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Effect of inspiratory flow rate on β_2-agonist induced bronchodilation in mechanically ventilated COPD patients

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Abstract *Objectives:* To test the effect of two different inspiratory flow rates on the bronchodilation induced by β_2-agonists administered by metered dose inhaler (MDI).
Patients: Ten patients with acute exacerbation of chronic obstructive pulmonary disease and receiving mechanical ventilation with constant inspiratory flow (V'_I).
Design: Patients received four puffs of salbutamol (100 μg/puff) with either low V'_I (0.6 l/s) or high V'_I (1.2 l/s) administered with an MDI adapted to inspiratory limb of the ventilator circuit using an aerosol cloud enhance spacer. After a 6-h washout patients were crossed-over to receive the drug by the alternative mode of administration.
Measurements and results: Static and dynamic airway pressures, intrinsic positive end-expiratory pressure, and minimum and maximum inspiratory resistance values showed a significant decrease after salbutamol. These changes were not affected by the inspiratory flow rate and were evident 15, 30, and 60 min after administration. Heart rate, static end-inspiratory respiratory system compliance, and the difference between minimum and maximum inspiratory resistance were unchanged after salbutamol.
Conclusions: Salbutamol delivered by MDI and spacer device induces significant bronchodilation in mechanically ventilated patients with chronic obstructive pulmonary disease, but the magnitude of the effect is not affected by the inspiratory flow rate. These results do not support flow rate manipulations when bronchodilators are administered during controlled mechanical ventilation.

Key words Metered dose inhaler · Respiratory system mechanics · Salbutamol · Inspiratory resistance

Introduction

It has been shown in mechanically ventilated patients that the delivery of bronchodilators with metered-dose inhaler (MDI) adapted to the inspiratory line of the ventilator using a spacer device results in bronchodilation comparable to that achieved with nebulizers [1, 2, 3]. The use of MDI has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing, lower drug dose, and reduced risk of contamination [3, 4, 5, 6, 7].

The technique of administering bronchodilators in mechanically ventilated patients using an MDI and a spacer is an important factor in determining the efficacy of this therapy. The timing of drug delivery and the ventilator settings during the administration have been reported to affect drug delivery to target sites and thus bronchodilation [1, 2, 8, 9, 10]. These reports, however, are based on in vitro studies with models of mechanical ventilation. On the other hand, in mechanically ventilated patients suffering acute exacerbation of chronic obstructive pulmonary disease (COPD) we recently dem-

onstrated the lack of additional bronchodilator effect with either an end-inspiratory pause of 5 s or a 50 % increase in tidal volume when bronchodilators were administered [11, 12]. Furthermore, we have shown that the mode of mechanical ventilation during drug administration does not influence the bronchodilation; similar bronchodilation is observed between pressure control and volume control [13]. These studies raise the question of whether ventilator settings are not a critical factor for the bronchodilation.

In vitro and in vivo studies have shown that the inspiratory flow rate (V'_I) during mechanical ventilation is an important determinant of bronchodilator delivery to target sites when the drug is administered by MDI; a significant decrease in drug delivery has been observed with increasing V'_I [9]. It has been suggested that a high V'_I may produce greater impaction of aerosol particles in the ventilator circuit, thus reducing drug delivery into the endobronchial tree [9]. On the other hand, it is recommended that patients with obstructive lung disease should be mechanically ventilated at high V'_I and low duty cycle in order to increase the time available for expiration and thus to reduce the dynamic hyperinflation [14]. The increased V'_I might reduce the response to bronchodilators by decreasing the drug delivery to target sites, counterbalancing to some extent the beneficial effect of high V'_I on dynamic hyperinflation. The effect of V'_I on bronchodilation, however, has not been studied. Therefore the purpose of the present study was to examine the effect of V'_I at constant tidal volume on the bronchodilation induced by β_2-agonists administered by an MDI and a spacer, in a homogeneous group of mechanically ventilated patients with acute exacerbation of COPD.

Methods and materials

Ten patients (seven men and three women; aged 68.2 ± 5.6 years) with COPD, requiring mechanical ventilation to manage acute respiratory failure due to an acute exacerbation of chronic airflow obstruction, were studied. This group of patients was completely different than those studied in our previous reports [11, 12, 13]. All patients had a previous diagnosis of COPD and met established criteria for this diagnosis [15]. 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' physical characteristics and baseline ventilator settings were as follows: fractional concentration of inspired O_2 (FIO_2), 0.39 ± 0.09 %; partial pressure of O_2 (PaO_2), 70.1 ± 4.8 mmHg; partial pressure of CO_2 ($PaCO_2$), 56.5 ± 7.5 mmHg; tidal volume (V_T), 0.53 ± 0.05 l; breathing frequency, 10.8 ± 0.9 breaths/min; inspiratory time (T_I), 1.23 ± 0.1 s; constant V'_I, 0.59 ± 0.02 l/s; duty cycle (T_I/T_{TOT}), 0.22 ± 0.02; minute ventilation (V'_E), 5.62 ± 0.58 l/min.

The patients were studied in 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 in internal diameter, heavily sedated (propofol and fentanyl), and ventilated on volume controlled mode using Servo 300 (Siemens, Solna, Sweden) ventilators. The ventilator was set to deliver a specific tidal volume with a square wave flow-time profile. V'_I was set at 0.55–0.60 l/s, and no end-inspiratory pause was applied. V_T and breathing frequency were adjusted in each individual by the attending physician to maintain normal arterial pH and remained constant throughout the study. Extrinsic positive end-expiratory pressure (PEEP) was set to zero.

Flow at the airway opening was measured with a heated pneumotachograph (Hans-Rudolf 3700, Kansas, USA) and a differential pressure transducers (MicroSwitch 140PC, Honeywell, Ontario, Canada), placed between the endotracheal tube and the ventilator. Flow was electronically integrated to provide volume. Airway pressures (Paw; MicroSwitch 140PC) were measured from a side port between the pneumotachograph and the endotracheal tube. All signals were sampled at 150 Hz (Windaq Instruments, Ohio, USA) and stored on a computer disk for later analysis.

Patients were prospectively randomized to receive four puffs of salbutamol (100 µg/puff given by an MDI canister, Aerolin inhaler, Glaxo Wellcome) at either low V'_I (baseline 0.6 ± 0.02 l/s) or high V'_I (1.2 l/s). V_T was kept constant, and no end-inspiratory pause was applied. This caused, when the drug was administered at high V'_I, a proportional decrease in T_I and T_I/T_{TOT}. At high V'_I the T_I and T_I/T_{TOT} values were 0.68 ± 0.07 s and 0.12 ± 0.01, respectively. These values were considerably lower than those at low V'_I (baseline). After a 6-h washout patients were crossed-over to receive the drug by the alternative mode of administration. The technique of drug administration using an MDI and a spacer (ACE, Diemolding Healthcare Division, USA) has been described in detail elsewhere [11, 12, 13]. All bronchodilators were withheld at least 6 h before the study. Patients received corticosteroids (240 mg methylprednisolone/day), and this regimen was not modified during the study. None of the patients was on theophylline. Arterial blood gases were measured before the drug administration. Saturation of hemoglobin (SaO_2) was measured continuously using a pulse oxymeter (Critikon, Tampa, Fla., USA).

Respiratory system mechanics and heart rate were assessed before (baseline) and 15, 30, and 60 min after each series of puffs. The mechanical properties of the respiratory system were determined while the patient was ventilated on volume control at baseline ventilator settings (see above). The mechanics of the respiratory system were measured using the occlusion technique [16, 17] as described elsewhere [11, 12, 13]: dynamic and static airway pressures, minimum (R_{int}) and maximum (R_{rs}) inspiratory resistance, the difference between R_{rs} and R_{int} (ΔR), static end-inspiratory respiratory system compliance ($C_{st,rs}$), and intrinsic PEEP.

Data were analyzed by paired *t* test and two-way analysis of variance for repeated measurements where appropriate. When the *F* value was statistically 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 heart rate before the administration of each series of puffs of salbutamol are shown in Table 1. There was no significant difference in any of these variables between the two conditions of drug delivery (analysis of variance). Furthermore, baseline arterial blood gases did not differ significantly between the two modes of salbutamol ad-

Table 1 Airway pressures, respiratory system mechanics and heart rate before and after Salbutamol administered at low (0.6 l/s) and high (1.2 l/s) V'_I. Respiratory system mechanics were measured when the patients were on volume control with square-wave inspiratory flow time profile and ventilated at baseline ventilator settings[a] (P_{pk} P_I P_p dynamic and static airway pressures at end-inspiration, R_{int} Minimum airflow resistance, R_{rs} maximum airflow resistance, ΔR difference between minimum and maximum airflow resistance, $C_{st,rs}$ respiratory system static inflation end-inspiratory compliance)

	Low V'_I				High V'_I			
	Baseline	15 min	30 min	60 min	Baseline	15 min	30 min	60 min
P_{pk} (cmH_2O)	33.5 ± 4.3	29.6 ± 4.8*	30.1 ± 3.9*	30.2 ± 4.7*	32.6 ± 4.2	29.5 ± 4.6*	29.3 ± 4.5*	29.2 ± 4.5*
P_I (cmH_2O)	21.8 ± 4.5	20.3 ± 4.7*	20.5 ± 4.4*	20.6 ± 4.8*	21.0 ± 4.9	19.8 ± 5.3*	19.5 ± 5.1*	19.5 ± 5.2*
P_p (cmH_2O)	19.1 ± 4.6	17.6 ± 4.8*	17.8 ± 4.5*	17.8 ± 5.3*	18.4 ± 4.8	17.1 ± 5.2	16.9 ± 5.1*	16.8 ± 5.1*
R_{int} ($cmH_2O\ l^{-1}\ s^{-1}$)	19.4 ± 4.1	15.3 ± 3.2*	15.8 ± 3.3*	15.8 ± 3.3*	19.4 ± 3.5	16.1 ± 2.9*	16.3 ± 2.6*	16.1 ± 2.9*
R_{rs} ($cmH_2O\ l^{-1}\ s^{-1}$)	24 ± 3.9	19.9 ± 2.8*	20.1 ± 3.2*	20.5 ± 2.9*	24.2 ± 3.3	20.6 ± 2.4*	20.6 ± 2.4*	20.6 ± 2.5*
ΔR ($cmH_2O\ l^{-1}\ s^{-1}$)	4.5 ± 1.3	4.5 ± 1.4	4.5 ± 1.4	4.7 ± 1.6	4.5 ± 1.4	4.6 ± 1.4	4.3 ± 1.1	4.4 ± 1.5
$C_{st,rs}$ (ml/cmH_2O)	54.7 ± 18.3	52.6 ± 18.5	51.7 ± 16.6	52.6 ± 18.7	58.3 ± 22.1	52.4 ± 15.5	52.4 ± 14.3	53.2 ± 14.7
Intrinsic PEEP (cmH_2O)	8.2 ± 2.3	6.3 ± 2.4*	6.3 ± 2.6*	6.3 ± 2.5*	8.0 ± 2.5	6.2 ± 2.6*	6.2 ± 2.8*	6.2 ± 2.7*
Heart rate (bpm)	85.1 ± 16.1	84.7 ± 15.7	84.9 ± 15.8	84.5 ± 16.1	85.3 ± 17	86.5 ± 17.1	87.4 ± 17.4	86.8 ± 17.1

*$p < 0.05$ vs. baseline (two-way analysis of variance)
[a]FIO_2 0.39 ± 0.09 %; PaO_2 70.1 ± 4.8 mmHg; $PaCO_2$ 56.5 ± 7.5 mmHg; V_T 0.53 ± 0.05 l; 10.8 ± 0.9 breaths/min; T_I 1.23 ± 0.1 s; V'_I 0.59 ± 0.02 l/s; T_I/T_{TOT}, 0.22 ± 0.02; V'_E 5.62 ± 0.58 l/min

ministration. Similarly, baseline (before salbutamol administration) respiratory system mechanics and arterial blood gasses did not differ during the 6 h of observation (paired t test, $p > 0.05$). Therefore factors other than salbutamol did not appreciably affect the lung function.

The effects of salbutamol, administered at low and high V'_I, on respiratory system mechanics and heart rate are shown in Table 1. The V'_I (and T_I) did not have any significant effect on the salbutamol induced bronchodilation. At each V'_I rates four puffs of salbutamol caused a significant decrease in dynamic and static airway pressures, R_{int}, R_{rs} and intrinsic PEEP. These effects were evident 15 min after drug delivery and remained relatively constant for at least 60 min. Figure 1 shows individual values of R_{int} at baseline and 60 min after salbutamol. Differences in heart rate, ΔR, and $C_{st,rs}$ as regards V'_I values were not significant at any point after salbutamol administration. SaO_2 remained constant throughout the study, indicating that no clinical significant changes in PaO_2 occurred as a result of salbutamol administration.

There was a significant linear relationship between the response of R_{int} to salbutamol administered at low and high V'_I (Fig. 2), indicating that within patients the response to salbutamol was quite consistent and independent of V'_I during drug administration. In one patient significant bronchodilation was observed only when salbutamol was given at low V'_I (Figs. 1, 2).

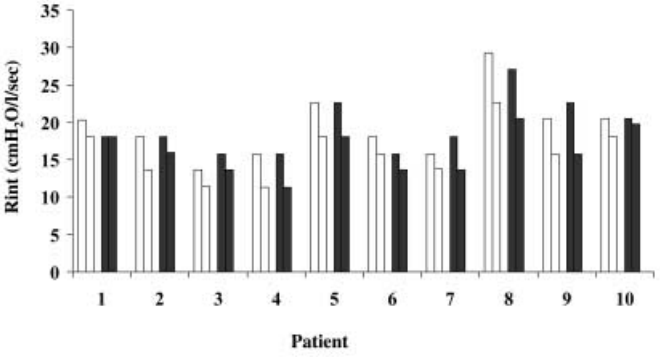

Fig. 1 Individual values of minimum inspiratory resistance *(Rint)* before and 60 min after 400 μg salbutamol administration. *Open bars* At low V'_I, *closed bars* at high V'_I. For a given patient and mode of drug administration *the two bars* represent Rint at baseline (before salbutamol administration) and 60 min after salbutamol administration. Rint after 15 and 30 min were omitted for clarity of presentation

Discussion

Our findings confirm those of previous studies showing that β_2-agonists delivered by MDI and a spacer produce a significant and sustained decrease in inspiratory resistance in mechanically ventilated patients with COPD [3, 11, 12, 13]. We also observed no effect of V'_I or T_I on the response.

All patients were on corticosteroids, and this regimen remained unaltered during the study. We do not believe that the administration of corticosteroids influenced, at least qualitatively, the results. The patients were on corticosteroids for at least 24 h before being studied. It has been shown that the administration of corticosteroids during acute exacerbation of COPD induces significant bronchodilation that reach near maximum by 24 h [18]. 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 func-

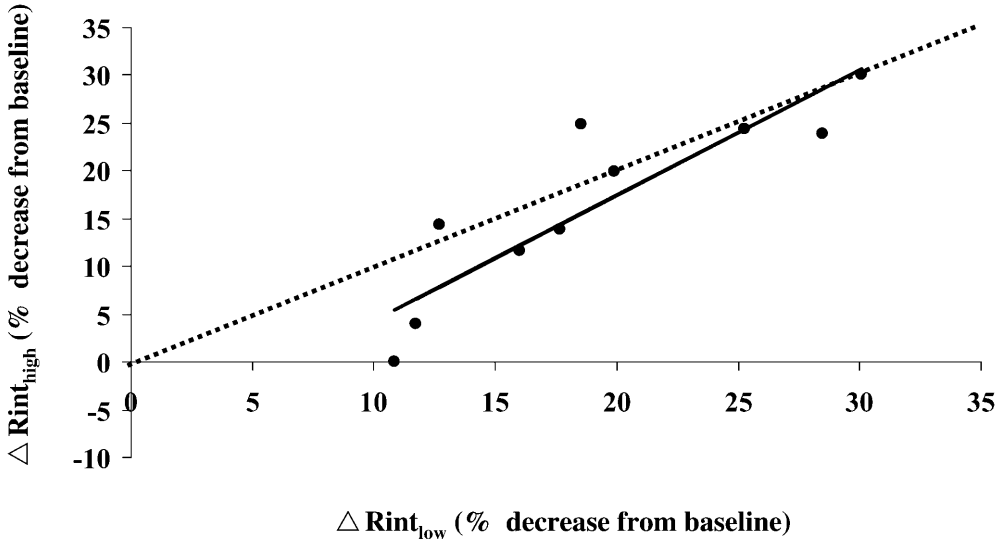

Fig. 2 Relationship between the mean bronchodilatory response of minimum inspiratory resistance (*Rint*; % decrease from baseline) when 400 μg salbutamol was given at low V'_I ($\Delta Rint_{low}$) and high V'_I ($\Delta Rint_{high}$). The mean bronchodilatory response was obtained by averaging the Rint response 15, 30, and 60 min after salbutamol. *Continuous line* Regression line; *broken line* identity ($r = 0.87$, $p < 0.05$). For clarity of presentation mean bronchodilatory response was used instead of data at various time intervals after drug administration. The significant linear relationships did not change by pooling all data

tion during the study period was not significantly affected by factors other than salbutamol. Nevertheless, the response to salbutamol that we observed might have been limited by the corticosteroid-induced bronchodilation.

In mechanically ventilated patients the optimal ventilatory pattern during the delivery of the bronchodilators with MDI and a spacer is not well known. The use of low V'_I, high V_T (> 500 ml) and T_I/T_{TOT}, decelerating rather than square-wave V'_I/T_I profile, and 3–5 s end-inspiratory pause has been suggested to increase the effectiveness of MDI therapy [1, 2, 8, 9, 10]. However, these recommendations are based mainly on aerosol delivery data [8, 9, 10] which may not reflect drug bronchodilator effect. Indeed, our recent studies show that the use of a 5-s end-inspiratory pause [11], increasing the V_T at constant V'_I [12] and pressure control ventilation [13], strategies which likely enhance drug delivery [1, 2, 8, 9, 10], do not augment the bronchodilator effect of salbutamol. It is of interest to note that pressure control ventilation did not influence the bronchodilation induced by 200 μg or 600 μg of salbutamol [13]. The current study demonstrated that, at constant V_T, increasing the V'_I, which causes a proportional decrease in T_I, has no effect on salbutamol-induced bronchodilation given by MDI and a spacer. The findings of the present work combined with those of the previous studies [11, 12, 13] do not support alterations in ventilator settings (i.e., V'_I, T_I, V_T, end-inspiratory pause) when bronchodilator drugs are administered in mechanically passively ventilated patients.

One patient (no. 1) responded differently to the two modes of salbutamol administration, exhibiting a bronchodilatory response only when the drug was administered at low V'_I. This, however, does not necessarily mean that the flow rate is the main factor in explaining the different response. In this patient, when salbutamol was given at high V'_I, baseline R_{int} was considerably lower than that at low V'_I (Fig. 1). It is possible that salbutamol, at a background of relatively low airway resistance, was not able to reduce R_{int} further. Similar observation has been made previously [11].

It has been shown in an in vitro model of mechanical ventilation that albuterol delivery to target sites increases linearly with increasing T_I/T_{TOT} [9]. Furthermore, there is evidence, also based on models of mechanical ventilation, that drug delivery decreases with increasing V'_I [9, 10]. Thus, although we did not measure drug delivery to the lower respiratory tract, it is likely that the administration of salbutamol at relatively low V'_I and high T_I/T_{TOT} is associated with increased drug delivery. However, this enhancement was not associated with additional bronchodilation. This suggests that maximal or near maximal bronchodilation may be achieved in patients receiving controlled mechanical ventilation when at least 400 μg salbutamol is administered by a high volume spacer, a V_T of approximately 500 ml, and MDI actuation synchronized with V'_I. It is likely that under these circumstances V'_I and T_I do not represent critical factors for bronchodilation. Although salbutamol doses less than 400 μg were not studied, we recently demonstrated similar bronchodilation induced by doses of 200 and 600 μg [13], indicating that maximal bronchodila-

tion may be achieved with doses as low as 200 μg in mechanically ventilated patients with acute exacerbation of COPD.

The response to salbutamol was examined when V'_I increased from 0.6 to 1.2 l/s and T_I decreased from 1.2 to 0.68 s. Therefore it is not known whether these findings apply to V'_I and T_I values outside of this range. However, a previous study demonstrated at constant V'_I that increasing T_I from 1.2 to 1.7 s by increasing V_T has no effect on the bronchodilation induced by salbutamol [12]. It seems that, at V_T of approximately 500 ml, changing T_I from 0.6 to 1.7 s does not influence the β_2-agonist bronchodilator effect. Nevertheless, the range of V'_I and T_I values studied are those commonly used in clinical practice in cases of obstructive lung disease [14].

In summary, we found that salbutamol given by an MDI and spacer device induced significant bronchodilation lasting for at least 60 min in mechanically ventilated patients with acute exacerbation of COPD. The magnitude of bronchodilation was not affected by V'_I or T_I during drug administration. Thus, these results do not favor the routine manipulation of flow rate when bronchodilators are administered in passively ventilated patients with obstructive pulmonary disease. Provided that the technique of administration is proper (use of spacer with high volume, actuation at the beginning of inspiration) significant bronchodilation may be achieved without modifying the ventilator settings. Minimizing the importance of manipulation in ventilator settings, the use of MDI in mechanically ventilated patients is more attractive because it is more easily applicable.

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