Bronchodilator Therapy with Metered-Dose Inhaler and Spacer Versus Nebulizer in Mechanically Ventilated Patients: Comparison of Magnitude and Duration of Response

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OBJECTIVE: Four-hour comparison of the bronchodilator response of albuterol administered via metered-dose inhaler (MDI) with spacer versus small-volume nebulizer (SVN) to mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). DESIGN: Prospective randomized clinical trial. SETTING: Medical intensive care unit in a university hospital. PATIENTS: Thirteen mechanically ventilated COPD patients. INTERVENTION: Albuterol administration of 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via MDI with spacer or 2.5 mg via SVN to mechanically ventilated patients in order to assess the bronchodilator response over 4 hours. MEASUREMENTS AND RESULTS: Mechanically ventilated patients were enrolled in a randomized crossover study wherein one group received 4 puffs (0.4 mg) or 2.5 mg of albuterol and another group received 10 puffs (1.0 mg) or 2.5 mg of albuterol on separate days. Respiratory mechanics measurements were obtained over 4 hours. Total airway resistance declined by 14.4 ± 3.8% after 4 MDI puffs, 18.3 ± 1.8% after 10 MDI puffs, or 13.7 ± 2.6% after 2.5 mg via SVN, compared to baseline ($p < 0.01$). After albuterol delivery, airway resistance remained improved for 90–120 minutes ($p < 0.05$) and returned to baseline by 4 hours with all treatments. CONCLUSION: The airway response to albuterol administration via MDI and SVN to mechanically ventilated patients was similar in magnitude and duration, returning to baseline by 240 minutes. In stable, mechanically ventilated COPD patients, albuterol may be administered via MDI with spacer or via SVN every 4 hours. [Respir Care 2000;45(7):817–823] *Key words: bronchodilator, albuterol, obstructive lung disease, inhalation therapy, aerosols, mechanical ventilation.*

Background

Inhaled bronchodilators are frequently used in the management of mechanically ventilated patients because this route of administration provides the greatest benefit with the least adverse effects. Bronchodilators have traditionally been delivered via small-volume nebulizer (SVN), although factors related to cost and convenience support the use of metered-dose inhaler (MDI) administration to ventilator-supported patients.[1] Several investigators have conducted randomized, controlled trials of limited duration comparing bronchodilator delivery via SVN and MDI to intubated, mechanically ventilated patients.[2–4] However, concerns were raised regarding stability of the radioisotope, the heterogeneous nature of the patient populations, and the techniques of delivery, thereby making interpretation of these studies difficult.[5]

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Recommendations by a panel of experts regarding dosing of inhaled bronchodilators to intubated, mechanically ventilated patients suggested individualizing therapy according to the severity of disease through "dose increases. . . titrated to carefully monitored objective responses."[6] Though titration to a physiologic response is appealing, tachyarrhythmias have been reported with this approach.[3]

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Furthermore, several investigators have reported significant dose responses to inhaled bronchodilator administration via either MDI or SVN.[7–9] These reports have assisted in the formulation of guidelines for bronchodilator delivery to ventilator-supported patients. However, there are little data addressing the duration of action.[5] Accordingly, we conducted a prospective, randomized, controlled trial to compare the airway response of albuterol administration via MDI with spacer and via SVN over a 4-hour interval in mechanically ventilated patients using a standard ventilator setup.

Materials and Methods

Patients

Thirteen patients with chronic obstructive pulmonary disease (COPD), as defined by the American Thoracic Society guidelines, were enrolled in the study.[10] The etiologies of acute respiratory failure were upper respiratory tract infection ($n = 8$), pneumonia ($n = 2$), airway obstruction ($n = 2$), and pulmonary embolism ($n = 1$). Pulmonary function studies were available for 5 patients (mean forced expiratory volume in the first second [FEV_1] = 1.01 mL, range 0.48–1.63 mL). The mean age was 63 ± 3 years, with the majority being male (Table 1). Less than one third of the group (4/13) were previously intubated for respiratory failure, and 9/13 had been prescribed domiciliary oxygen within the past 3 months. Patients were studied during stable phases of their intensive care unit courses, and those with a history of asthma, angina, life threatening arrhythmias, myocardial infarction within the past 3 months, or hemodynamic instability were excluded. The diagnosis of asthma was based on the medical history, and because pulmonary function studies were not available for all patients, it is conceivable that some patients with asthma may have been enrolled. All patients received intravenous steroids as part of their medical regimen, and one patient received an aminophylline infusion. The study was approved by the investigational review board, and signed, written, informed consent was obtained from all patients.

Table 1. Patient and Mechanical Ventilator Profile*

Age (y)	63 ± 3
V_T (mL)	630 ± 22
f (breaths/min)	12.0 ± 0.4
$\dot{V}_E$ (L/min)	7.5 ± 0.4
F_{IO_2}	0.35 ± 0.03
T_I (s)	0.65 ± 0.01
T_E (s)	4.50 ± 0.02
T_I/T_{TOT}	0.13 ± 0.01

*Values are mean ± standard error.
V_T = tidal volume. f = respiratory frequency. $\dot{V}_E$ = minute ventilation. F_{IO_2} = fraction of inspired oxygen. T_I = inspiratory time. T_E = expiratory time. T_I/T_{TOT} = duty cycle (ratio of inspiratory time to total breathing cycle time).

Protocol

Mechanical ventilation was instituted with a BEAR 1000 ventilator (Bear Medical Systems, Riverside, California) using constant inspiratory flow and volume. Inspired gas was heated to 35 ± 1° C and humidified to 98 ± 2% relative humidity using a heated-wire circuit (Isothermal circuit, Allegiance Healthcare, McGaw Park, Illinois) throughout the study. Bronchodilators were withheld 4 hours prior to the study. Prior to commencing, tracheal secretions were removed from the endotracheal tube. Patients were sedated with continuous infusions of lorazepam ($n = 10$) or propofol ($n = 3$) and received the same form of sedation during the two arms of the study. Passive ventilation was achieved by increasing delivered tidal volume (V_T) to 500–1000 mL. Passive ventilation was defined as absence of a negative deflection in the pressure tracing prior to inspiration, a smooth convex pressure waveform, and matching ventilator and patient respiratory rate.[11] A randomized crossover design was used, whereby patients were randomly selected to receive albuterol via MDI or SVN (Misty-Neb, Allegiance Healthcare, McGaw Park, Illinois) on Day 1, followed by the alternate method of administration 24 hours later. Patients selected to receive albuterol via MDI were randomly assigned to receive 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via a chamber style spacer (Aerovent, Monaghan Medical, Plattsburgh, New York). All but one patient received albuterol via MDI and SVN, and that patient received medication only via MDI. The albuterol MDI canister (Glaxo Wellcome, Research Triangle Park, North Carolina) (manufacturer-estimated dose of 100 μg/puff) was warmed to hand temperature, well shaken, primed, and discharged into the Aerovent chamber, which was in the inspiratory limb of the ventilator circuit 10 cm from the endotracheal tube. Each actuation was performed at the onset of inspiration, with successive doses actuated from the MDI at 30-second intervals. The SVN (Misty-Neb) was attached to the ventilator circuit 30 cm from the endotracheal tube. The nebulizer cup was filled with 2.5 mg of albuterol sulfate and normal saline (Dey Laboratories, Napa, California) (for a total volume of 3 mL) and driven by an external gas compressor at 50 psi. The SVN was operated continuously at a flow of 6 L/min and intermittently tapped until it sputtered without interruption.

Airway Measurements

Once passive ventilation was achieved, airway measurements were obtained using a respiratory monitor (BiCore, Irvine, California). Pressure, flow, and volume measure-

ments were collected using a precalibrated pneumotachograph attached to the end of the endotracheal tube. The pressure and flow signals were continuously digitized at 50 and 100 Hz, respectively, using a 12-bit analog-to-digital converter linked to a computer, and were stored for later analysis. Airway measurements were obtained prior to administration and at 10, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after albuterol administration. Airway measurements consisted of 5–8 rapid end-inspiratory and end-expiratory airway occlusions performed during the previously mentioned time points. Heart rate, blood pressure, oxygen saturation, and cardiac rhythm were continuously monitored and recorded.

Respiratory Mechanics Calculations

Representative breaths were selected and studied to determine the corresponding airway pressures. During an end-inspiratory occluded breath, peak and plateau airway pressures were determined. Initial pressure was obtained by intersection of the peak airway pressure and a tangent back-extrapolated from the plateau pressure.[11,12] Intrinsic positive end-expiratory pressure ($PEEP_I$) was determined as the static pressure during an end-expiratory occlusion. Total or maximum airway resistance (Rrs_{max}) was calculated as the difference between peak and plateau pressures, divided by the inspiratory flow. The ohmic resistance of the airway or minimum airway resistance (Rrs_{min}) was calculated as the difference between peak and initial pressures, divided by the inspiratory flow. Resistance (ΔRrs) resulting from tissue viscoelastance and time constant differences was calculated as the difference between Rrs_{max} and Rrs_{min}. The percent change in resistance was calculated as the difference between the pre-bronchodilator and post-bronchodilator values divided by the pre-bronchodilator value. Static lung compliance was calculated as the delivered V_T divided by the difference between plateau pressure and $PEEP_I$. Calculations were performed for each timed measurement point.

Statistical Analysis

Results are expressed as mean ± standard errors. Respiratory mechanics measurements and vital signs prior to drug administration were compared with values obtained after albuterol administration, using one-way analysis of variance (ANOVA) with repeated measures and the Tukey test for multiple comparisons between individual means, when appropriate. Comparison of the changes in respiratory mechanics on Day 1 and Day 2 was performed using ANOVA. Statistical analysis was performed using SigmaStat for Windows, Version 2.0 (Jandel, San Rafael, California).

Table 2. Baseline Pulmonary Mechanics*

	MDI 0.4 mg	MDI 1.0 mg	SVN 2.5 mg
Rrs_{max} (cm H_2O/L/s)	18.0 ± 1.3	18.1 ± 1.3	18.4 ± 1.2
Rrs_{min} (cm H_2O/L/s)	16.1 ± 1.3	16.8 ± 1.1	16.7 ± 1.1
ΔRrs (cm H_2O/L/s)	1.9 ± 0.5	1.4 ± 0.8	1.7 ± 0.8
C_{st} (mL/cm H_2O)	28 ± 6	32 ± 8	29 ± 4
$PEEP_I$ (cm H_2O)	9.4 ± 2.4	18.1 ± 1.5†	12.9 ± 2.3

*Values are mean ± standard error. Rrs_{max} = maximum airway resistance. Rrs_{min} = minimum airway resistance. ΔRrs = tissue resistance, time constant differences. C_{st} = compliance. $PEEP_I$ = intrinsic positive end-expiratory pressure.
†0.4 mg vs 1.0 mg, $p < 0.01$.

Results

Baseline airway resistances were similar among the groups ($p > 0.7$) (Table 2). The greatest decrease in Rrs_{max} occurred 10 minutes after albuterol administration of 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via MDI with spacer or 2.5 mg via SVN ($p < 0.01$) (Fig. 1). Following administration of 4 puffs or 10 puffs via MDI or 2.5 mg via SVN, Rrs_{max} decreased by 14.4 ± 3.8%, 18.3 ± 1.8%, and 13.7 ± 2.6%, respectively, compared to baseline ($p < 0.01$). The decrease in Rrs_{max} was 5–33% after 4 puffs, 5–22% after 10 puffs, and 3–33% after 2.5 mg of albuterol. Similarly, minimum (or the true ohmic) airway resistance (Rrs_{min}) decreased significantly after 4 puffs (decrease of 15.9 ± 4.6%), 10 puffs (decrease of 19.8 ± 2.5%), or 2.5 mg (decrease of 14.5 ± 2.5%), compared to baseline ($p < 0.01$) (Fig. 2). Compared to baseline, there was no significant difference in the mean maximum percent decrease in Rrs_{max} and Rrs_{min} following either MDI or SVN administration.

Total Rrs_{max} remained significantly decreased for 90–120 minutes after 4 puffs, 10 puffs, or 2.5 mg via SVN ($p < 0.05$) (see Fig. 1). By 240 minutes after MDI or SVN delivery, Rrs_{max} returned to baseline (see Fig. 1). Similarly, Rrs_{min} remained significantly decreased 90–120 minutes after albuterol delivery, and returned to baseline by 240 minutes. A comparison of the percent decrease in airway resistance among the three groups revealed no significant difference with respect to albuterol dose over time ($p > 0.05$).

Baseline $PEEP_I$ was greater in the group receiving 10 puffs of albuterol than in the group receiving 4 puffs ($p < 0.01$) or 2.5 mg via SVN (not significant). Compared to baseline, $PEEP_I$ declined significantly with administration of 4 puffs, 10 puffs, or 2.5 mg of albuterol, with the greatest decrease occurring 10 minutes after albuterol delivery ($p < 0.05$). $PEEP_I$ remained significantly diminished 90 minutes after drug delivery with either dose or device ($p < 0.05$). Compared to baseline, ΔRrs did not

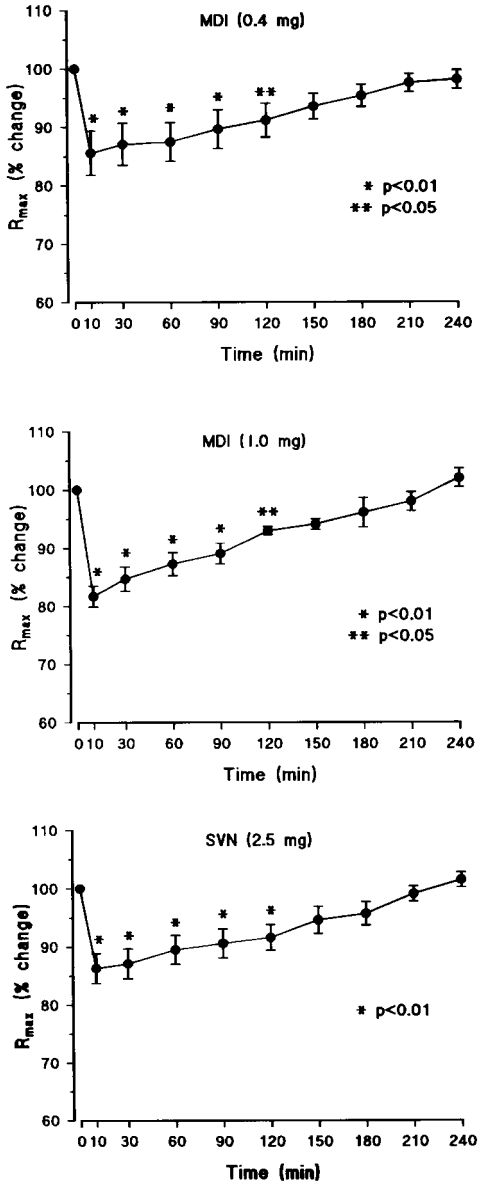

Fig. 1. Change in total (or maximum) airway resistance (Rrs_{max}) after albuterol administration of (top) 4 puffs (0.4 mg) via MDI with spacer, (middle) 10 puffs (1.0 mg) via MDI with spacer, and (bottom) 2.5 mg via SVN, in ventilator-supported COPD patients. Rrs_{max} significantly declined from baseline ($p < 0.01$) and the response was sustained for 120 minutes ($p < 0.05$), returning to baseline within 240 minutes of MDI or SVN albuterol administration. The airway response was similar for albuterol dose or delivery device. Values are means and error bars represent standard error of the mean.

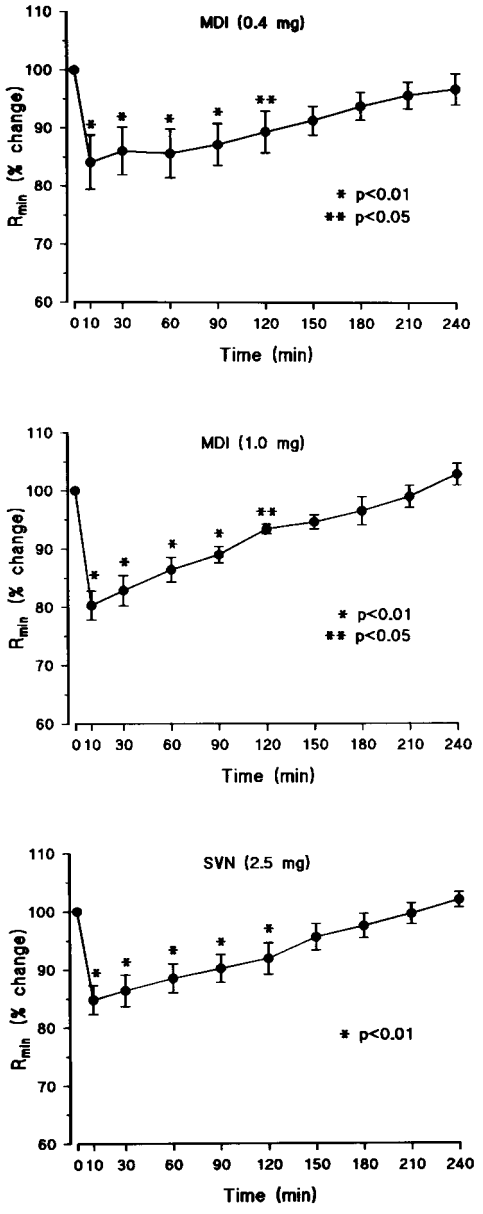

Fig. 2. The effect on minimum airway resistance (Rrs_{min}) after albuterol administration of (top) 4 puffs (0.4 mg) via MDI with spacer, (middle) 10 puffs (1.0 mg) via MDI with spacer, and (bottom) 2.5 mg via SVN to mechanically ventilated COPD patients. A significant decline in Rrs_{min} occurred at 10 minutes and was sustained for 120 minutes, returning to baseline within 240 minutes of MDI or SVN albuterol administration. The airway response was similar among the albuterol doses and delivery devices. Values are means and error bars represent standard error of the mean.

decline significantly after MDI or SVN albuterol delivery. There was no significant change in static lung compliance following MDI or SVN albuterol administration. After albuterol delivery, heart rate, blood pressure, and oxygen saturation were not significantly different than baseline values (Table 3).

Discussion

Although several investigators have examined the action of inhaled bronchodilators in mechanically ventilated patients, we were interested in evaluating the duration of bronchodilator response over 4 hours. We conjectured that

Table 3. Patient Hemodynamics and Oximetry Profile*

	MDI - 0.4 mg		MDI - 1.0 mg		SVN - 2.5 mg	
	Baseline	10 min	Baseline	10 min	Baseline	10 min
HR (beats/min)	77.8 ± 5.1	76.8 ± 5.9	89.7 ± 6.8	91.2 ± 5.4	77.7 ± 5.2	79.4 ± 5.0
MAP (mm Hg)	86.4 ± 2.8	87.1 ± 2.7	93.5 ± 6.6	88.5 ± 5.9	86.5 ± 5.1	89.2 ± 5.0
S_{pO_2} (%)	98.0 ± 0.4	97.7 ± 0.5	97.8 ± 0.7	97.4 ± 0.8	97.4 ± 0.5	97.1 ± 0.7

*Values are mean ± standard error.
HR = heart rate. MAP = mean arterial pressure. S_{pO_2} = arterial oxygen saturation measured via pulse oximetry.

in mechanically ventilated COPD patients the duration of bronchodilator response would be different than in nonintubated patients because of differences in aerosol administration, the presence of an endotracheal tube, or difference in the degree of airway inflammation. To our knowledge, a study of the bronchodilator response beyond 2 hours in ventilator-supported patients has not been previously conducted. Several groups have evaluated the bronchodilator response in ventilator-dependent patients for 30–120 minutes following MDI or SVN delivery.[3,4,7,9,13–16] However, it was unclear from these reports whether the bronchodilator duration of action would persist beyond 120 minutes in ventilator-supported patients. In the present study, we observed a significant decrease in airway resistance for 120 minutes, and resistance returned to baseline within 240 minutes of albuterol delivery. This bronchodilator response profile differs from a previous report in nonintubated COPD or asthma patients.[17] Our findings serve as a useful guide in establishing bronchodilator dosing schedules in stable, mechanically ventilated COPD patients. However, rigid application of this dosing regimen to every ventilator-supported patient would be too simplistic, and under other circumstances more frequent dosing may be required.

Another finding was the similar bronchodilator response profiles following delivery of 0.4 mg via MDI and 2.5 mg of SVN albuterol to mechanically ventilated patients. The maximum airway resistance at baseline was comparable to previously reported values in mechanically ventilated patients.[7,11] Similarly, other authors have reported a rapid onset of action following bronchodilator administration.[13–15,18] However, direct comparison studies examining the peak airway response after MDI and SVN bronchodilator administration to mechanically ventilated patients have yielded various results.[2–4,14] Recently, Guerin et al reported similar decreases in Rrs_{max} 30 minutes after MDI or SVN administration of fenoterol and ipratropium to ventilator-supported COPD patients.[14] They observed a decline in resistance (ΔRrs) because of tissue viscoelasticity and time constant differences following SVN administration, and concluded this was due to greater peripheral pulmonary drug deposition. We observed a decrease in Rrs_{max} but no decline in ΔRrs following MDI or SVN albuterol administration. The observed differences between the studies may be because Guerin et al[14] simultaneously delivered a β agonist and anticholinergic solution, producing a central and peripheral airway response. Additionally, had the peak anticholinergic effect been assessed at 60 minutes rather than at 30 minutes, a similar finding may have been noted following MDI and SVN administration. Nonetheless, a clinically significant airway response may be obtained by selection of an efficient aerosol delivery device in conjunction with a reliable technique of administration.

We speculate that the resemblance between the response profiles following 0.4 mg, 1.0 mg, and 2.5 mg of albuterol may be related to the shallowness of the bronchodilator dose response curve. There are also other factors to explain this observation, such as the genetics of the β receptor, drug distribution, and deposition in the lower airways. Lack of further significant bronchodilator effect with increasing doses of inhaled β agonist is characteristic of the log-linear response, such that a 10-fold increase in the dose is required to achieve a doubled effect.[19] Furthermore, other investigators have demonstrated that the addition of doses exceeding 2.5 mg of albuterol via SVN or 4 puffs via MDI to stable, mechanically ventilated patients provides little further clinically important bronchodilation.[3,8] We recognize that a limitation of this study involves the relatively small number of study patients, and it is conceivable that a larger population might show small differences in response between doses and administration techniques. Yet, it is remarkable that the airway response profile was characteristically similar following 3 separate bronchodilator doses.

Given the similar clinical responses following MDI or SVN bronchodilator administration to ventilator-supported patients, it would appear that the MDI with spacer combination was a more efficient delivery device than the Misty-Neb nebulizer. This is illustrated by the fact that a significant change in airway resistance was observed following MDI administration of a nominal dose 2.5–6 times less than the nebulizer dose. The disparity between the MDI and SVN nominal drug doses is due to losses stemming from drug retention in the nebulizer receptacle

(~50%) and aerosol exhalation during continuous nebulization.[1]

We designed this study to compare the airway response to albuterol administration under common clinical conditions, while attempting to optimize drug delivery. Although a number of actuator devices are commercially available, we selected an MDI and spacer reported to provide adequate deposition and a clinically significant response.[15,20] Selection of the Misty-Neb nebulizer was based on its widespread clinical use and published performance compared with other commonly used commercial units.[21] In addition, we addressed the technique of aerosol administration as this influences lower respiratory tract deposition, and selected an MDI technique of delivery demonstrating substantial respiratory tract deposition and airway response.[15,22–24] Other methods of MDI delivery techniques involve application of an end-inspiratory pause or disconnection of the ventilator circuit followed by manual delivery of a large tidal breath.[4,13,25] However, lack of proven benefit following an end-inspiratory hold maneuver and the potential development of nosocomial airway infection limit these techniques.[25,26] Likewise, the nebulizer technique of administration was similar to previous reports.[3,5,7] Data gathered from bench model studies indicate improvements in respiratory tract delivery, with increased V_T, prolonged duty cycle, dry ventilator circuits, and use of an inspiration-triggered nebulizer.[23,27–30] However, selection of a technique of administration during mechanical ventilation requires a compromise between mechanical ventilator settings and the operating characteristics of the aerosol generating device.[5] Thus, we employed a common ventilator strategy in which V_T ranged from 6–8 mL/kg, producing readily tolerated duty cycles, and sufficient heat and humidity were applied to the respiratory system in order to not worsen pre-existing hyperinflation and airway irritation. In addition, use of continuous nebulization was based on the fact that approximately 30 minutes are required for complete aerosolization with an inspiration-triggered system, and this would have affected our ability to adequately compare the peak responses. After taking into account the different aerosol generating devices, the various techniques of administration, and the mechanical ventilation settings, we demonstrated a similar bronchodilator response following delivery via SVN or MDI with spacer.

Conclusions

In summary, we found a similar pattern of bronchodilator response following albuterol administration of 4 puffs or 10 puffs via MDI with spacer or 2.5 mg via SVN to mechanically ventilated COPD patients. The airway response to albuterol administration via MDI and SVN was similar in magnitude and duration, returning to baseline within 240 minutes. Thus, albuterol may be administered via inhalation on a 4-hour dosing schedule to stable ventilator-supported COPD patients.

Finally, it should be kept in mind that the conditions under which this study was performed were nearly ideal and may not necessarily replicate everyday practice in administering bronchodilators to mechanically ventilated patients.

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