Influence of Nebulizer Type, Position, and Bias Flow on Aerosol Drug Delivery in Simulated Pediatric and Adult Lung Models During Mechanical Ventilation

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BACKGROUND: The effectiveness of aerosol drug delivery during mechanical ventilation is influenced by the patient, ventilator, and nebulizer variables. The impact of nebulizer type, position on the ventilator circuit, and bias flow on aerosol drug delivery has not been established for different age populations. OBJECTIVE: To determine the influence of nebulizer position and bias flow with a jet nebulizer and a vibrating-mesh nebulizer on aerosol drug delivery in simulated and mechanically ventilated pediatric and adult patients. METHOD: Albuterol sulfate (2.5 mg) was nebulized with a jet nebulizer and a vibrating-mesh nebulizer, using simulated pediatric and adult lung models. The 2 nebulizer positions were: (1) jet nebulizer placed 15 cm from the Y-piece adapter, and vibrating-mesh nebulizer attached directly to the Y-piece; and (2) jet nebulizer placed prior to the heated humidifier with 15 cm of large-bore tubing, and vibrating-mesh nebulizer positioned at an inlet to the humidifier. A ventilator with a heated humidifier and ventilator circuit was utilized in both lung models. The adult ventilator settings were VT 500 mL, PEEP 5 cm H2O, respiratory rate 20 breaths/min, peak inspiratory flow 60 L/min, and descending ramp flow waveform. The pediatric ventilator settings were VT 100 mL, PEEP 5 cm H2O, respiratory rate 20 breaths/min, inspiratory time 1 s. We tested bias flows of 2 and 5 L/min. The adult and pediatric lung models used 8-mm and 5-mm inner-diameter endotracheal tubes, respectively. Each experiment was run 3 times (n = 3). The albuterol sulfate was eluted from the filter and analyzed via spectrophotometry (276 nm). RESULTS: Nebulizer placement prior to the humidifier increased drug delivery with both the jet nebulizer and the vibrating-mesh nebulizer, with a greater increase with the vibrating-mesh nebulizer. Higher bias flow reduced drug delivery. Drug delivery with the vibrating-mesh nebulizer was 2–4-fold greater than with the jet nebulizer at all positions (P < .05) in both lung models. CONCLUSION: During simulated mechanical ventilation in pediatric and adult models, bias flow and nebulizer type and position impact aerosol drug delivery. Key words: jet nebulizer; vibrating-mesh nebulizer; bias flow; nebulizer position; mechanical ventilation; drug administration; aerosol drug delivery. [Respir Care 2010;55(7):845–851. © 2010 Daedalus Enterprises]

Introduction

Over the past few decades, aerosol drug delivery has become one of the major treatments for patients with pulmonary diseases.1 While aerosol drug delivery is very...
mon in mechanically ventilated patients, there is an incomplete understanding of factors influencing aerosol drug deposition in intubated and mechanically ventilated patients, and the standards for aerosol delivery to different age populations are still being explored.\textsuperscript{2,3} The efficacy of aerosol drug delivery is deeply influenced by the physical, pharmacokinetic, and pharmacodynamic properties of the drug, and by the suitability of the delivery system.\textsuperscript{4} Previous studies indicated that several variables, such as type of aerosol generator, placement in the ventilator circuit, ventilator settings, and humidification, affect aerosol drug deposition during simulated mechanical ventilation.\textsuperscript{5-17}

\section*{Methods}

\subsection*{Design and Funding}

This study was designed, performed, and analyzed at Georgia State University by and under the direct supervision of the first author, who was also the principal investigator. Aerosol devices were donated by the manufacturers, and laboratory supplies were purchased with funds from an unrestricted research grant from Aerogen, Galway, Ireland. One of the authors also serves as a scientific advisor and consultant to Aerogen. This study was initiated as part of an ongoing aerosol research program at Georgia State University and was not initiated or reviewed by any sponsor prior to its design, initiation, and analysis.
In all the experiments the model included a ventilator (Galileo, Hamilton Medical, Reno, Nevada), a heated humidifier (Fisher & Paykel, Auckland, New Zealand), a heated-wire ventilator circuit (Allegiance Healthcare, McGaw Park, Illinois) and an 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 (Respirgard II, 303, Vital Signs, Totowa, New Jersey). The tip of the ETT was 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 (Fig. 1). The natural curve of the ETT was maintained, and the filter was connected to a test lung (Michigan Instruments, Grand Rapids, Michigan) set to simulate a mechanically ventilated adult or small pediatric patient.

Nebulizer Type, Operation, and Doses

Two types of aerosol generators were tested:

- Jet nebulizer. We used the Misty Finity (Cardinal Health, Dublin, Ohio), which is a pneumatic Bernoulli type nebulizer. The nebulizer was attached to the ventilator circuit with a T-piece adaptor and was operated with oxygen at a flow of 2.5 L/min. The jet nebulizer uses pressurized gas to form a jet passing over a capillary tube that draws liquid formulation into the jet stream, where it is sheared from the capillary or feed tube to produce aerosol. Baffles are used to take large particles out of suspension, returning the drug to the medication reservoir, where it can be re-nebulized. The emitted dose of the small-volume jet nebulizer may be as little as 50% of the dose placed in the nebulizer, with reported residual drug volume of 0.8 –1.4 mL. The continuous gas flow propels aerosol from the jet nebulizer into the ventilator circuit as it is generated.

- Vibrating-mesh nebulizer. We used the AeroNeb Solo (Aerogen, Mountain View, California), which 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 micropumping action. The liquid in the reservoir is positioned above the ventilator circuit, and passes through the mesh as aerosol is generated. The emitted dose of the vibrating-mesh nebulizer can exceed 90% of the dose, with a residual drug volume of 0.1– 0.3 mL. The aerosol plume from the vibrating mesh is relatively low velocity, compared to the plume from a jet nebulizer or metered-dose inhaler.

Albuterol sulfate (2.5 mg in 3 mL of normal saline) was placed in the reservoir of each nebulizer. Three of each nebulizer type/model were used for each experiment. All of the nebulizers were run continuously until they no longer produced aerosol. Each experiment was run 3 times (n = 3).
Nebulizer Placement

Each nebulizer was tested in 2 ventilator circuit positions:

- Position 1. The jet nebulizer was placed 15 cm from the Y-piece adapter, using standard aerosol tubing, whereas the vibrating-mesh nebulizer was attached between the Y-piece and the circuit, as suggested by the manufacturer (see Fig. 1).

- Position 2. The jet nebulizer was placed proximal to the ventilator and prior to the heated humidifier, using 15 cm of large-bore tubing to connect the nebulizer T-piece to the humidifier inlet. The vibrating-mesh nebulizer was placed with the adult 22 mm T-piece adapter at the humidifier inlet (see Fig. 1).

In Vitro Measurements

Each aerosol device was tested 3 times, at both positions, with the heated/humidified ventilator circuit (see Fig. 1). In each experiment the drug mass exiting the ETT (inhaled mass) was collected on an absolute filter at the distal tip of the ETT. On completion of each experiment, the filter was 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 quantified and expressed as a percentage of the total drug dose placed into the nebulizer. The means and standard deviations were calculated for each component of the total inhaled drug mass. Differences in means between the inhaled mass for the 2 bias flow rates, the 2 ventilator positions, and the 2 nebulizers were compared with a 3-way factorial analysis of variance. To investigate the differences in inhaled drug mass between jet nebulizer and vibrating-mesh nebulizer at each position, a series of independent t tests were performed. Paired t tests were performed to examine the differences between the inhaled drug mass of each aerosol generator at each position and each bias flow. The differences were considered statistically significant when P < .05.

Results

The mean ± SD percent of the total dose of albuterol sulfate deposited on the inspiratory filter for each type of aerosol generator and position for adult and pediatric lung models and settings are shown in Table 1.

Effect of Nebulizer Type on Aerosol Drug Delivery

The mean inhaled percent of dose delivered by the vibrating-mesh nebulizer was 2–4-fold greater than that of the jet nebulizer, under all conditions, in both the adult (P < .001) and the pediatric (P < .001) lung models. Drug delivery with the jet nebulizer was similar in the adult and pediatric models, whereas delivery with the vibrating-mesh nebulizer was greater with the adult model than with the pediatric model (P < .05).

Effect of Nebulizer Position on Aerosol Drug Delivery

While the amount of aerosol deposition with jet nebulizer was similar at both positions in the adult and the pediatric models, the vibrating-mesh nebulizer was more efficient at position 2 with both lung models. In the adult model, placement of the vibrating-mesh nebulizer prior to the humidifier (position 2) significantly increased drug delivery at both 2 L/min (P = .01) and 5 L/min (P = .001),

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Table 1. Albuterol Sulfate Deposited Distal to the Endotracheal Tube

<table>
<thead>
<tr>
<th></th>
<th>Adult Lung Model</th>
<th>Pediatric Lung Model</th>
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<tbody>
<tr>
<td></td>
<td>Position 1</td>
<td>Position 2</td>
</tr>
<tr>
<td></td>
<td>Bias flow 2 L/min</td>
<td>Bias flow 5 L/min</td>
</tr>
<tr>
<td>Jet nebulizer</td>
<td>4.7 ± 0.1*</td>
<td>4.0 ± 0.1*</td>
</tr>
<tr>
<td>Vibrating-mesh nebulizer</td>
<td>13.4 ± 1.1</td>
<td>9.7 ± 0.6</td>
</tr>
</tbody>
</table>

* Significant difference between jet nebulizer and vibrating-mesh nebulizer (P < .05).
compared to placement at the Y-piece adapter (position 1). With the pediatric model there was a trend toward greater delivery with position 2, but the increase was only significant with the vibrating-mesh nebulizer at bias flow of 5 L/min ($P < .01$) (Fig. 2).

**Effect of Bias Flow on Aerosol Drug Delivery**

With jet nebulizer the higher bias flow trended to reduce aerosol drug delivery in the adult and pediatric lung models, but only position 1 in the adult model was significant ($P = .006$). The vibrating-mesh nebulizer (see Fig. 2) showed significant differences between bias flow levels at position 1 ($P = .03$) and position 2 ($P = .02$) with the adult model and position 1 ($P = .01$) but not position 2 ($P = .07$) with the pediatric model.

**Discussion**

The present study demonstrates the influence of nebulizer type, position, and bias flow on aerosol drug delivery in models of adult and pediatric mechanical ventilation. According to the findings of this study, both position and level of bias or trigger flow impact aerosol delivery during mechanical ventilation with both adult and pediatric models.

**The Effect of Nebulizer Type**

The vibrating-mesh nebulizer consistently delivered more drug than the jet nebulizer, under all conditions tested. This is consistent with previous reports, and may be a function of how the aerosol is generated, the percent of dose that is emitted as aerosol, and the residual drug remaining in the nebulizer.12,15,19,24

**The Effect of Nebulizer Position**

With bias flow, the vibrating-mesh nebulizer in position 2 (proximal to the ventilator) delivered up to 2-fold more aerosol than at position 1. The impact of aerosol delivery with the jet nebulizer was less than with the vibrating-mesh nebulizer, but there was a strong trend of greater delivery with position 2.

These results are consistent with a previous study,11 which found greater deposition from a jet nebulizer placed proximal to the ventilator (6.0 ± 0.1% of dose) compared to placement at position 1 (3.6 ± 0.2%) with an adult ventilation model with no bias flow. However, in that study the vibrating-mesh nebulizer delivered less drug when positioned at the ventilator (8.4 ± 2.1%) than near the patient Y-piece (16.7%).

The authors speculated that this effect was due in large part to the continuous gas output of the jet nebulizer, compared to the vibrating-mesh nebulizer, which generates aerosol without a secondary gas flow added to the ventilator circuit. With the jet nebulizer, during inspiration the aerosol is inhaled with the ventilator breath, but between inspirations the aerosol is driven downstream from the nebulizer. When positioned proximal to the patient, this aerosol passes into the expiratory limb. When operated at position 2, aerosol fills the inspiratory limb between the nebulizer and the patient, acting as an aerosol reservoir equivalent to the internal volume of the circuit tubing and humidifier chamber.

In contrast, aerosol generated by the vibrating-mesh nebulizer remains in the vicinity of the nebulizer until a secondary gas source, such as the ventilator breath, carries the aerosol toward the patient. When placed near the patient Y-piece (our position 1), there is a bolus of aerosol that is inhaled at the beginning of the tidal breath. When placed at the ventilator, the aerosol bolus must pass through the volume of the circuit and humidifier chamber before being inhaled. For a typical 183-cm, 22-mm inner-diameter ventilator circuit (600 mL internal volume) and heater/humidifier chamber (> 80 mL) a VT of 500 mL would not be sufficient to carry the bolus to the patient with a single breath. The aerosol bolus would then be suspended in the inspiratory limb until delivered with the next breath, resulting in several seconds during which gravitational sedimentation would reduce the aerosol available for inspiration.
a circuit of a set volume will decrease. Our findings sug-
ggest that increasing bias flow results in a dilutive effect,
with a trend toward a decrease in drug delivered, independ-
ent of the aerosol generator or position.

The internal circuit volume between the aerosol gener-
ator and the patient airway is greater with position 2. This
allows the inspiratory limb to contain aerosol and act as
more of a reservoir than position 1, in which aerosol is
transported past the patient into the expiratory limb be-
tween inspirations.

With the vibrating-mesh nebulizer the bias flow carries
aerosol downstream from the point of generation, through
the inspiratory and expiratory limbs of the ventilator cir-
cuit. When placed proximal to the ventilator, position 2,
in the adult circuit, the aerosol fills the inspiratory tubing,
acting as a reservoir, increasing the delivered aerosol. With
the smaller internal volume of the pediatric circuit, the
impact of this reservoir effect is considerably less.

With the jet nebulizer the bias flow, in addition to the
continuous flow from the jet nebulizer, increases the clear-
ance rate of aerosol through the ventilator circuit. A greater
reduction in delivery would be seen with jet nebulizers
that utilize higher operating flows than the 2.5 L/min used
in this study.

Adult Versus Pediatric Model

Aerosol delivery, with both aerosol generators, was sim-
ilar at position 1 in both the adult and pediatric models. In
contrast, at position 2 the deposition with the vibrating-
mesh nebulizer was much higher with the adult model than
with the pediatric model. This may be explained by the
greater internal volume of the adult ventilator circuit and
the enhanced reservoir effect described above.

Placement of the vibrating-mesh nebulizer in the pedi-
atriatric circuit at position 2 resulted in similar drug delivery
as position 1 in the adult circuit. With the jet nebulizer,
delivery was similar at both positions across the adult and
pediatric models.

Clinical Implications

While there are many findings in this study that are
statistically significant (eg, effect of bias flow), the actual
effect was minor and would not be expected to influence
efficacy or patient safety. The findings of greatest clinical
relevance are the 2–4-fold increase in drug delivery with
the vibrating-mesh nebulizer, versus the jet nebulizer, in
all positions, and the greater delivery in the adult circuit
with the vibrating-mesh nebulizer in position 2 versus po-
sition 1. These increases in drug delivery may or may not
improve bronchodilation, but may contribute to toxicity
(eg, tachycardia, tremor) and may require a dose adjust-
ment downward.

In a recent report, Moraine and co-workers found no
difference in ipratropium in the urine of mechanically ven-
tilated adult patients after 500 μg of ipratropium via neb-
ulizer placed before the heated humidifier and at the Y-
piece in the inspiratory limb.29 This supports the premise
that small statistical differences in vitro may not result in
important clinical response differences, and, perhaps more
importantly, that placement of the nebulizer before the
heated humidifier did not reduce the amount of drug de-
ivered and subsequently secreted in vivo.

Perhaps more important than the increase of delivered
dose under some conditions are the potential benefits of
nebulizer placement proximal to the ventilator, at or near
the humidifier inlet. First, placement proximal to the ven-
tilator takes the bulk and weight of the nebulizer away
from the patient airway, which is of particular interest in
the treatment of smaller patients.

Second, the aerosol generator is isolated from retro-
grade contamination of the inspiratory limb of the venti-
lator circuit, often introduced from the patient airway. Even
should contaminated condensate enter the reservoir of the
humidifier, there is no mechanism for bacteria to pass
from the reservoir water to the nebulizer. It has long been
established that water molecules do not offer a vehicle of
transmission for bacteria.30 In addition, there is a constant
or intermittent flow of gas downstream, away from the
nebulizer.

Third, a large proportion of rain-out from the aerosol
generator deposits in the humidifier rather than in the cir-
cuit, reducing the liquid condensate load. This reduces the
risk of nebulizers with lower residual volume of deposit-
ing greater volumes of liquid in the inspiratory limb, re-
ducing the risk of occlusion of the airway by condensate.

This raises a concern of the effect of heating the med-
ication in the heated humidifier reservoir for an extended
period. While most drugs have been studied for stability
up to 40°C, few are studied at the ≧ 70°C that may exist
in the heater reservoir for periods of a week or more.
Additional research should be performed to determine the
impact on drug integrity and the production of hazardous
vapors under such conditions.

Limitations

While the results of this study provide insights into the
effect of placement of 2 types of aerosol generator in the
ventilator circuit and the impact of bias flow, results may
vary with different nebulizers commonly used in clinical
practice. For example, the jet nebulizer used in this study
required an operating flow of 2.5 L/m, whereas other jet
nebulizers utilize flows as high as 10 L/min, which may
further reduce aerosol transit time through the circuit, re-
ducing aerosol drug delivery. Similarly, the ventilator set-
tings tested, while representative of adult and pediatric
settings, do not speak to the broad array of settings and ventilation modes used in clinical practice.

Common to other in vitro models that have collected drug on an absolute filter, the deposited dose does not reflect the amount of inhaled aerosol that would be exhaled in vivo (typically a small percentage of what is inhaled), consequently underestimating the in vitro dose. However, this in vitro model does provide perspective on the inhaled dose as compared across the variables tested.

Future Research

Additional studies with a broader range of devices and settings would help to provide additional guidance to clinicians in evaluating their ability to optimize aerosol delivery with both adult and pediatric patients.

Conclusions

In conclusion, aerosol delivery depends on the nebulizer type, position, and bias flow during simulated adult and pediatric mechanical ventilation. With bias flow, placement of the vibrating-mesh nebulizer and jet nebulizer prior to the humidifier delivered more aerosol than placement at the Y-piece. Higher bias flow decreased aerosol drug delivery in our models of adult and pediatric mechanical ventilation. A better understanding of these factors and their effects on aerosol delivery can help to guide clinicians to increase the efficiency of aerosol therapy administered to mechanically ventilated patients.

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