

Albuterol Aerosol Delivered via Metered-Dose Inhaler to Intubated Pediatric Models of 3 Ages, With 4 Spacer Designs

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OBJECTIVE: To determine the amount of albuterol, in various particle size ranges, delivered from a hydrofluoroalkane-propelled metered-dose inhaler (AiroMir) in 3 models of pediatric intubation (ages 8 months, 4 years, and 16 years) using 4 types of aerosol reservoir: 3 spacers (ACE, AeroChamber HC MV, metal NebuChamber without 1-way valve) and 1 holding chamber (metal NebuChamber with 1-way valve). **METHODS:** Five reservoirs of each type were tested with albuterol sulfate delivered via metered-dose inhaler that delivers 100 μg of albuterol per actuation. Each reservoir was connected to an endotracheal tube (ETT) that corresponded to the given patient age (8 months = 4 French; 4 years = 5 French; 16 years = 7.5 French) and to a valved system that allowed connection of the ETT to a cascade impactor. Simulated tidal volumes representative of children of the given ages were passed through the reservoir. Both the cascade impactor and the ETT were enclosed within a 100% humidity, 37° C environment. **RESULTS:** For the total amount of albuterol inhaled onto the impactor, and both the 1.1–4.7 μm and 1.1–3.3 μm inhaled fine-particle fractions, the NebuChamber-with-valve showed significantly greater drug delivery than the NebuChamber-without-valve, the AeroChamber HC MV, or the ACE ($p < 0.001$). Among the reservoirs without valves the NebuChamber showed significantly greater delivery than the AeroChamber HC MV or ACE ($p < 0.001$) for total drug deposition and for both the 1.1–4.7 μm and 1.1–3.3 μm fine-particle fractions. These results were consistent over all age groups. The AeroChamber HC MV had significantly greater delivery (total deposition) than the ACE ($p < 0.001$), except in the 4-year-old model. There were no significant differences between the AeroChamber HC MV and the ACE for either the 1.1–4.7 μm or the 1.1–3.3 μm fine-particle fraction. **CONCLUSION:** An aerosol reservoir with 1-way valve positioned between the spacer and the ETT improved the amount of inhaled albuterol 300–900%, compared to the other reservoirs. *Key words:* pediatric, intubation, spacer, albuterol, salbutamol, metered-dose inhaler, drug delivery systems, aerosols, inhalation administration, aerosol therapy. [Respir Care 2003;48(10):948–955. © 2003 Daedalus Enterprises]

Introduction

Metered-dose inhalers (MDIs) are commonly used to deliver aerosolized drugs to the lungs. Within the ambulatory pediatric population, young children and infants are usually unable to coordinate their breathing with the MDI

actuation. Typically, an MDI with a holding chamber (with 1-way valve) is used to improve lung deposition. Holding chambers with valves prevent rebreathing of the exhaled (low drug concentration) air; otherwise little drug may be inhaled from the holding chamber. A special group within the out-patient population is pre-term infants. For pre-term, nonintubated infants Fok et al suggested that a non-valved spacer is more effective for MDI delivery.¹ The rationale was that pre-term infants are unable to generate enough inspiratory force to open the 1-way valve for drug delivery. Our study, however, does not evaluate pre-term infants. For the intubated patients analyzed in this study, an adequate driving force would be applied to open the holding chamber valve.

The intubated pediatric population poses a unique set of challenges to effective drug delivery.^{2,3} Factors affecting lung deposition include abnormal pulmonary mechanics due to disease states, humidification, inhalation volumes,

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Table 1. Survey of Canadian Albuterol Delivery Methods

Location	Spacer	Spacer Position	Frequency of Spacer Cleaning	Puffs Per Administration (<i>n</i>)	Breaths Per Puff (<i>n</i>)	Volume Per Breath
Edmonton	AHC or ACE	In-line: AHC Bagged: ACE	Between patients and a minimum of once a week	Approximately 4–5	Approximately 10–15	Tidal volume
Calgary	AHC or ACE	In-line: AHC Bagged: ACE	Between patients and a minimum of once a week	≥ 1–2, depending on patient size	Not consistent between different RTs	Tidal volume
Vancouver	ACE	In-line: ACE NICU: in line adapter for MDI without a spacer	Minimum of once a week	2.5 μg/5 kg = approximately 6–12 puffs/d	Not consistent between different RTs	Tidal volume
Toronto	AHC	In-line: AHC (chamber removed from circuit after each use)	Between patients and a minimum of once a week	2–4	Minimum 5–10	Tidal volume
Montreal	ACE	In-line: ACE Bagged: If significant risk of hyperreactive airways	Between patients and a minimum of once a week	—	—	Tidal volume
Winnipeg	AHC or ACE	In-line: AHC or ACE Bagged: AHC or ACE	Between patients and a minimum of once a week	2–3	Minimum 5	Tidal volume
Halifax	50% nebulizer	Bagged: Nebulizer	—	—	—	Tidal volume
Saskatoon	In-line adapter	In-line: MDI adapter Bagged: neonates with high PEEP, requiring little dead space, 100% F _{IO₂}	—	—	—	Tidal volume

AHC = Aerochamber HC MV.
 ACE = Aerosol Cloud Enhancer.
 RT = respiratory therapist.
 NICU = neonatal intensive care unit.
 MDI = metered-dose inhaler
 PEEP = positive end-expiratory pressure.
 F_{IO₂} = fraction of inspired oxygen.

use of a breath-hold, coordination of actuation with inhalation, and the electrostatic charge inside the reservoir. Alternatives for drug delivery include a small-volume nebulizer, an in-line reservoir with an MDI (using the ventilator as the driving force), or a reservoir with an MDI using a bag-valve-mask.^{4–6} Both in vivo and in vitro studies have suggested that MDI is as effective as small-volume nebulizer for medication delivery.^{7–11} The most commonly used method of delivering MDI medication to pediatric patients is by putting a spacer on the inspiratory limb of the ventilator circuit (in-line). This setup creates the equivalent of a 1-way valve within the spacer, as the expired air moves through the expiratory limb of the ventilator circuit and not through the spacer. However, this method has been associated with low efficiency.²

Our survey of centers across Canada (Table 1) showed that they are inconsistent in their albuterol delivery methods. Although most centers use the in-line method of MDI albuterol delivery, over 50% of those centers surveyed had

a provision for bag-valve-mask delivery of albuterol. Two local centers, Edmonton and Calgary, Alberta, employ the alternative method of delivering medication to the intubated pediatric population, by connecting the MDI to a spacer and attaching this to the endotracheal tube (ETT) (see Table 1).¹² The respiratory therapist then simulates tidal volume (V_T) for the patient, using a bag-valve-mask (assisted ventilation).¹³ This method of drug delivery is a modification of the product monograph recommendations for use of the spacer with a bag-valve-mask. With the bag-valve-mask the respiratory therapist can time actuation with inhalation, but the patient must be disconnected from the ventilator. Disadvantages of this method include the potential for human error with respect to timing and V_T , and the difficulty in maintaining positive end-expiratory pressure with the bag-valve-mask. On the other hand, high humidity within the in-line ventilator circuit affects the evaporation and aerosolization of the albuterol MDI,¹⁴ which decreases delivery of medication. The bagging

method has the advantage of minimizing the effects of humidity on the drug prior to entering the respiratory tract. Bag-valve-mask delivery of MDI aerosol also allows for greater coordination of drug delivery than having the spacer in-line,¹⁵ which would eliminate the potential of medication “looping” from the inspiratory limb directly to the expiratory limb without entering the patient (a potentially higher-resistance circuit). The timing of actuation to inspiration is believed to be more accurate with assisted ventilation.¹³

Several different spacers are available for use with intubated patients. Clinical data comparing these devices are very limited.^{16,17} An *in vitro* study has shown differences in the fine-particle fraction of inhaled drug from different reservoirs.¹⁸ These differences were attributed to variables such as chamber size, V_T , and ETT size. Currently, plastic spacers designed for intubated patients do not eliminate electrostatic charge. Previous research showed that elimination of this electrostatic charge can improve the passage of fine particles through the spacer by 50–100%.¹⁹ For out-patients a common method of eliminating electrostatic charge in the spacer is to wash it with common dishwashing detergent. The product monographs for intubated patient spacers, however, do not describe a way to eliminate electrostatic charge. To maintain a clean, closed system, spacers in most centers are not manipulated prior to patient use. In addition most centers use the same spacer for the same patient, only cleaning between patients or once a week (see Table 1). It is unclear whether this type of long-term use decreases electrostatic charge. Previous studies of the clinical effects of electrostatic charge have shown comparable efficacy for spacers with and without electrostatic charge.²⁰

Additionally, none of the commercially available spacers for use with intubated patients have a 1-way valve. The use of such a valve, in which case the reservoir is commonly known as a holding chamber, would be expected to give significant benefit when using a bag-valve-mask for drug delivery. The valve would allow exhaled gas to be directed into the environment, which would prevent the exhaled gas from further diluting the drug within the holding chamber. No research has been done to evaluate the effect of inserting a 1-way valve within the bagging apparatus. The NebuChamber was used in the present study to eliminate electrostatic effects. By comparing the NebuChamber (a metal reservoir) with and without a 1-way valve we directly assessed the effect of the valve. The aim of our study was to compare the *in vitro* delivery of hydrofluoroalkane-propelled albuterol within 4 different aerosol reservoirs, including one with a valve, in 3 pediatric age groups, with simulated delivery from a bag-valve-mask.

Methods

The apparatus illustrated in Figure 1 was used to simulate a tidal breathing pattern through the reservoirs while

the “inhaled” aerosol was collected at a constant flow of 28.3 L/min into a cascade impactor (Anderson Mark II; Graseby Anderson, Smyrna, Georgia). The setup used is similar to that of Lange and Finlay’s investigations of humidity effects during mechanical ventilation.¹⁴ Table 2 shows the ventilation variables used for the 3 age groups, which are near the predicted values for intubated children of the given ages.^{18,21}

During simulated inhalation at a flow of Q the 2-way solenoid valve (Asco Electric, Brantford, Ontario, Canada) remained open, with the valve on the compressor adjusted to supply 56.6 L/min, the piston drawing $28.3 + Q$ L/min, and the cascade impactor drawing 28.3 L/min, resulting in inhalation through the holding chamber at Q L/min. During exhalation at the same flow Q , the solenoid valve remained closed, the impactor drew 28.3 L/min, and the piston pushed $28.3 + Q$ L/min into the 3-way T-piece, resulting in exhalation through the holding chamber of Q L/min. No inspiratory or expiratory pauses were used.¹³ Flow rates were set using a dry gas flow meter (model DTM-115; American Meter, Nebraska City, Nebraska).

Two of the spacers were chosen because of their ready availability in our pediatric intensive care unit (PICU): Aerosol Cloud Enhancer, or ACE (DHD Healthcare, Wampsville, New York) and the AeroChamber HC MV (Trudell, London, Ontario, Canada). The other 2 reservoirs tested, a metal spacer without a 1-way valve and a modified metal holding chamber with a 1-way valve (NebuChamber; Astra, Lund, Sweden), were chosen because of their metal construction, which minimizes electrostatic effects.¹³ This spacer can also easily be adapted for use with a 1-way valve, as explained below. Figure 2 shows the specific setups for each reservoir type. In Figure 2 unit F is a filter (model #303; Marquest Medical Products, Englewood, Colorado). This filter collected all particles that would normally be deposited within the bag-valve-mask or expiratory limb of the ventilation circuit on exhalation (exhalation filter). For testing the ACE and AeroChamber HC MV the Y-piece and adapter/1-way valve were not used (see Fig. 2, setup 1). The exhalation filter was placed behind the holding chamber to collect any particles that would normally be deposited within the bag-valve-mask (Box B in Fig. 1). To use the NebuChamber in the testing apparatus, a Y-piece was placed at the outlet of the chamber (Box A in Fig. 1). The complete NebuChamber setup corresponds to setup 2 in Figure 2. A spare valve from one of the NebuChamber spacers was placed in reverse to allow exhalation through one leg of the Y-piece and filter collection of the exhaled aerosol. Inhalation was through the other leg of the Y piece attached to the spacer. To use the NebuChamber-without-valve (see Fig. 2, setup 3), the exhalation line of the Y-piece was blocked and a free-flow adapter was created with the same internal and external dimensions as the inhalation 1-way valve and inserted in

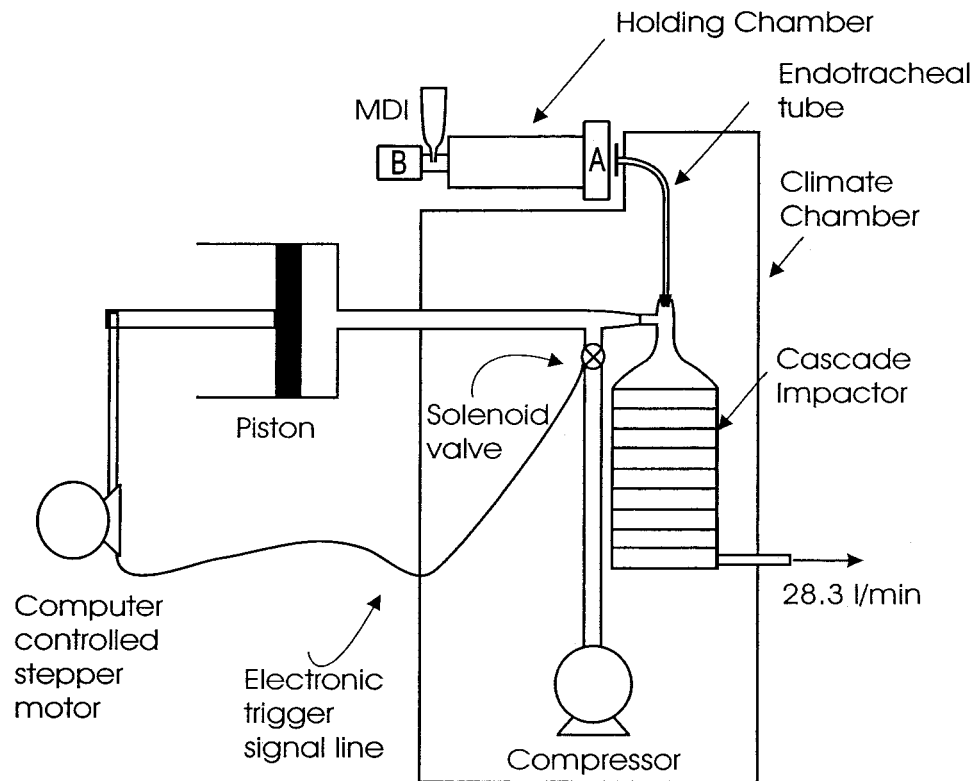


Fig. 1. Testing apparatus. MDI = metered-dose inhaler. Depending on the setup, the box labeled "A" is either a Y-piece or a direct line (as shown in Figure 2) and the box labeled "B" is either a filter or nothing.

Table 2. Ventilation Variables Relative to the Age Groups

Group (age)	Weight (kg)	Tidal Volume (mL)	ETT size (French)	f (breaths/min)	Flow (L/min)
Infant (8 mo)	4	75	4	30	4.8
Child (4 y)	15	190	5	18	8.2
Adolescent (16 y)	50	450	7.5	10	11.1

ETT = endotracheal tube.
f = respiratory rate.

place of the inhalation 1-way valve. This allowed testing of the NebuChamber with and without a valve, without changing the overall dimensions, shape of the spacer, or the testing setup. We used 5 identical spacers for each of the 4 types of spacers tested, for each age.

Each trial consisted of 10 actuations, using 5 breaths per actuation (per the package instructions). After each trial, the spacer or holding chamber was cleaned of all residue, and amounts deposited in the various parts of the circuit were measured. The data were subsequently divided by 10 to produce the amounts per single actuation.

The hydrofluoroalkane-propelled MDI (Airomir Autohaler; 3M, Maplewood, Minnesota) chosen to test the spacers was the albuterol formulation currently available on

the market in Canada. Airomir is a chlorofluorocarbon-free preparation that has replaced Ventolin, which used chlorofluorocarbon propellant. According to the manufacturer, the nominal dose of 120 μg albuterol per actuation is equivalent to 100 μg of albuterol per actuation. The MDI was actuated during the inspiratory phase of the set tidal breathing pattern. The spacer or holding chamber was removed after 5 completed breaths. This procedure was repeated at 1-minute intervals 10 times for each trial.

When not being tested, the MDI was stored on its side. Immediately prior to testing, 5 MDI puffs were fired to waste, well away from the test apparatus. The MDI was shaken for > 5 seconds between all actuations. To ensure there were no contaminants that would compromise the

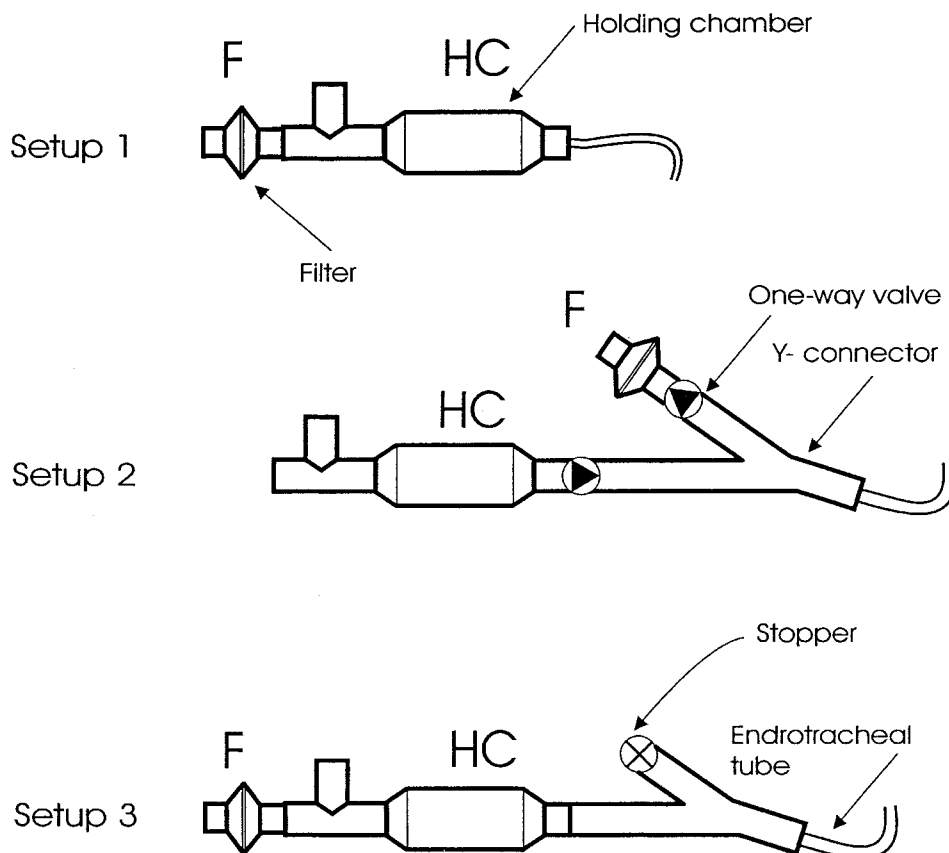


Fig. 2. Reservoir connections in each setup. The inverted T-piece corresponds to the MDI receptacle. F = filter, HC = spacer/holding chamber.

spectrophotometric analysis, prior to use all reservoirs were (1) washed with soap and water, (2) cleaned further with distilled water, (3) rinsed with methanol, (4) allowed to air dry.

The amounts of drug deposited within the reservoir, ETT, exhalation filter, connector between the ETT and spacer, and the various stages of the impactor were assayed using ultraviolet spectrophotometry (model 8452A, Hewlett-Packard, Mississauga, Ontario). Drug was washed from the system parts and the impactor plates using distilled water.

To better simulate *in vivo* conditions the impactor and the ETT were situated within a 37° C, 100% humidity environment (Hotpack, Waterloo, Ontario, Canada). The reservoir and its connection to the ETT were within ambient conditions of $50 \pm 10\%$ relative humidity, as measured with a hygrometer (Fisher Scientific, Ottawa, Ontario, Canada).

Statistical analysis was done with statistics software (SYSTAT; Systat Software, Evanston, Illinois), using analysis of variance. We used Tukey's "highest significant difference" test with multiple mean comparisons to determine whether the holding chamber methods differed sig-

nificantly. Output was expressed as a total of a single 100- μ g equivalent albuterol actuation. Differences were deemed significant when $p < 0.01$, unless otherwise specified.

Results

Mean values of mass median aerodynamic diameter, which ranged from 2.4 μ m to 2.9 μ m, did not differ significantly ($p > 0.05$) among the reservoirs, within or between the age groups.

For aggregate total amounts collected from all parts of the circuit there were no significant differences between any of the trials ($p > 0.05$). This reflects the mass balance of the assay. Table 3 shows the amount of drug deposited in the various parts of the circuit. Amounts collected from the ETT were significantly greater ($p < 0.001$) with the NebuChamber (with and without the valve) than with the other spacers. There was no significant difference in ETT deposition between the AeroChamber HC MV and the ACE. These results may be due to electrostatic effects. Because the NebuChamber has lower propensity for electrostatic deposition in the chamber, there is probably more

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Table 3. Average Amounts of Albuterol Collected in Various Parts of the Circuit*

Age Group and Spacer Type	Total Cascade Impactor Deposition (μg)	Particles of 1.1–3.3 μm (μg)	Particles of 1.1–4.7 μm (μg)	Spacer Residue (μg)	Y-Piece Residue (μg)	ETT residue (μg)	Exhalation Filter Residue (μg)	Total Drug Collected (μg)
Age 8 Months								
Nebuchamber with valve	57.19 \pm 1.01	42.94 \pm 0.93	50.97 \pm 0.49	25.49 \pm 2.03	11.21 \pm 0.96	6.79 \pm 0.52	0.0	100.65 \pm 1.37
Nebuchamber without valve	19.12 \pm 0.75	11.12 \pm 0.72	14.79 \pm 0.89	29.82 \pm 1.81	11.02 \pm 0.47	12.18 \pm 0.94	28.04 \pm 2.56	100.56 \pm 1.85
AHC	12.66 \pm 0.43	7.18 \pm 0.37	9.29 \pm 0.58	40.67 \pm 1.12	NA	1.04 \pm 0.22	47.57 \pm 2.42	101.94 \pm 2.01
ACE	8.91 \pm 0.31	5.26 \pm 0.38	6.72 \pm 0.55	57.40 \pm 1.75	NA	4.87 \pm 0.69	29.82 \pm 1.39	100.98 \pm 1.95
Age 4 Years								
Nebuchamber with valve	55.06 \pm 1.14	40.35 \pm 1.22	48.19 \pm 0.86	29.31 \pm 3.05	11.38 \pm 1.40	4.78 \pm 0.41	0.0	100.52 \pm 1.76
Nebuchamber without valve	16.83 \pm 1.30	10.02 \pm 0.21	11.38 \pm 0.31	36.41 \pm 1.83	10.78 \pm 0.49	2.65 \pm 0.32	35.85 \pm 3.38	102.50 \pm 0.92
AHC	8.79 \pm 0.81	5.05 \pm 0.32	6.17 \pm 0.31	39.79 \pm 1.10	NA	1.05 \pm 0.23	50.57 \pm 2.53	101.48 \pm 2.15
ACE	7.64 \pm 0.58	3.97 \pm 0.31	5.31 \pm 0.24	79.39 \pm 1.73	NA	0.38 \pm 0.11	14.20 \pm 0.71	101.61 \pm 1.70
Age 16 Years								
Nebuchamber with valve	62.67 \pm 0.93	45.57 \pm 1.10	57.64 \pm 1.48	24.00 \pm 1.38	14.21 \pm 5.87	2.50 \pm 0.18	0.0	100.79 \pm 1.80
Nebuchamber without valve	23.55 \pm 0.46	13.97 \pm 0.66	19.19 \pm 0.47	32.97 \pm 3.31	10.32 \pm 0.36	1.67 \pm 0.30	32.05 \pm 3.02	100.56 \pm 2.41
AHC	14.11 \pm 0.40	8.26 \pm 0.52	10.39 \pm 0.68	41.98 \pm 2.03	NA	0.51 \pm 0.04	44.36 \pm 2.95	100.95 \pm 1.67
ACE	12.18 \pm 0.46	6.00 \pm 0.49	7.86 \pm 0.78	70.56 \pm 2.45	NA	0.83 \pm 0.15	16.34 \pm 0.73	100.58 \pm 2.06

*Values are mean \pm SD. All values are normalized to 1 actuation.

AHC = AeroChamber HC MV.

NA = not applicable.

ACE = Aerosol Cloud Enhancer.

electrostatic deposition within the ETT. With the ACE and the AeroChamber HC MV, these particles probably deposit onto the interior of the spacer.

Regarding the total amounts deposited in the impactor, the NebuChamber-with-valve showed significantly greater impactor deposition than all the other spacers, including the NebuChamber-without-valve. The total impactor deposition values with the NebuChamber-with-valve were between 55.06% and 62.67%, which is 3–6 times larger than the deposition values for the other reservoirs (see Table 3). The NebuChamber-without-valve showed greater impactor deposition (averages of 16.83–23.55%) than both the AeroChamber HC MV and the ACE ($p < 0.001$). These results were similar for all age groups.

Among the spacers commonly available in PICUs the AeroChamber HC MV had greater impactor deposition than the ACE. For the 8-month and 16-year age groups this difference in deposition was significant ($p < 0.001$), whereas in the 4-year-old age group the difference between AeroChamber HC MV and ACE was not statistically significant.

When evaluating amounts inhaled in the fine-particle ranges 1.1–3.3 μm and 1.1–4.7 μm , significant differences were again found with the NebuChamber holding chamber. The NebuChamber-with-valve had significantly greater impactor deposition of fine particles than all the other spacers ($p < 0.001$): the average values were 40.35–45.57% in the 1.1–3.3 μm range and 48.19–57.64% in

1.1–4.7 μm , which is 3–10 times larger than with the other aerosol reservoirs. The NebuChamber-without-valve had greater deposition in both fine-particle ranges than AeroChamber HC MV or ACE ($p < 0.001$), with all age groups.

There was no significant difference in the 1.1–3.3 μm fine-particle range between the AHC-MV and the ACE, but in the 8-month age group the AeroChamber HC MV deposited more 1.1–4.7 μm particles in the impactor than did the ACE ($p < 0.005$). For the other ages there were no significant differences.

Discussion

The NebuChamber showed higher total and fine-particle fractions deposited onto the impactor. Our results also suggest that for the present intubated pediatric model, the valves within the Y-piece, which direct exhalation through a separate limb from the MDI aerosol (placed on the inspiratory limb), can profoundly increase drug delivery to the lungs. Our findings confirm the results of previous research with the NebuChamber, which used an ambulatory pediatric model.²²

For smaller particle sizes, the holding chamber proved to be the most effective. The valved holding chamber delivered 30–39 μg more inhaled particles in the 1.1–3.3 μm range, which is 300–900% more than the spacer.

Research by Diot et al showed wide variability in the amount of albuterol delivered within an in vitro mechan-

ical ventilation model.⁷ Between 15.4% (with humidification) and 25.1% (without humidification) of the albuterol was delivered. However, a number of factors were identified that affected drug deposition, including reservoir design (Aerovent spacer vs Marquest 172275 MDI adaptor) and MDI actuation synchronization. For the 16-year-old group, comparing similar V_T to the research of Diot et al, our results have similar total impactor deposition for both the AeroChamber HC MV and the ACE spacers within a humidified environment.

Recently, within an ambulatory pediatric population (ages 2–9 y) average *in vivo* MDI lung deposition was between 21.6 μg for the younger children and 38.4 μg for the older children.²³ That study had 2 groups: the first group, younger children, used a face mask, and the second group, older children, used a mouthpiece. This *in vivo* model, with the mouthpiece, is comparable to our holding chamber model with limited humidity. The second group of the Wildhaber et al study had minimal deposition on the exhalation valve (0.2%), which is analogous to our NebuChamber 1-way valve study. Wildhaber et al found that the lung deposition was $9.6 \pm 3.9\%$, which is equivalent to $38.4 \pm 15.6 \mu\text{g}$. In comparison, the fine-particle fraction in the 1.1–3.3 μm range for our 4-year-old NebuChamber-with-valve group was $40.35 \pm 1.22 \mu\text{g}$. Our results suggest good correlation between our *in vitro* research and their *in vivo* research. Though there are differences between the *in vitro* and *in vivo* findings, Fink et al recently found that there is a correspondence between the two and that results and tendencies from *in vitro* research are useful within clinical practice.²⁴

Even without the valves, the NebuChamber spacer still performed better than the other spacers, which suggests that electrostatic charge may have played an important role in determining deposition. Eliminating electrostatic charge can improve drug deposition 50–100%. In comparing the NebuChamber-without-valve to the other charged spacers, we obtained similar results. The significant deposition difference between the NebuChamber-with-valve and the NebuChamber-without-valve supports the value of a 1-way valve in improving deposition. Among the spacers regularly available in our PICU, the AeroChamber HC-MV provided greater medication delivery than the ACE, although the difference was not statistically significant in the 4-year-old group.

The aerosol collected in the impactor represents the aerosol that would enter the respiratory tract *in vivo*. The fate of these particles once they reach the respiratory tract was not considered in this study, although the large differences in the amount of drug in the particle size ranges discussed here would be expected to cause large differences in the amounts deposited in the lungs.

In addition to the present results, there are practical issues with each spacer. With the AeroChamber HC MV

and the ACE, the lack of a 1-way valve may allow drug deposition within the delivery device (eg, the bag-valve-mask). With the NebuChamber-with-valve, less drug deposits in the holding chamber, but more deposits in the ETT. Unlike the spacer or holding chamber, which is readily discarded or cleaned, an ETT with greater drug deposition could affect air flow, resistance, and bacterial growth within the ETT. In Canadian PICUs ETTs are changed weekly. The higher ETT deposition with the NebuChamber (with and without the valve) may result from less drug loss in the metal spacer and not because of the valve itself.

The apparatus used for the present study provides a unique set of variables not present in previous research. To emulate *in vivo* conditions the impactor and part of the ETT were kept at 37° C and 100% relative humidity. Additionally, the first inhaled breath drew ambient air, whereas without the valve all subsequent breaths drew exhaled air, which was at body temperature and humidity conditions. The design best replicates the conditions when a patient has an MDI puff delivered via bag-valve-mask. Currently, the effect of humidity on the Airomir is not fully understood, so this method was needed to ensure minimal deviation from the *in vivo* model.¹⁴

This study did not explore the medication delivery method in which the spacer is in-line on the inspiratory limb of the ventilator circuit, which has advantages and disadvantages to the method we used. The primary advantage is that with the in-line spacer, an artificial 1-way valve is created. With this in-line setup, expiration is through the other half of the circuit, away from the holding chamber. However, because the entire circuit is at 37° C and 100% relative humidity, the behavior of the drug may be different. The results of our study may not extrapolate to the in-line delivery system, which was the subject of another investigation.¹⁴ Our valved setup would also be different from the bag-valve-mask system (with a 1-way valve built into the bag) for delivery of MDI puffs (as per the product monograph). Within the bag the valve position at the rear of the chamber would still allow exhaled gas to mix in the spacer, whereas the valve position in our design prevents that dilution of the aerosol in the holding chamber.

Conclusions

Measurements of hydrofluoroalkane-propelled albuterol delivered through 4 types of aerosol reservoir (3 spacers and 1 holding chamber) during simulated intubated pediatric tidal breathing indicated that more drug overall and a greater percentage of particles in the 1.1–3.3 μm and 1.1–4.7 μm ranges were delivered by the NebuChamber-with-valve than by the other reservoirs. The experimental setup was representative of an MDI-puff delivery with a bag-valve-mask. Of the 2 spacers (ie, reservoir without a valve) commonly used in the PICU setting, the AeroChamber HC

MV showed more deposition than the ACE. Clinical trials are needed to determine whether the observed differences are clinically relevant.

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REFERENCES

1. Fok TF, Lam K, Chan CK, Ng PC, Zhuang H, Wong W, et al. Aerosol delivery to non-ventilated infants by metered dose inhaler: should a valved spacer be used? *Pediatr Pulmonol* 1997;24(3):204–212.
2. Garner SS, Wiest DB, Bradley JW, Leshner BA, Habib DM. Albuterol delivery by metered-dose inhaler in a mechanically ventilated pediatric lung model. *Crit Care Med* 1996;24(5):870–874.
3. Newhouse MT. Pulmonary drug targeting with aerosols: principles and clinical applications in adults and children. *Am J Asthma Allergy Pediatr* 1993;7:23–35.
4. Dhand R, Tobin MJ. Bronchodilator delivery with metered-dose inhalers in mechanically ventilated patients. *Eur Respir J* 1996;9(3):585–595.
5. Rau JL, Harwood RJ, Groff JL. Evaluation of a reservoir device for metered-dose bronchodilator delivery to intubated adults: an in vitro study. *Chest* 1992;102(3):924–930.
6. Arnon S, Grigg J, Nikander K, Silverman M. Delivery of micronized budesonide suspension by metered dose inhaler and jet nebulizer into a neonatal ventilator circuit. *Pediatr Pulmonol* 1992;13(3):172–175.
7. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation. *Am J Respir Crit Care Med* 1995;152(4 Pt 1):1391–1394.
8. Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma. *Arch Pediatr Adolesc Med* 1995;149(2):201–205.
9. Idris AH, McDermott MF, Raucci JC, Morrabel A, McGorray S, Hendeles L. Emergency department treatment of severe asthma: metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. *Chest* 1993;103(3):665–672.
10. Fuller HD, Dolovich MB, Posmituck G, Pack WW, Newhouse MT. Pressurized aerosol versus aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. *Am Rev Respir Dis* 1990;141(2):440–444.
11. Duarte AG, Dhand R, Reid R, Fink JB, Fahey PJ, Tobin MJ, et al. Serum albuterol levels in mechanically ventilated patients and healthy subjects after metered-dose inhaler administration. *Am J Respir Crit Care Med* 1996;154(6 Pt 1):1658–1663.
12. Grigg J, Arnon S, Jones T, Clarke A, Silverman M. Delivery of therapeutic aerosols to intubated babies. *Arch Dis Child* 1992;67(1 Spec No):25–30.
13. Arnon S, Grigg J, Silverman M. Effectiveness of budesonide aerosol in ventilator-dependent preterm babies: a preliminary report. *Pediatr Pulmonol* 1996;21(4):231–235.
14. Lange CF, Finlay WH. Overcoming the adverse effect of humidity in aerosol delivery via pressurized meters-dose inhalers during mechanical ventilation. *Am J Respir Crit Care Med* 2000;161(5):1614–1618.
15. Dhand R, and Tobin M. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med* 1997;156(1):3–10.
16. Bahl TL, Lux CR, Bertling P, Ahrens RC. Evidence that MDI holding chamber affect on aerosol delivery varies with the drug being used. *J Aerosol Med* 1995;8:87.
17. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. *J Aerosol Med* 1996;9:55–70.
18. Wildhaber JH, Hayden MJ, Dore ND, Devadason SG, LeSouef PN. Albuterol delivery from a hydrofluoroalkane pressurized metered-dose inhaler in pediatric ventilator circuits: an in vitro study. *Chest* 1998;113(1):186–191.
19. Pierart F, Wildhaber JH, Vrancken I, Devadason SG, Le Souëf PN. Washing plastic spacers in household detergent reduces electrostatic charge greatly improves delivery. *Eur Respir J* 1999;13(3):673–678.
20. Dompeling E, Oudesluys-Murphy AM, Janssens HM, Hop W, Brinkman JG, Sukhai RN, et al. Randomised controlled study of clinical efficacy of spacer therapy in asthma with regard to electrostatic charge. *Arch Dis Child* 2001;84(2):178–182.
21. Taussig LM, Harris TR, Lebowitz MD. Lung function in infants and young children: functional residual capacity, tidal volume, and respiratory rates. *Am Rev Respir Dis* 1977;116(2):233–239.
22. Finlay WH, Gehmlich MG. Inertial sizing of aerosol inhaled from 2 dry powder inhalers with realistic breath patterns versus constant flow rates. *Int J Pharm* 2000;210(1–2):83–95.
23. Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouëf PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr* 1999;135(1):28–88.
24. Fink JB, Dhand R, Grychowsky J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and definition efficiency-enhancing factors. *Am J Respir Crit Care Med* 2002;159(1):63–68.