI [1–5]. Studies that delivered bronchodilators with MDI directly to the endotracheal tube failed to demonstrate any beneficial effect, even after the administration of high doses of bronchodilators [6]. The use of MDI has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing and a 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 the drug delivery, adequate

tidal volumes, relatively low inspiratory flows and application of end-inspiratory pause (EIP) (breath-hold) are some of the variables that have been suggested to enhance drug delivery to target sites [4, 5]. In particular, EIP of 3–5 s duration has been thought to be an important factor in the success of MDI therapy [1, 11]. However, although breath-holding is a prerequisite for optimal drug delivery in spontaneously breathing nonintubated patients, the effect of EIP on the efficacy of MDI therapy in mechanically ventilated patients is not known. The purpose of the present study was, therefore, to examine the effect of EIP on the bronchodilation induced by β_2 -agonists administered with an MDI and a spacer, in a homogeneous group of mechanically ventilated patients with chronic obstructive pulmonary disease (COPD).

Methods

Twelve patients (9 males and 3 females) with COPD, requiring mechanical ventilation to manage acute respiratory

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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 [12]. 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, 2–6 days after the onset of mechanical ventilation. All patients were intubated with an endotracheal tube 8–9 mm in internal diameter, sedated (propofol) and ventilated on volume-controlled mode using Evita 2 (Dräger, Lübeck, Germany) or Servo 300 (Siemens, Solna, Sweden) ventilators. The absence of respiratory muscle activity was based on specific criteria, including the absence of negative deflection of airway pressure (P_{aw}), stabilization of the P_{aw} waveform, constancy of peak inspiratory pressure from breath to breath, and exponential decline of expiratory flow [13]. The ventilator was set to deliver a specific tidal volume (V_T) with a square wave flow-time profile. No EIP 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, KS, USA) and a differential pressure transducer (Micro-Switch 140PC; Honeywell, Ontario, Canada), placed between the endotracheal tube and the ventilator. Flow was electronically integrated to provide volume. P_{aw} were measured (Micro-Switch 140PC; Honeywell) from a side port between the pneumotachograph and the endotracheal tube. All signals were sampled at 50 Hz (Windaq Instruments, Akron, OH, USA) and stored on a computer disk for later analysis.

Patients were prospectively randomized to receive six puffs of salbutamol either with or without EIP of 5 s duration. After a 6 h wash-out, patients were crossed over to receive the drug by the alternative mode of administration. Inspiratory flow and V_T during drug administration were kept constant at baseline values. Each puff contained 100 μ g salbutamol and was given by an MDI canister (Aerolin inhaler, GlaxoWellcome, Nottingham, UK). The MDI canister was adapted to the inspiratory limb of the ventilator circuit using an aerosol cloud-enhancer spacer (ACE, Diemolding Healthcare Division, NY, USA), whereby the MDI flume is directed away from the patient. The spacer was placed just before the Y-ventilator connector. The canister was shaken before each series of puffs. Each actuation was performed at 20–30-s intervals, immediately before the initiation of airflow by the ventilator. Between the intervals the patients were ventilated at baseline ventilator settings. All bronchodilators were withheld for at

least 6 h before the study. All patients received corticosteroids (120–240 mg·day⁻¹ methylprednisolone) and this regimen was not modified during the study. None of the patients was receiving theophylline. Arterial blood gases were measured before the drug administration.

Respiratory system mechanics and cardiac frequency (f_C) 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 the baseline ventilator settings shown in table 1. The mechanics of the respiratory system were measured using the occlusion technique [14, 15]. In brief, the airways were occluded at end-inspiration and there was an immediate drop in airway pressure from a peak (P_{pk}) to a lower value (P_1), followed by a gradual decay to a plateau (P_p). In each patient at least five breaths with a satisfactory plateau were analysed and the mean values were reported. Intrinsic PEEP (PEEP_i) was measured by occluding the airways at the end of a tidal expiration and observing the airway pressure. Again, five breaths were analysed. Respiratory system static inflation end-inspiratory compliance ($C_{st,rs}$) and minimum (R_{min}) and maximum resistance (R_{max}) of the respiratory system were computed according to standard formulae [14, 15]. The difference between R_{max} and R_{min} (ΔR), caused by time-constant inequalities and/or viscoelastic behaviour (stress relaxation), was also calculated. R_{min} and R_{max} were corrected for the finite occlusion time of the occlusion valve of the ventilator [16]. The endotracheal tube resistance was not taken into account, because each patient served as his or her own control.

Data were analysed by paired t-test, nonparametric Mann-Whitney U-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 \pm SD.

Results

Baseline respiratory system mechanics and f_C before the administration of each series of puffs of salbutamol are shown in table 2. Figure 1 shows individual baseline R_{min} between the two modes of salbutamol administration. As a group there was no significant difference in any of these variables between the two conditions of drug delivery (ANOVA). Furthermore, baseline arterial blood gases did not differ significantly between the two modes of salbutamol administration (paired t-test). When salbutamol was given without EIP, baseline arterial oxygen tension (P_{a,O_2}) and arterial carbon dioxide tension (P_{a,CO_2}) were 9.50 ± 1.7 and 7.91 ± 1.2 kPa, respectively, while the corresponding values with EIP were 9.56 ± 1.7 and 7.98 ± 1.2

Table 1. – Patient characteristics and baseline ventilator settings

Age yrs	F_{I,O_2} %	V_T L	V_I L·s ⁻¹	f_R breaths·min ⁻¹	t_I/t_{tot}	$V'E$ L·min ⁻¹
66.9 \pm 8.3	0.40 \pm 0.07	0.55 \pm 0.07	0.63 \pm 0.1	13.0 \pm 2.6	0.19 \pm 0.03	7.2 \pm 1.7

Values are mean \pm SD. F_{I,O_2} : fractional concentration of inspired O_2 ; V_T : tidal volume; V_I : constant inspiratory flow; f_R : respiratory frequency; t_I/t_{tot} : duration of inspiration/duration of breathing cycle (duty cycle); $V'E$: minute ventilation.

Table 2. – Airway pressures, respiratory system mechanics and cardiac frequency before and after salbutamol administration with and without end-inspiratory pause (EIP) of 5-s duration

	Without EIP				With EIP			
	B	15 min	30 min	60 min	B	15 min	30 min	60 min
P_{pk} cmH ₂ O	35.1±5.7	31.3±4.7*	30.6±4.3*	30.7±4.4*	34.8±4.8	30.6±5.6*	31.4±4.9*	31.6±5.1*
P_l cmH ₂ O	26.3±5.3	24.8±4.5	24.3±4.6*	23.4±4.6*	25.4±4.6	23.8±3.8*	23.7±3.7*	24.0±4.1*
P_p cmH ₂ O	21.8±5.3	19.9±3.6*	19.8±3.8*	19.5±3.4*	21.3±4.6	19.1±3.2*	19.0±3.0*	19.5±3.7*
R_{min} cmH ₂ O·L ⁻¹ ·s	14.3±3.7	10.7±3.0*	10.4±2.1*	11.9±2.6*	14.9±1.7	11.9±2.8*	12.3±2.8*	12.4±2.5*
R_{max} cmH ₂ O·L ⁻¹ ·s	21.5±5.3	18.4±3.0*	17.8±2.8*	18.0±2.5*	21.6±1.9	18.2±4.3*	20.0±3.2*	19.5±2.7*
ΔR cmH ₂ O·L ⁻¹ ·s	7.2±2.1	7.8±1.7	7.4±2.3	6.1±2.3	6.7±1.5	6.3±2.2	7.7±2.2	7.1±1.2
$C_{st,rs}$ mL·cmH ₂ O ⁻¹	49.6±22.8	46.9±19.0	48.6±20.1	46.2±14.1	46.8±20.1	46.4±15.2	47.7±14.9	47.3±15.9
PEEP _i cmH ₂ O	8.6±4.6	7.3±4.2*	7.3±4.3*	6.7±3.1*	8.1±4.8	6.7±4.1*	6.9±4.2*	7.1±4.3*
f_c beats·min ⁻¹	85.9±17.6	91.8±13.5	89.7±16.0	87.8±17.3	84.8±18.7	88.6±19.4	89.9±20.1	86.8±18.7

Values are mean±SD. B: baseline; P_{pk} , P_l , P_p : Peak, lower and plateau airway pressures at end-inspiration; R_{min} , R_{max} : minimum and maximum airflow resistances; ΔR : difference between R_{max} and R_{min} ; $C_{st,rs}$: respiratory system static inflation end-inspiratory compliance; PEEP_i: intrinsic positive end-expiratory pressure; f_c : cardiac frequency. *: significantly different from baseline values (p<0.05, two-way analysis of variance).

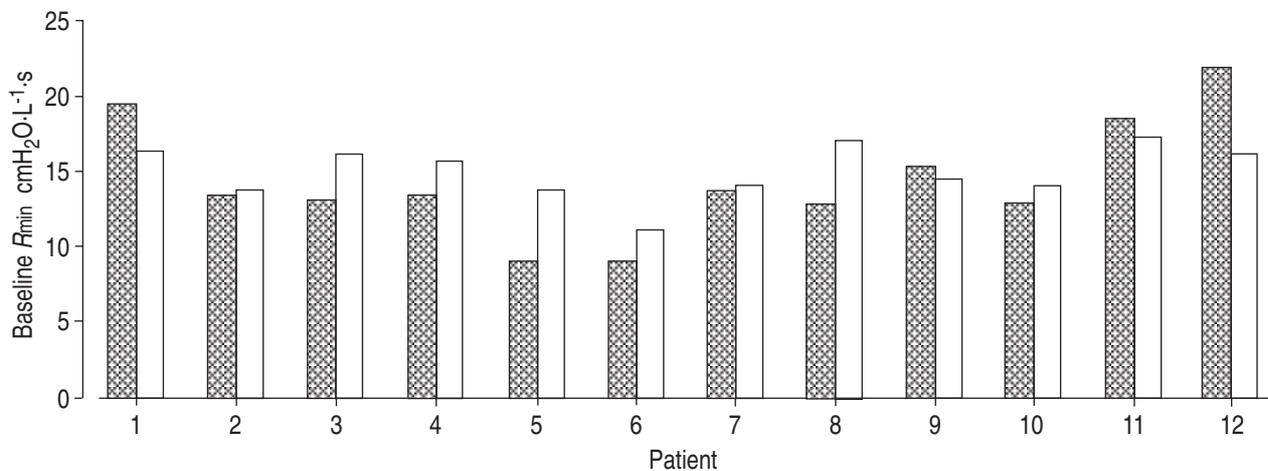


Fig. 1. – Individual baseline minimum airflow resistance (R_{min}) between the two modes of salbutamol administration. ▨: without end-inspiratory pause (EIP); □: with EIP.

kPa. Similarly, baseline (before salbutamol administration) respiratory system mechanics and arterial blood gases did not differ during the 6 h of observation (paired t-test, p>0.05). In the first part of the study baseline R_{min} and R_{max} were 15.2±3.1 and 22.9±2.6 cmH₂O·L⁻¹·s, respectively, while the corresponding values after 6 h were 15.0±2.6 and 21.3±3.3 cmH₂O·L⁻¹·s, indicating that factors other than salbutamol did not appreciably affect the lung function.

The effects of salbutamol, administered with and without EIP, on respiratory system mechanics and f_c are shown in table 2. With both modes of administration, six puffs of salbutamol caused a significant decrease in dynamic and static airway pressures, R_{min} , R_{max} and PEEP_i (ANOVA). These effects were evident at 15 min after the drug delivery and were maintained relatively constantly for at least 60 min. Changes in ΔR and $C_{st,rs}$ were not significant at any time interval after salbutamol administration, either with or without EIP. There was a slight increase in f_c after salbutamol, but the difference was not significant.

EIP of 5 s duration did not have any significant effect on the salbutamol-induced bronchodilation. Without EIP, salbutamol decreased R_{min} by 24.6±5.1%, 24.1±5.2% and

14.8±5.8% from baseline at 15, 30 and 60 min after its administration, respectively. The corresponding values with EIP were 19.8±4.6%, 17.5±4.1% and 17.0±3.4%. Similarly, without EIP salbutamol decreased R_{max} by 12.1±4.0%, 13.4±4.8% and 12.7±5.1% from baseline at 15, 30 and 60 min after the drug delivery, respectively, while the corresponding values with EIP were 15.5±5.6%, 8.0±3.4% and 9.7±3.3%. Figure 2 shows individual changes in R_{min} when salbutamol was delivered with and without EIP. In patients 1 and 5 an opposite response was observed between the two modes of salbutamol delivery. Patient 1 exhibited a bronchodilatory response only when the drug was administered without EIP, while in patient no. 5 a decrease in R_{min} was evident only when salbutamol was delivered with EIP. In the remaining 10 patients salbutamol caused a decrease in R_{min} that was very similar both with and without EIP. In these 10 patients there was a significant linear relationship ($r=0.73$, $p<0.05$) between the average response of R_{min} to salbutamol (mean value of the response at 15, 30 and 60 min) given without EIP and that with EIP. This indicates that within patients the response to salbutamol was quite consistent and independent of the mode of drug administration.

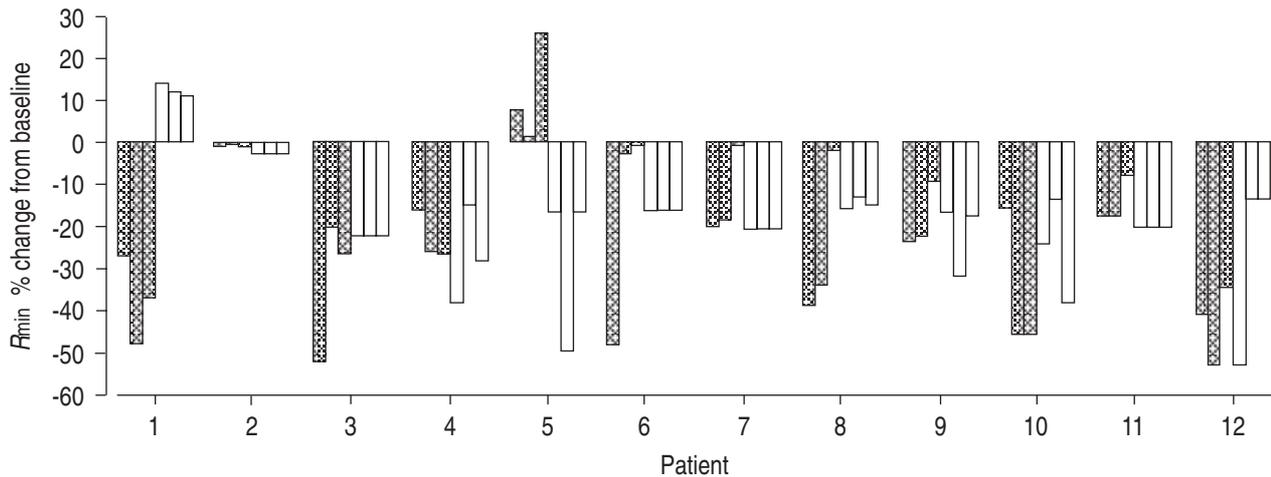


Fig. 2. – Individual changes in minimum airflow resistance (R_{\min}) (% of baseline value) after salbutamol administration. \square : without end-inspiratory pause (EIP); \square : with EIP. For a given patient and mode of drug administration the three bars represent R_{\min} changes at 15, 30 and 60 min after salbutamol administration.

The order of treatments did not affect the response to bronchodilator, in that the decrease in resistance (R_{\min} and R_{\max}) with salbutamol did not differ in the patients who received the drug without EIP first and those who received it with EIP first (Mann-Whitney U-test, $p > 0.05$).

Discussion

This investigation confirmed 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 (R_{\min} and R_{\max}) [1–3]. Although expiratory resistance was not measured in the present study, this was probably decreased by salbutamol, as indicated by the significant reduction in PEEP_i and end-inspiratory static plateau pressure, indirect indices of dynamic hyperinflation. Furthermore, it was demonstrated that application of a 5 s EIP during the drug delivery did not enhance the salbutamol-induced bronchodilation.

A dose of six puffs of salbutamol ($100 \mu\text{g}\cdot\text{puff}^{-1}$) was used. Previous studies have shown that this dose gives the best combination of bronchodilatory effect and safety in mechanically ventilated patients with COPD [3]. Higher doses simply increased the side-effects of the drug (increase in cardiac frequency), without any additional bronchodilation [3]. This, however, does not exclude the possibility that in an individual patient higher doses may be necessary in order to achieve the maximum bronchodilation. For example, it is not known whether or not patient no. 2 would respond to a higher dose of salbutamol.

The patients studied were receiving corticosteroids and this regimen remained unaltered during the study. We do not believe that the administration of corticosteroids influences the results. The patients were receiving corticosteroids for at least 24 h before being studied (most of them > 48 h). It has been shown that administration of corticosteroids during acute exacerbation of COPD induces significant bronchodilation that reaches near maximum by 24 h [17]. This is also supported by the fact that baseline (before salbutamol) respiratory system mechanics and

blood gases 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 the delivery of the bronchodilators with MDI and a spacer is not known. The use of low inspiratory flow, high V_T (> 500 mL), high duty cycle (duration of inspiration (t_i)/duration of breathing cycle (t_{tot})) and 3–5 s EIP has been suggested to increase the effectiveness of MDI therapy [4, 5]. However, these recommendations are based mainly on data from *in vitro* lung models [18], which may not apply in patients. Furthermore, the use of EIP has not been studied either *in vitro* or *in vivo*. To the authors' knowledge the present study is the first to examine the influence of EIP on the effectiveness of β_2 -agonists in mechanically ventilated patients with COPD. It was demonstrated that at constant V_T and inspiratory flow rate, EIP of 5 s duration did not have any beneficial effect on salbutamol-induced bronchodilation, given by an MDI and a spacer.

Two out of 12 patients responded differently between the two modes of salbutamol administration (fig. 2). Patient 1 exhibited a bronchodilatory response only when the drug was administered without EIP, while in patient 5 a decrease in R_{\min} was evident only when salbutamol was delivered with EIP. This, however, does not necessarily mean that the mode of drug delivery is the main factor that underlies the different response. Several other factors, such as the presence of mucus and baseline airway resistance, may influence the response. It is of interest to note that in patient 5, when salbutamol was administered with EIP, baseline R_{\min} was 52% higher than the corresponding value without EIP (the highest difference from all patients). In contrast, in patient 1 the reverse occurred, baseline R_{\min} being 20% higher without EIP than that with EIP (fig. 1). In these two patients the baseline R_{\min} when they did not respond to salbutamol was comparable to values achieved when they responded. Therefore, it is likely that salbutamol, at a background of relatively low airway resistance, was not able to reduce R_{\min} further.

In the current study, in each patient, V_T and inspiratory flow were set by the primary physician according to the needs of the patient. These values were not modified during drug delivery. In previous studies higher tidal volumes were used when bronchodilators were administered [1–3]. It has been suggested that high V_T may increase the effectiveness of bronchodilator drugs in mechanically ventilated patients [4, 5]. However, the magnitude of bronchodilation observed in the present study was comparable to that of studies that used higher V_T [1–3], raising the possibility that changing V_T between 500–1000 mL may have little impact on bronchodilation. Nevertheless, further studies are needed to clarify this point.

Based on current recommendations [4, 5] a pause time of 5 s was used. Thus, it is not known whether these results apply to longer pause times. Nevertheless, a longer pause time may impose a significant risk of hypoxaemia and reduction in cardiac output, with possible detrimental effects on the status of the patient, and increased time taken for personnel to administer salbutamol. However, the bronchodilation achieved in this study (with and without EIP) was comparable to that observed by FERNANDEZ *et al.* [1], who administered bronchodilators using an EIP of 10 s.

The reasons why the application of EIP did not influence the bronchodilation induced by salbutamol are not entirely clear. The use of a high volume spacer, the inspiratory flow profile, the timing of actuation and the relatively high doses of salbutamol may be able to achieve a maximal or near maximal bronchodilation. It is likely that under these circumstances EIP does not represent a critical factor for bronchodilation. Although the design of the study does not permit further clarification of the possible factors involved in the response, the dose of salbutamol may play a cardinal role. Indeed, DHAND *et al.* [3] have shown, in mechanically ventilated patients with COPD, that the decrease in airway resistance with four puffs of salbutamol ($90 \mu\text{g}\cdot\text{puff}^{-1}$) was comparable to that observed with cumulative doses of 28 puffs [3]. Thus, it is possible that six puffs of salbutamol, used in the current study, masked any beneficial effect of EIP by producing a plateau in the bronchodilatory response.

In summary, this study demonstrated in mechanically ventilated patients with acute exacerbation of chronic obstructive pulmonary disease, that six puffs of salbutamol given by a metered-dose inhaler and a spacer device induced significant bronchodilation lasting for at least 60 min. Application of an end-inspiratory pause of 5 s duration did not have any additional bronchodilatory effect. Thus, these results do not favour the routine use of the end-inspiratory pause when bronchodilators are administered in passively ventilated patients with obstructive pulmonary disease. Provided that the dose of the bronchodilator drug is adequate and the technique of administration is proper (use of a high volume spacer and actuation at the beginning of inspiration), significant bronchodilation can be achieved without modification of the ventilator settings.

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