

Evaluation of Aerosol Generator Devices at 3 Locations in Humidified and Non-humidified Circuits During Adult Mechanical Ventilation

Arzu Ari PhD RRT PT CPFT, Hasan Areabi MSc RRT, and James B Fink PhD RRT FAARC

BACKGROUND: The position of the jet or ultrasonic nebulizer in the ventilator circuit impacts drug delivery during mechanical ventilation, but has not been extensively explored, and no study has examined all of the commonly used nebulizers. **METHODS:** Drug delivery from jet, vibrating-mesh, and ultrasonic nebulizers and pressurized metered-dose inhaler (pMDI) with spacer was compared in a model of adult mechanical ventilation, with heated/humidified and non-humidified ventilator circuits. Albuterol sulfate was aerosolized at 3 circuit positions: (1) between the endotracheal tube and the Y-piece; (2) 15 cm from Y-piece; and (3) 15 cm from the ventilator, with each device ($n = 3$) using adult settings (tidal volume 500 mL, ramp flow pattern, 15 breaths/min, peak inspiratory flow 60 L/min, and PEEP 5 cm H₂O). The drug deposited on an absolute filter distal to an 8.0-mm inner-diameter endotracheal tube was eluted and analyzed via spectrophotometry (276 nm), and is reported as mean \pm SD percent of total nominal or emitted dose. **RESULTS:** The vibrating-mesh nebulizer, ultrasonic nebulizer, and pMDI with spacer were most efficient in position 2 with both non-humidified ($30.2 \pm 1.0\%$, $24.7 \pm 4.4\%$, and $27.8 \pm 3.3\%$, respectively) and heated/humidified circuits ($16.8 \pm 2.6\%$, $16.5 \pm 4.3\%$, and $17 \pm 1.0\%$, respectively). In contrast, the jet nebulizer was most efficient in position 3 under both non-humidified ($14.7 \pm 1.5\%$) and heated/humidified ($6.0 \pm 0.1\%$) conditions. In positions 2 and 3, all devices delivered approximately 2-fold more drug under non-humidified than under heated/humidified conditions ($P < .01$). At position 1 only the pMDI delivered substantially more drug than with the non-humidified circuit. **CONCLUSION:** During mechanical ventilation the optimal drug delivery efficiency depends on the aerosol generator, the ventilator circuit, and the aerosol generator position. *Key words:* aerosols; jet nebulizer; vibrating-mesh nebulizer; ultrasonic nebulizer; metered-dose inhaler; pMDI; ventilator circuit; mechanical ventilation; heat; humidity; drug administration; aerosol drug deposition; nebulizers. [Respir Care 2010;55(7):837–844. © 2010 Daedalus Enterprises]

Introduction

Aerosol drugs are commonly administered to patients during mechanical ventilation.¹⁻⁴ A range of aerosol generators have been used, including jet pneumatic nebulizer, vibrating-mesh nebulizer, ultrasonic nebulizer, and pressurized metered-dose inhaler (pMDI) with spacer. Much

SEE THE RELATED EDITORIAL ON PAGE 942

of what is known about aerosol drug delivery during mechanical ventilation is based on research with in vitro models.^{5,6} In vitro models provide a cost-effective opportunity to study variables such as aerosol generator type, ventilator

Arzu Ari PhD RRT PT CPFT, Hasan Areabi MSc RRT, and James B Fink PhD RRT FAARC are affiliated with the Division of Respiratory Therapy, School of Health Professions, Georgia State University, Atlanta, Georgia.

Dr Ari presented a version of this paper at the 53rd International Respiratory Congress of the American Association for Respiratory Care, held December 1-4, 2007, in Orlando, Florida.

Dr Fink has disclosed relationships with Aerogen, Aridis, Cubist, Dance Pharma, Kalobios, and Novartis. The other authors have disclosed no conflicts of interest.

type, ventilation parameters, presence or absence of humidification, and position of the device in the ventilator circuit to be isolated to quantify impact on aerosol drug delivery.^{1,7}

A number of *in vitro* studies have reported that aerosol delivery through a heated/humidified ventilator circuit is associated with a > 40% reduction in efficiency with the full range of aerosol generators.⁸⁻¹⁰ When using wet aerosols prone to hygroscopic effects, the use of humidification in the ventilator circuit may affect aerosol delivery. However, hygroscopic growth of particles may not explain reduction with chlorofluorocarbon pMDIs, in which particles may be coated with hydrophobic surfactants. Lange and Finlay, using a pMDI hydrofluoroalkane (HFA) formulation without hydrophobic surfactants, demonstrated that absolute humidity is predictive of decreased delivery with pMDIs.¹¹

Over the last 25 years, researchers have reported that operating aerosol generators at different positions relative to the patient and the ventilator can increase or decrease drug delivery. Early reports indicate that the jet nebulizer placed in the inspiratory limb of the ventilator circuit, either midway between the patient and the ventilator, which is defined as manifold position,^{12,13} or proximal to the ventilator,⁸ increase aerosol delivery efficiency, compared to placement proximal to the patient. In contrast, operating an ultrasonic nebulizer at the airway or 50 cm from the patient in the inspiratory limb had little effect on delivery,⁸⁻¹⁴ while placement proximal to the ventilator was least efficient. The effect of nebulizer placement with either pMDI with spacer or vibrating-mesh nebulizer on drug delivery efficiency has not been reported.

The ability to compare and contrast results of these individual studies is difficult because they were conducted with different combinations of models, ventilators, parameters, nebulizers, and measured end points. We hypothesized that when tested under similar conditions, delivery efficiency of all 4 types of aerosol generators would be impacted by their position in the ventilator circuit, and that delivery pattern would be similar, albeit reduced by approximately 40% with heated and humidified conditions.

This study was designed to compare the delivery efficiency of 4 types of aerosol generators (jet nebulizer, vibrating-mesh, ultrasonic nebulizer, and pMDI with spacer) operated in 3 commonly accessible positions during mechanical ventilation with both heated/humidified and non-humidified circuits.

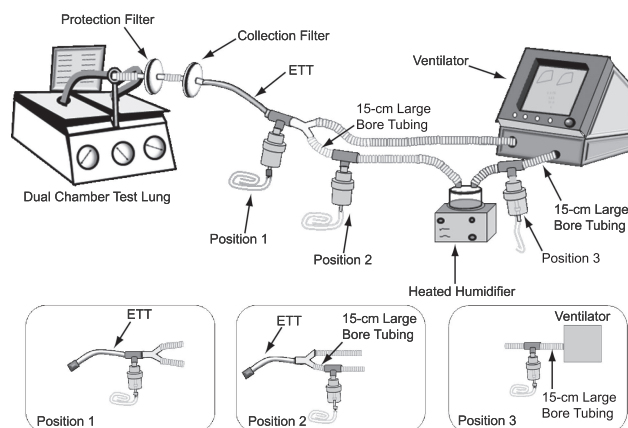


Fig. 1. Model of aerosol delivery during adult ventilation, consisting of a dual-chamber test lung, filters, endotracheal tube, ventilator circuit (with and without humidifier and heated wire), and mechanical ventilator. The 3 aerosol generator positions are shown.

Methods

Design and Funding

As part of an ongoing aerosol research program at Georgia State University, this study was designed, performed, and analyzed in the Division of Respiratory Therapy at Georgia State University, by or under the direct supervision of the first author, who was the principal investigator of this study. Aerosol devices and laboratory supplies were purchased with an internal research grant obtained from Georgia State University. One of the authors also serves as a scientific advisor and consultant to Aerogen, Galway, Ireland. Also, this study was not initiated or reviewed by any sponsor prior to its design, initiation, and analysis.

Lung Model

The lung model is represented in a diagram of experimental set-up (Fig. 1). A ventilator (Esprit, Respiroics/Philips Healthcare, Murrysville, Pennsylvania) was operated with a heated pass-over humidifier (Fisher & Paykel, Auckland, New Zealand) with heated-wire circuit and a standard non-humidified ventilator circuit (Allegiance Healthcare, McGaw Park, Illinois) attached to an 8-mm inner-diameter endotracheal tube (ETT) (Portex, Hythe Kent, United Kingdom). The ETT cuff was inflated in a 15-mm inner-diameter/22-mm outer-diameter adapter, which was then inserted into the housing of an absolute bacterial/viral filter (Respigard II, 303, Vital Signs, Totowa, New Jersey), fixing the tip of the ETT 1–2 cm from the filter media. The filter was positioned superior to the distal tip of the ETT to prevent condensate or liquid medication from reaching the filter media (see Fig. 1). The natural curve of the ETT was maintained, as the filter was

Correspondence: Arzu Ari PhD RRT PT CPFT, Division of Respiratory Therapy, School of Health Professions, Georgia State University, PO Box 4019, Atlanta GA 30302-4019. E-mail: aari1@gsu.edu.

connected to a test lung (Michigan Instruments, Grand Rapids, Michigan) set to simulate a mechanically ventilated adult patient (resistance 5 cm H₂O/L/s, compliance 0.1 L/cm H₂O).

Ventilator Settings

The same adult ventilation parameters of time-cycled volume-controlled ventilation were used for all experiments: minute ventilation 7.5 L/min, tidal volume (V_T) 500 mL, respiratory rate 15 breaths/min, peak inspiratory flow 60 L/min, PEEP 5 cm H₂O, ramp flow pattern, and no bias or trigger flow.

For testing under humidified conditions, the pass-over humidifier and heated-wire circuit were heated and humidified for approximately 20–30 min, until the temperature at the airway was stable at $35 \pm 1^\circ\text{C}$. For non-humidified conditions the simple circuit was used with no humidifier in line.

Aerosol Generator Types

Four types of aerosol generator were used in this study:

- Jet nebulizer (Misty-neb, Allegiance Healthcare, McGaw Park, Illinois) is the traditional pneumatic Bernoulli type nebulizer. The nebulizer was attached to the ventilator circuit with a T-piece adapter, and the jet nebulizer was operated with oxygen at a flow of 8 L/min.
- Vibrating-mesh nebulizer (AeroNeb Pro, Aerogen, Galway, Ireland) uses electricity to vibrate an aperture plate (containing 1,000 funnel-shaped holes) at 128 kHz. The vibrating-mesh produces aerosol through the holes by means of a micro-pumping action.
- Ultrasonic nebulizer (EasyNeb, Nellcor Puritan Bennett, Pleasanton, California) generates aerosol particles by means of a piezoelectric crystal that converts an electrical signal into high-frequency vibrations (1.2 MHz). The high-frequency vibrations travel through a fluid couplant and medication cup to form a standing wave in the medication, which produces aerosol particles.
- pMDI, containing HFA-propelled albuterol sulfate (ProAir HFA, Teva Specialty Pharmaceuticals, Atlanta, Georgia), with a manufacturer-estimated dose of 108 μg /puff was discharged into a spacer (AeroVent, Monaghan Medical, Plattsburgh, New York). ProAir HFA does not contain hydrophobic surfactants.

Dose and Generator Operation

Nebulizers. Albuterol sulfate (2.5 mg in 3 mL of normal saline) was placed in the reservoir of each nebulizer. Three of each nebulizer model/type were used for each experi-

ment. All of the nebulizers were run continuously until they no longer produced aerosol.

pMDI with Spacer. Each pMDI canister was warmed to hand temperature, well shaken, and primed using the standard boot supplied by the manufacturer before each experimental run. During testing, 8 puffs were actuated at the onset of inspiration at more than 15-s intervals. The same operator activated all pMDI doses, to minimize inter-operator variability. The spacer was fully extended and held horizontally, with the pMDI in a vertical position during dosing.

Aerosol Generator Placement

Each aerosol generator was operated at each of 3 positions in the ventilator circuits: Position 1: between the ETT and the Y-piece adapter; Position 2: 15 cm from the Y-piece in the inspiratory limb of the ventilator circuit; and Position 3: 15 cm from the ventilator. Each aerosol device type was tested 3 times ($n = 3$) at each position, with both the heated/humidified and non-humidified ventilator circuit (see Fig. 1).

Assay Technique

On completion of each experiment, the filters were removed from the circuit, labeled, and capped. Drug was eluted with 10 mL of 0.1 molar normal hydrochloric acid, with gentle agitation for 3 min. The albuterol concentration was determined via spectrophotometry (Beckman Instruments, Fullerton, California) at a wavelength of 276 nm. The spectrophotometer was calibrated before the trials, using a holmium oxide filter (Beckman Instruments, Fullerton, California) to determine wavelength accuracy. It was then set to zero before the next trial.

Data Analysis

The amount of drug deposited on the filter was expressed in 2 ways: (1) the absolute amount of drug inhaled (mg), or (2) the fraction of the nominal dose placed in each liquid aerosol generator or the labeled emitted dose from the pMDI. The differences between the inhaled mass were compared with a mixed-model analysis of variance. Specifically, the fractions of nominal and emitted dose associated with each aerosol generator across positions were tested for relative difference. This was done using repeated-measures analysis of variance. To investigate differences in the inhaled drug mass between the jet, vibrating-mesh, and ultrasonic nebulizers and the pMDI at each position, a series of one-way analysis of variance calculations were performed. The Scheffé procedure was employed for post-hoc comparisons of the aerosol generators.

Paired *t* tests were performed to examine the differences between the inhaled drug mass of each aerosol generator and between the non-humidified and heated/humidified ventilator circuits. The differences were considered statistically significant when $P < .05$.

Results

The amount of albuterol collected from the inspiratory filter (distal to the ETT) for each type of aerosol generator, position, and humidity level is shown in Figure 2. The percentages of nominal or emitted dose of albuterol delivered are shown in Table 1.

Delivery by Device

Jet Pneumatic Nebulizer. The amount of albuterol delivered from the jet nebulizer was greater at position 3 than at position 2, regardless of whether the ventilator circuit was heated/humidified ($P = .02$) or non-humidified ($P = .006$). Drug delivery in the non-humidified circuit was greater with the jet nebulizer at all 3 positions ($P = .008$, $P = .019$, and $P = .005$, respectively).

Vibrating-Mesh Nebulizer. In the heated/humidified ventilator circuit, drug delivery from the vibrating-mesh nebulizer was greater at positions 1 and 2 than at position 3 ($P = .042$). In contrast, in the non-humidified circuit, delivery in position 2 was significantly higher than in position 1 or 3 ($P = .001$ and $P = 0.029$, respectively). When we compare the heated/humidified circuit to the non-humidified circuit, no difference was found at position 1, whereas deposition was greater in the non-humidified circuit at positions 2 and 3 ($P = .02$, and $P = .01$, respectively).

Ultrasonic Nebulizer. The ultrasonic nebulizer delivered more albuterol in position 2 than the other positions, under both heated/humidified and non-humidified conditions; however, the only significant difference was at position 3 ($P = .049$).

Pressurized Metered-Dose Inhaler. The pMDI consistently delivered more drug at position 2 than at position 3 ($P = .008$ heated/humidified, and $P = .02$ non-humidified). The trend of lower delivery at position 1 was not significant. In the non-humidified circuit the difference between position 1 and position 3 was significant ($P = .045$). Inhaled drug mass with the non-humidified circuit was larger than with the heated/humidified circuit in all positions ($P = .002$, $P = .031$, and $P = .023$, respectively).

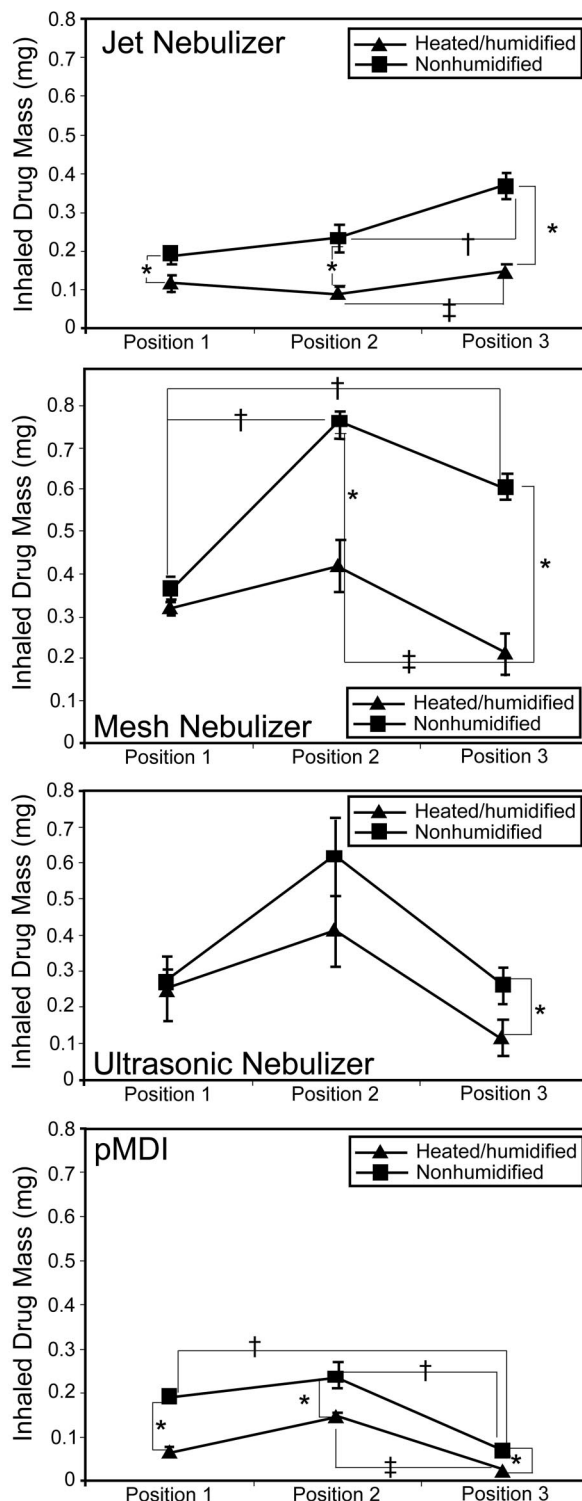


Fig. 2. Mean \pm SD inhaled drug mass (mg) with 4 types of aerosol generator, 3 aerosol-generator positions, and with and without heating and humidification of the ventilator circuit. * Significant difference between with and without heating and humidification. † Significant difference between positions with the non-humidified ventilator circuit. ‡ Significant difference between positions with the heated/humidified ventilator circuit.

Table 1. Albuterol Sulfate Deposited Distal to the Endotracheal Tube

	Percent of Nominal or Emitted Dose (mean ± SD %)					
	Position 1 (between ETT and Y-piece)		Position 2 (15 cm from Y-piece)		Position 3 (15 cm from ventilator)	
	Heated/ Humidified	Non- humidified	Heated/ Humidified	Non- humidified	Heated/ Humidified	Non- humidified
Jet nebulizer	4.7 ± 0.5	7.6 ± 0.9	3.6 ± 0.2	9.7 ± 1.5	6.0 ± 0.1	14.7 ± 1.5
Vibrating-mesh nebulizer	12.8 ± 0.5	14.5 ± 1.0	16.8 ± 2.6	30.2 ± 1.0	8.4 ± 2.1	24.2 ± 1.2
Ultrasonic nebulizer	10.1 ± 3.9	10.7 ± 1.5	16.5 ± 4.3	24.7 ± 4.4	4.6 ± 2.0	10.5 ± 0.3
Pressurized metered-dose inhaler	7.6 ± 1.3	22.1 ± 1.5	17.0 ± 1.0	27.8 ± 3.3	2.5 ± 0.8	7.9 ± 1.5

Delivery by Position

There was a tendency for each aerosol generator to deliver higher inhaled drug mass with the non-humidified ventilator circuit than with the heated/humidified ventilator circuit, regardless of position (Fig. 3). Especially in positions 2 and 3, all devices delivered approximately 2-fold more drug under non-humidified than under heated/humidified conditions ($P < .01$). The vibrating-mesh and ultrasonic nebulizers and the pMDI each deposited more albuterol from position 2 than from other positions, in both the heated/humidified and non-humidified ventilator circuits. In contrast, as the distance between the jet nebulizer and the ETT increased, the jet nebulizer delivered greater inhaled drug mass.

At Position 1. In the non-humidified circuit, the pMDI deposited a higher proportion of medication than the other aerosol generators ($P = .001$). The vibrating-mesh nebulizer was more efficient than the ultrasonic or jet nebulizer ($P = .001$ for each comparison). In the heated/humidified ventilator circuit the percentage of drug delivered by the pMDI sharply decreased, and the only significant difference was between the vibrating-mesh nebulizer and the jet nebulizer ($P = .01$).

At Position 2. Using the non-humidified circuit, the vibrating-mesh nebulizer delivered the greatest amount of drug, while in the heated/humidified circuit the percent of dose delivered with the vibrating-mesh and ultrasonic nebulizers and the pMDI were similar. The jet nebulizer delivered far less medication than the other aerosol generators ($P < .002$), regardless of the presence of heat and humidity.

At Position 3. In the non-humidified circuit, the vibrating-mesh nebulizer delivered a higher percent of nominal dose than the other devices ($P = .001$), while the jet nebulizer was greater than ultrasonic ($P = .03$), and pMDI was lowest ($P = .002$). With the heated/humidified circuit the vibrating-mesh nebulizer delivered more than the pMDI ($P = .01$).

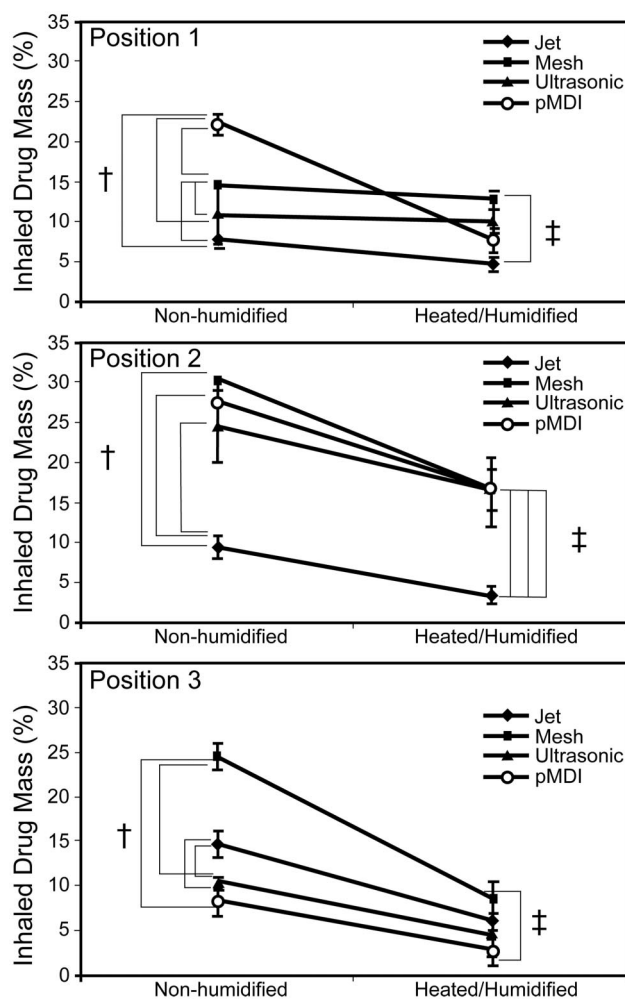


Fig. 3. Mean ± SD inhaled drug mass (mg) in each position, comparing the 4 aerosol generators with and without heating and humidification of the ventilator circuit. * Significant difference with the unheated ventilator circuit. ‡ Significant difference with the heated ventilator circuit

Discussion

There is no consensus on which nebulizer or aerosol generator to use (ie, jet nebulizer vs ultrasonic nebulizer vs pMDI vs vibrating-mesh nebulizer), where to place the

nebulizer (position 1, 2, or 3), during humidified versus non-humidified conditions, or how these factors may affect drug delivery *in vivo*. During mechanical ventilation of this *in vitro* model, delivery of albuterol distal to the ETT was significantly influenced by the type of aerosol generator, the position in the ventilator circuit, and the presence of heat/humidity. By varying the device, position, and humidity, albuterol delivery to filters distal to the ETT ranged from 20 μg to 755 μg , representing 2.5–30.2% of the emitted or nominal dose.

Characteristics of the Model

Although other bench studies with jet,^{6,12-15} vibrating-mesh, and ultrasonic⁸ nebulizers and pMDIs^{5,6,9-11,16} have been reported, our model has certain unique features. This is the first study to compare all 4 aerosol generator types under the same conditions and ventilation parameters.

The positions chosen for this study were somewhat different than those previously reported. For example, we chose not to use the manifold position, halfway between the ventilation and patient Y-piece, which was popular with earlier-generation mechanical ventilators and studied by several authors.^{6,12,13} Today, heated/humidified ventilator circuits commonly incorporate a heated wire that runs the length of the inspiratory limb, making placement at the manifold position impractical.

Positioning an aerosol generator proximal to the ventilator brought up additional concerns with the heated/humidified circuits, in which thermistors and other probes are typically inserted into adapters built into the inspiratory limb of the circuit. Placement of a jet nebulizer at the humidifier outlet introduces cold gas, reducing the temperature at the thermistor, resulting in possible overheating of the humidifier and alarms with some models. Nebulizer placement at the inlet of the humidifier allows gas and aerosol to be warmed before exiting the humidifier and reduces the probability of such overheating or alarms.

A 15-cm piece of tubing is commonly used between the T-piece adapter and the Y-piece with both jet and ultrasonic nebulizers. This additional gas volume between the nebulizer and thermistor allows better mixing of the aerosol with the heated/humidified gas and may serve to reduce humidifier compensation to the nebulizer and the incidence of alarms. We modified the placement for the pMDI chamber and the vibrating-mesh nebulizer to be consistent with the placement of the jet and ultrasonic nebulizers in this study.

To provide a direct comparison of the aerosol generator types, these modified positions were used with both a heated/humidified circuit and a simple non-humidified circuit. The risk of this strategy was that adding 15 cm of tubing between the Y-piece and the pMDI or vibrating-mesh nebulizer may not provide relevant data to guide the clinician. However, our findings were consistent with the

data reported for pMDI with the same spacer placed at the Y-piece (16% and 30% for heated/humidified and non-humidified, respectively).¹⁰ The additional 15-cm volume did appear to trend toward increased delivery efficiency, which was previously reported with the vibrating-mesh nebulizer, by up to 4%.

In contrast to previous studies that used indirect measurement methods such as visual colimetry scales,¹⁴ we measured albuterol delivery via direct assay of the drug. Like other investigators, we found that direct assay of albuterol with spectrophotometry is a simple, inexpensive, and reliable method of measuring albuterol delivery.^{17,18}

The placement of the filter in a position superior to the ETT reduced the risk of contamination of the filter by drug in any form other than aerosol. The aerosol dose has greater potential for homogenous distribution than an instilled bolus of drug into the central airway. The instilled drug would tend to distribute in a more gravity-dependent manner and presumably would have less ability to reach the peripheral airways.

Effect of Position

Placement of the vibrating-mesh and ultrasonic nebulizers in position 2 with 15-cm of tubing yielded slightly higher delivery than previously reported testing with the vibrating-mesh and ultrasonic nebulizer attached directly to the Y-piece.¹⁵ This may be due to a small cooling effect distal to the heated wire, leading to less hygroscopic growth of particles. Observing the aerosol plume from the vibrating-mesh nebulizer placed directly at the Y-piece, some of the aerosol bolus is pushed into the expiratory limb at the initiation of inspiration. This may be due to pressurization and expansion of the expiratory limb of the ventilator circuit that occurs before gas from the ventilator is directed down the ETT. With the addition of the 15-cm tubing the aerosol bolus does not appear to enter the expiratory limb, suggesting more aerosol may be delivered via the ETT. In contrast, the continuous gas flow of the jet nebulizer appears to carry aerosol past the patient into the expiratory limb at all times except during inspiration.

With placement between the ETT and Y-piece (position 1) the aerosol bolus from the vibrating-mesh and ultrasonic nebulizers is inhaled during inspiration, and blown into the expiratory limb during expiration, resulting in less inhaled aerosol available than with position 2. In contrast, placement of the jet nebulizer at position 1 did not result in a significant difference from position 2, which may be a factor of the continuous gas flow used to drive the nebulizer. Placement of the jet nebulizer at the ETT and at the Y-piece yielded similar efficiency for both heated/humidified and non-humidified circuits, while placement of the jet nebulizer proximal to the ventilator (position 3) achieved the greatest efficiency for the jet nebulizer with both the heated/humidified and the non-humidified venti-

lator circuits. However, even in position 3 the jet nebulizer was less efficient than the other 3 aerosol generators when placed at positions 1 and 2, with position 2 being the most efficient position for all of the other aerosol generators.

To our knowledge, this is the first study to look at placement of all 4 types of aerosol generators proximal to the ventilator. As previously reported,^{12,13} the jet nebulizer deposition was greatest in position 3. It has been hypothesized that the continuous gas flow driving the jet nebulizer allows aerosol to charge (fill) the inspiratory limb of the ventilator circuit and function as a reservoir. This is consistent with the work of Harvey and colleagues, who demonstrated that placement of a reservoir/spacer in the inspiratory limb of the ventilator circuit increased deposition delivery of a jet nebulizer¹⁵ and an ultrasonic nebulizer.^{17,18} In all cases, the volume of the reservoir and tubing volume en route to the ETT were less than the V_T used.

In contrast, aerosol from the ultrasonic and vibrating-mesh nebulizers at position 3 tends to collect at the aerosol generator and not to be transported to the patient until gas from the ventilator flows from the ventilator. When placed at the ventilator, the bolus of aerosol generated, similar to firing the pMDI at the beginning of inspiration, requires the aerosol to pass down the 2-m inspiratory-limb tubing, which for an adult 22-mm inner-diameter circuit has an internal volume of approximately 600 mL (dry circuit) to 680 mL (with the humidifier inline). With the 500 mL V_T used in this model, the aerosol bolus is moved down the tubing but stops short of entering the patient airway. Consequently, the aerosol inhaled is that which had charged the inspiratory limb in the previous breath, with consequent losses from gravitational sedimentation. The pMDI was the least efficient in position 3, with a 3-fold difference between position 1 and position 3. Performance of the pMDI with spacer in this position has not been previously reported.

We used 8 pMDI puffs in this study. While effective dosing in stable patients in vivo has been described with 4 puffs,¹⁹ it is difficult to elute sufficient drug from the filter. Fink et al established that 8 puffs was sufficient for determining relative delivered efficiency.^{10,17} Though practice varies, Dhand et al tested doubling doses of 4, 8, and 16 puffs and found no difference in clinical response,¹⁹ and our selection of 8 puffs is within that range.

Effect of Heat and Humidity

As previously reported, heated humidity decreased delivered drug amounts for both jet nebulizer and pMDI in all positions.^{1,9,10,17,20-23} Drug delivery efficiency at position 2 with the pMDI and spacer was consistent with previous reports with the spacer attached directly to the Y-piece. Fink et al¹⁷ reported deposition of 16% and 30%, for wet and dry conditions, respectively, using a chlorofluo-

rocarbon albuterol pMDI with an AeroVent spacer placed directly at the Y-piece. Fink and colleagues¹⁷ also reported that using an HFA pMDI resulted in approximately 20% reduction of aerosol delivery under both wet (22%) and dry (13%) conditions. Fuller et al²³ reported 30% delivery with a pMDI in a circuit humidified to 32°C. However, they preheated the circuit for only 5 min prior to measurements, so the absolute humidity may have been lower than in our model. Lange and Finlay demonstrated that changes in deposition were more a factor of absolute humidity than of relative humidity and temperature.¹¹

In contrast, when the vibrating-mesh and ultrasonic nebulizers were placed at the ETT, there were no significant differences between the wet and dry conditions. This may be due to the relatively high density aerosol produced by the vibrating-mesh and ultrasonic nebulizers, resulting in a higher exhaled absolute humidity with the model, that achieved with the jet nebulizer and pMDI. Further study is warranted to better understand this observation.

Clinical Importance

There is no consensus on which nebulizer to use (ie, jet nebulizer vs ultrasonic vs pMDI vs vibrating-mesh), where to place the nebulizer (position 1, 2, or 3), how to operate the nebulizer (breath-actuated vs continuous, humidified vs non-humidified), or how these factors may affect drug delivery in vivo. The magnitude of aerosol delivered to the lower respiratory tract influences the response to a drug. Although doubling the dose of albuterol from a pMDI to a stable COPD patient receiving mechanical ventilation did not reduce airway resistance,¹⁹ there is substantial evidence that greater than standard doses of albuterol may be required during exacerbation of bronchospasm.²⁴⁻²⁶ Therefore, it is important to define techniques that maximize albuterol delivery to achieve the best therapeutic benefit in mechanically ventilated patients.

Limitations of Method

In this study, the liquid aerosol generators were operated continuously, whereas the pMDI with spacer was actuated at the beginning of inspiration. The jet nebulizer was operated with a secondary gas flow that was in addition to inspiratory flow delivered by the ventilator.

The ventilator was operated with only one set of parameters, without bias or trigger flow, which are commonly used in some modern ventilators. Data on the impact of bias flow are lacking, and further studies are warranted to more fully explore the impact of these variables. Consequently, these data should not be extrapolated for ventilators that use a bias-flow system, and it is likely that the performance of the jet, vibrating-mesh, and ultrasonic nebulizers under those conditions would be different. Similarly, changes in basic parameters such as inspiratory flow and pattern, and inspiratory-expiratory ratio can greatly impact

the relative efficiency of aerosol delivery and may impact the efficiency of the devices tested.⁷

Representative devices were selected for each type of aerosol generator. However, performance should not be too broadly generalized to other devices within each type of aerosol generator. For example, selection of spacer for use with pMDI has demonstrated a broad range of drug delivery efficiency.^{3,9,16,17,24} It should also be noted that jet nebulizer may vary greatly between models in terms of particle size, output, and gas flow required, resulting in a broad range of relative efficiencies.^{14,15,20,22} Such differences have also been shown with ultrasonic nebulizers.^{8,18}

It should be noted that during normal clinical use, drug may enter the lung as both aerosol and liquid condensate. This model was configured to position the filter above the tip of the ETT so that condensate in the ETT would not reach the filter and not be assayed. While quantifying drug delivered as aerosol past the ETT, this method may underestimate drug delivery, compared to other in vitro models. In contrast, small particles may be captured on the absolute filter that might otherwise be exhaled in patients, resulting in a moderate overestimation of delivered dose in vivo, as previously described in an in vitro/in vivo comparison by Fink et al.¹⁷

Conclusions

During simulated adult mechanical ventilation with no bias or trigger flow, placement of a vibrating-mesh nebulizer, an ultrasonic nebulizer, or a pMDI in the inspiratory limb 15 cm from the Y-piece provided the highest deposition, under both heated/humidified and non-humidified conditions. The jet nebulizer was less efficient than the other aerosol generators, and provided highest efficiency when placed proximal to the ventilator.

ACKNOWLEDGMENTS

We thank Meryl M Sheard MSc RRT, Division of Respiratory Therapy, College of Health and Human Sciences, Georgia State University, Atlanta, Georgia, for her drawings, genuine assistance, and insightful support throughout this study.

REFERENCES

- Fink J, Dhand R. Aerosol therapy in mechanically ventilated patients: recent advances and new techniques. *Semin Respir Crit Care Med* 2000;21(3):183-201.
- Fink J, Tobin M, Dhand R. Bronchodilator therapy in mechanically ventilated patients. *Respir Care* 1999;44(1):53-69.
- Duarte AG, Fink JB, Dhand R. Inhalation therapy during mechanical ventilation. *Respir Care Clin N Am* 2001;7(2):233-260.
- Dhand R. Aerosol therapy during mechanical ventilation: getting ready for prime time. *Am J Respir Crit Care Med* 2003;168(10):1148-1149.
- Fink J, Dhand R. Laboratory evaluation of metered-dose inhalers with models that simulate interaction with the patient. *Respir Care Clin N Am* 2001;7(2):303-317.
- Fuller H, Dolovich M, Chambers C, Newhouse M. Aerosol delivery during mechanical ventilation: a predictive in-vitro lung model. *J Aerosol Med* 1992;5(4):251-259.
- Dhand R. Maximizing aerosol delivery during mechanical ventilation: go with the flow and go slow. *Intensive Care Med* 2003;29(7):1041-1042.
- Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. *Am Rev Respir Dis* 1993;148(4):872-877.
- Diot P, Morra L, Smaldone G. Salbutamol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. *Am J Respir Crit Care Med* 1995;152(4):1391-1394.
- Fink J, Dhand R, Duarte A, Jenne J, Tobin M. Aerosol delivery from a metered-dose inhaler during mechanical ventilation. An in-vitro model. *Am J Respir Crit Care Med* 1996;154(2):382-387.
- Lange C, Finlay W. Overcoming the adverse effect of humidity in aerosol delivery via pressured metered-dose inhaler during mechanical ventilation. *Am J Respir Crit Care Med* 2000;161(5):1614-1618.
- Hughes J, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. *Respir Care* 1987;32(12):1131-1135.
- Quinn W. Effect of a new nebulizer position on aerosol delivery during mechanical ventilation. *Respir Care* 1992;37(5):423-431.
- O'Doherty MJ, Thomas SH, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation: effect of ventilator settings and nebulizer type, position, and volume of fill. *Am Rev Respir Dis* 1992;146(2):383-388.
- Harvey C, O'Doherty M, Page C, Thomas S, Nunan T, Treacher D. Effect of a spacer on pulmonary aerosol deposition from a jet nebulizer during mechanical ventilation. *Thorax* 1995;50(1):50-53.
- Rau J, Harwood R, Groff J. Evaluation of a reservoir device for metered-dose bronchodilator delivery to intubated adults: an in-vitro study. *Chest* 1992;102(3):924-930.
- Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. *Am J Respir Crit Care Med* 1999;159(1):63-68.
- Harvey C, O'Doherty M, Page C, Thomas S, Nunan T, Treacher D. Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. *Eur Respir J* 1997;10(4):905-909.
- Dhand R, Duarte A, Jubran A, Jenne J, Fahey R, Tobin M. Dose response to bronchodilator delivered by metered-dose inhaler in ventilator supported patients. *Am J Respir Crit Care Med* 1996;154(2):388-393.
- O'Riordan T, Palmer L, Smaldone G. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. *Am J Respir Crit Care Med* 1994;149(1):214-219.
- O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. *Am Rev Respir Dis* 1992;145(5):1117-1122.
- Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. *Am J Respir Crit Care Med* 2003;168(10):1205-1209.
- Fuller H, Dolovich M, Turpie F, Newhouse M. Efficiency of bronchodilator aerosol delivery to the lungs from metered-dose inhaler in mechanically ventilated patients: a study comparing four different actuator devices. *Chest* 1994;105(1):214-218.
- Manthous C, Hall C, Schmidt G, Wood L. Metered-dose inhaler versus nebulized salbutamol in mechanically ventilated patients. *Am Rev Respir Dis* 1993;148(6):1567-1570.
- Duarte A, Momi K, Bidani A. Bronchodilator therapy with metered dose inhaler and spacer versus nebulizer in mechanically ventilated patients: comparison of magnitude and duration of response. *Respir Care* 2000;45(7):817-823.
- Duarte A, Dhand R, Reid D, Tobin M, Jenne J. Serum salbutamol levels after metered-dose inhaler administration to ventilated patients and healthy controls. *Am J Respir Crit Care Med* 1996;154(6):1658-1663.