A Novel, Versatile Valved Holding Chamber for Delivering Inhaled Medications to Neonates and Small Children: Laboratory Simulation of Delivery Options


BACKGROUND: Delivery of bronchodilator to infants and small children from a pressurized metered-dose inhaler with valved holding chamber (pMDI-VHC) is limited by airway narrowness, short respiratory cycle time, and small tidal volume ($V_T$). There is a need for a versatile, efficient VHC, given the variety of treatment modalities. METHODS: We tested the AeroChamber Mini VHC (the internal geometry of which is optimized for aerosol delivery, and which accepts a pMDI canister that has a dose counter) in experiments to determine differences in the delivery of hydrofluoroalkane-propelled albuterol (90 µg/actuation) during: mechanical ventilation via endotracheal tube (ETT); manual resuscitation via ETT; and spontaneous breathing via face mask. We tested 5 units of the AeroChamber Mini VHC per test. We simulated the tidal breathing of a premature neonate ($V_T$ 6 mL), a term neonate ($V_T$ 20 mL), and a child approximately 2 years old ($V_T$ 60 mL). We collected the aerosol on an electret filter and quantitatively assayed for albuterol. RESULTS: The total emitted mass of albuterol per actuation that exited the VHC was marginally greater during spontaneous breathing ($12.1 \pm 1.8 \mu g$) than during manual resuscitation ($10.0 \pm 1.1 \mu g$) ($P = .046$). Albuterol delivery via mechanical ventilation, though comparable with the premature-neonate model ($3.3 \pm 1.2 \mu g$), the term-neonate model ($3.8 \pm 2.1 \mu g$), and the 2-y-old-child model ($4.2 \pm 2.3 \mu g$) ($P = .63$), was significantly lower than in the spontaneous-breathing and manual-resuscitation models ($P < .001$). In the neonatal models the total emitted mass was similar with the spontaneous-breathing model ($6.0 \pm 1.0 \mu g$ with the premature-neonate model, $10.5 \pm 0.7 \mu g$ with the term-neonate model) and the manual-resuscitation model ($5.5 \pm 0.3 \mu g$ premature-neonate model, $10.7 \pm 0.9 \mu g$ term-neonate model) ($P \geq .46$ via one-way analysis of variance). CONCLUSION: The reduced delivery of albuterol during mechanical ventilation (compared to during spontaneous breathing and manual resuscitation via ETT) was probably associated with the saturated atmosphere in the breathing circuit (37°C, relative humidity > 99%), compared to the ambient air ($22 \pm 1^\circ C$, 44 ± 7% relative humidity). The AeroChamber Mini VHC may provide a versatile alternative to VHCs that are designed exclusively for one aerosol treatment modality. Key words: neonate; small child; inhaler; aerosol; mechanical ventilation; manual resuscitation; spontaneous breathing; simulation. [Respir Care 2010;55(4):419–426. © 2010 Daedalus Enterprises]
Introduction

Inhaled bronchodilator therapy in pre-term and term infants may improve lung function among those who are developing chronic lung disease, at least in the short-term, despite the speculation that airway smooth muscle may not be clinically responsive in the acute treatment of pre-term infants.1 The case for inhaled bronchodilator therapy is clearer in children of toddler age, as β₂ agonists are routinely recommended for treatment of acute bronchoconstriction in this age group,2 and widely administered via nebulizer or pressurized metered-dose inhaler (pMDI) plus valved holding chamber (VHC).3 However, infants in particular have both small tidal volume (VT) and low inspiratory/expiratory ratio, compared to adults,4 resulting in short residence times for drug particle delivery to the airways. These factors combine to make it difficult to achieve optimum clinical benefit in terms of improving airway patency5 via the 3 alternative aerosol-delivery modalities available in the acute setting: via endotracheal tube (ETT) during mechanical ventilation; via ETT during manual resuscitation; and via tight-fitting face mask during spontaneous breathing. In particular, the challenges of delivering aerosols via mechanical ventilation to neonates are substantial, and there is evidence that the precise configuration of the ventilator circuit, the ETT size, and the gas flow rate and pattern can each influence the outcome.6 The situation is complicated further by the variety of aerosol-delivery devices available for mechanical ventilation,6 manual resuscitation7 and spontaneous breathing.8 Given these circumstances, the desirability of an efficient small-volume VHC that accepts commonly prescribed pMDI bronchodilators and that is not bulky, so that it can be used in all of the aforementioned clinical situations, becomes self-evident.

The objective of this in vitro investigation was to determine the differences in the delivery of inhaled β₂-agonist via a novel VHC between mechanical ventilation, manual resuscitation, and face-mask aerosol delivery. We simulated neonates and infants with normal lung mechanics.

We evaluated a novel small-volume (110 mL) VHC (AeroChamber Mini, Monaghan Medical, Plattsburgh, New York) (Fig. 1), which is designed to be adaptable without modification for mechanical ventilation, manual resuscitation, and face-mask aerosol delivery. We simulated neonates and infants with normal lung mechanics.

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We evaluated 5 AeroChamber Mini VHCs per test. We tested the VHCs immediately out-of-package, with no pre-washing. We used hydrofluoroalkane-propelled pMDI canisters of albuterol (Ventolin-HFA, GlaxoSmithKline, Research Triangle Park, North Carolina) that deliver 90 μg ± 15% albuterol base equivalent from the actuator nozzle per actuation. We simulated aerosol delivery via ETT during mechanical ventilation (Fig. 2), via ETT during manual resuscitation (Fig. 3), and via face mask during spontaneous breathing (Fig. 4). In each scenario we used a pre-primed pMDI-VHC setup and delivered 4 actuations, at 30-s intervals. We shook the canister between actuations to ensure reproducibility of the actuations. We allocated a separate pMDI for each of the 3 aerosol-delivery routes. Each batch of tests was undertaken without disassembling the setup, and with the breath simulator operating continuously.
We collected the aerosol from the VHC with a bacterial/viral electret filter (Respirgard-II, Vital Signs, Englewood, Colorado) after the fourth actuation. Preliminary method-validation studies confirmed that the deposited albuterol from 2–5 actuations was measurable ($n = 5$ replicate measurements), using methanol (95% volume/volume) as solvent, and the range of recovery was $\geq 98\%$. We quantified the albuterol with high-performance liquid chromatography (Star, Varian Canada, Mississauga, Ontario, Canada), under room ambient conditions. The mobile-phase proportions were 70/30 volume/volume methanol/5 mM sodium dodecyl-sulphate buffer (pH 2.5). The isocratic ternary pump (model 230) delivered mobile phase at a flow of 1.6 mL/min. We injected a 50-$\mu$L aliquot from each albuterol sample onto a 4.6 $\times$ 150-mm Allsphere octadecysilane-2 5-$\mu$m column (Grace Davison Discovery Sciences, Deerfield, Illinois) via the autosampler (ProStar, Varian Canada, Mississauga, Ontario, Canada). The ultraviolet-visible detector (model 325) was operated at a wavelength of 276 nm. Validation studies with standard solutions of analyte had correlation coefficients ($r^2$ values) $\geq 0.995$. The range of assay inter-day coefficients of variation with albuterol quality-control solutions was 0.5–1.3%. We converted absorbance units to micrograms of albuterol with the chromatography workstation’s software (version 6.41).

The simulations of aerosol-delivery via ETT during mechanical ventilation were all undertaken with a ventilator (Inspiration 1.5, eVent Medical, Galway, Ireland), with the target $V_T$ and frequency set shown in Table 1, and with positive end-expiratory pressure (PEEP) of 5 cm H2O. We used a 10-mm, flexible tube, universal, dual-heated, infant breathing circuit (model 4538850, Intersurgical, Syracuse, New York) in the premature-neonate model and the term-neonate model. We used a 15-mm, flexible tube, universal, dual-heated, child circuit (model 4525850, Intersurgical, Syracuse, New York) in the 2-year-old-child model. In the premature-neonate model we used a 2.0-mm diameter in-line suction catheter (Ballard Trach Care, Kimberley-Clark, Roswell, Georgia). In the term-neonate model and 2-year-old-child model we used a 2.6-mm diameter in-line suction catheter (Ballard Trach Care, Kimberley-Clark, Roswell, Georgia). In all the tests the breathing circuit was humidified (model MR290, Fisher & Paykel, Auckland, New Zealand) to achieve a humidity of 37 mg/L (saturated at 38°C), as in clinical use. Figure 2A schematically illustrates the setup for the mechanical-ventilation model, show-
ing the circuit humidification arrangement. Figure 2B shows the interface between the VHC-ETT and the test lung (ASL 5000, IngMar Medical, Pittsburgh, Pennsylvania), configured for appropriate age-specific breathing pattern and lung mechanics variables (see Table 1).4,9-11 We chose ETTs of inner diameter 2.5 mm, 3.5 mm, and 4.0 mm in the premature-neonate model, term-neonate model, and 2-year-old-child model, respectively.

Aerosol available for inhalation was determined via filter collection, with the filter placed at the distal end of the ETT, adjacent to the test lung. Two additional similar filters were placed in series, to protect the airway to the test lung.

The manual-resuscitation simulations (see Fig. 3A) were all undertaken with a Servo ventilator (SV900C, Siemens, Sweden), set to mimic manual resuscitation of either an infant (premature-neonate model and term-neonate model) via a 250-mL resuscitation bag (VBM, Sulz-am-Neckar, Germany) or child (2-year-old-child model) via a 500-mL capacity resuscitation bag (Mercury Medical, Clearwater, Florida). Reproducible external pressure changes could be applied by the ventilator to the bag while the bag was in a plethysmograph-type chamber (see Fig. 3B). The exit from the resuscitation bag was connected directly to the proximal end of the VHC, near where the pMDI canister is inserted, with the distal end of the ETT attached to the test lung via the same type of aerosol-collection filter as in the mechanical-ventilation scenarios. The target pressures and frequency applied to the plethysmograph-type chamber to compress the manual-resuscitation bag were configured so that the VT, frequency, and inspiratory time delivered to the test lung conformed to the values in Table 1. All measurements were undertaken at ambient temperature and relative humidity (22 ± 1°C and 44 ± 7% relative humidity).

The simulations of aerosol delivery via face mask during spontaneous breathing were undertaken with infant and small-child face models (ADAM-II, Trudell Medical International, London, Ontario, Canada) that have soft, responsive surfaces where they contact the face mask.12,13 The face mask was manually held against the face model, with sufficient force to ensure a seal between the mask and the face model; this was verified before conducting the breath simulations, by comparing the flow measurements between the model and the test lung to those made via thermal mass flow meter (model 4000, TSI, St Paul, Minnesota) located at the entry to the VHC, with a vacuum applied to the distal end of the model. The VHC was attached to the face mask (see Fig 4).

The aerosol available for inhalation was captured on an electret filter square (Filtrete media type G, 3M, St Paul, Minnesota) located immediately behind the half-closed lips of the face model. The target airway resistance and compliance and bag setup were configured so that the VT and frequency delivered conformed to the values in Table 1. All the measurements were made at ambient conditions (22 ± 1°C, 44 ± 7% relative humidity).

Statistical interpretation of the total emitted mass per actuation was via one-way analysis of variance (SigmaStat version 3.01, Aspire Software, Ashburn, Virginia). Differences were deemed significant when P < .05. The uncertainty limits in Table 2 each represent ± 1 standard deviation about the mean value.

**Results**

In the preliminary validation studies, the mass of albuterol per actuation emitted from the pMDI without the VHC (benchmark data) was 96.6 ± 3.9 µg (mean ± SD for 5 inhalers, one measurement per inhaler). The measurements of total emitted mass that exited the VHC with patient interface (ETT or mask) are summarized as absolute mass per actuation, and were also normalized to the...
label-claim 90 μg albuterol per actuation in each simulation (see Table 2).

Albuterol delivery through the ETT during mechanical ventilation, though comparable in the premature-neonate model (3.3 ± 1.2 μg), the term-neonate model (3.8 ± 2.1 μg), and the 2-year-old-child model (4.2 ± 2.3 μg) ($P = .63$), was significantly lower than in the spontaneous-breathing and manual-resuscitation models ($P < .001$). In the 2-year-old-child model the total emitted mass was marginally less in the manual resuscitation model (10.0 ± 1.1 μg) than in the spontaneous-breathing model (12.1 ± 1.8 μg) ($P = .046$). In the neonatal models the total emitted mass was similar in the manual resuscitation scenario (5.5 ± 0.3 μg in the premature-neonate model, 10.7 ± 0.9 μg in the term-neonate model) and the spontaneous-breathing scenario (6.0 ± 1.0 μg in the premature-neonate model, 10.5 ± 0.7 μg in the term-neonate model) ($P \geq .46$ via one-way analysis of variance).

**Discussion**

To our knowledge, our study is only the second systematic laboratory investigation of aerosol delivery via pMDI-VHC to neonates and infants via these 3 aerosol-delivery modalities. A few years ago, Cole et al. were the first to examine the problem in this way, but they used a previous generation of VHC prototypes that are not commercially available. Cole et al conducted the manual-resuscitation simulation by manually operating the resuscitation bag, based on previous clinical experience of one of the authors in a neonatal intensive care unit. We automated the operation of the resuscitation bag to make replication of these measurements easier and to reduce the breath-to-breath $V_T$ variability and inspiratory/expiratory-ratio variability of manual resuscitation.

Our hypothesis that there would be no differences in medication delivery within each simulated patient group with these treatment modalities was disproven, and the total emitted mass measurements (see Table 2) were small in relation to the label-claim emitted dose (90 μg). It should be noted that these small measures of total emitted mass should be interpreted in relation to the limited clinical data that exist for pMDI albuterol delivery to neonates and small children, rather than to older children or adults. On this basis, even the lowest values normalized to the label-claim values during the mechanical ventilation simulations (range 3.7–4.7% of label-claim value per actuation [see Table 2]) compared well with similar data from Tal et al. with 15 spontaneously breathing small children (mean age 21 months, age range 3–60 months) who had airway obstruction from asthma, cystic fibrosis, or bronchopulmonary dysplasia, treated via a 145-mL holding chamber and face mask. Tal et al determined the mean chlorofluorocarbon-propelled pMDI albuterol deposition to be 4.36% of the label claim (1.97% in the lungs, 1.28% in the oropharynx, and 1.11% in the stomach). We used their value of 4.36% of label claim for total patient-delivered albuterol as a benchmark, because, to the best of our knowledge, their study is the only one that has used radiolabeling to assess pMDI albuterol delivery in that very young age range. Furthermore, treatment of spontaneously breathing patients via VHC and face mask probably represented the
optimum modality, given the likelihood of decreased lung delivery via the narrow ETTs used with infants, compared to a tight-fitting and therefore probably leak-free face mask. The comparability we found between the values in our manual resuscitation models and spontaneous-breathing models is therefore somewhat surprising and probably indicates that the aerosol loss in the ETT is similar to the aerosol loss in the face mask.

Taking the value of 4.36% of label claim from Tal et al as a point of reference to the previous work, our values for the manual resuscitation and spontaneous-breathing scenarios (see Table 2) ranged from just under +140% (in the premature-neonate during manual resuscitation model) to about +300% (in the 2-year-old-child during spontaneous-breathing model). However, these apparent increases in drug delivery in our in vitro investigation need to be related to the fact that by not modeling either the upper airway or the effects of disease, we have almost certainly overestimated the mass of medication that would reach the lower respiratory tract in the patients we simulated. Our focus was to establish the mass of albuterol available for inhalation at the distal end of the ETT or face mask, as guidance for clinicians faced with providing treatment to infants and small children.

We might have anticipated greater medication delivery if the inspiratory/expiratory ratios were lower than the values used in our simulations (see Table 1), by virtue of the greater amount of time spent inhaling the aerosol. Likewise, increasing the VT would probably be associated with improved medication delivery, as seen when comparing equivalent measures of total emitted mass between the premature-neonate model (VT 6 mL) and the term-neonate model (VT 20 mL) in the manual resuscitation and spontaneous breathing simulations (see Table 2). However, considering the same simulations, when VT was increased to 60 mL and the inspiratory time per respiratory cycle was increased (inspiratory/expiratory ratio 1:2) in the 2-year-old-child model, the anticipated improvement in total emitted mass was not apparent. We conjecture that increased inertial deposition of particles at the higher instantaneous flow velocities in the 2-year-old-child model might have offset VT/inspiratory-time-related effects on aerosol transport via the patient interfaces that we studied. However, further work is needed to investigate this behavior in a more systematic way before definitive conclusions can be made.

During the mechanical ventilation and manual resuscitation scenarios, the additive imposed expiratory resistance caused by the PEEP valve (during manual ventilation) and the ventilator’s exhalation valve may have applied some back-pressure when exhaling down to PEEP. However, these effects are not deemed likely to have impacted drug delivery, given that an air dam exists at the entry to the VHC, by virtue of the VHC inhalation valve closure during exhalation, thereby preventing mixing of the aerosol with exhaled air.

It is interesting to interpret our data in the context of assessing the emitted mass of albuterol normalized by nominal patient weight (assuming 1 kg, 4 kg, and 12 kg in the premature neonate model, term-neonate model, and 2-year-old-child model, respectively). As a benchmark, an average value of 1.3 μg/kg has been reported for a spontaneously breathing 70-kg adult, based on the label-claim delivery of Ventolin-HFA without a VHC or face mask. In the present study, the total emitted mass/kg in the spontaneous-breathing models ranged from 1.0 μg/kg (in the 2-year-old-child model) to 6.0 μg/kg (in the premature-neonate model) (Table 3), and those values straddle the benchmark value. However, closer agreement is evident when the results from the present investigation are compared to the equivalent measurements reported in the current United States prescribing instructions for Ventolin-HFA for infant and small child use (range 0.8–2.6 μg/kg). Those estimates also originated from in vitro measurements with Ventolin-HFA and the same infant and small-child face models we used, albeit with sampling at constant flows of 4.9 L/min and 12.0 L/min, respectively, rather than mimicking tidal breathing as in the present study, and with slightly larger (149-mL) anti-static and non-conducting VHC and mask devices. Given that the AeroChamber Mini VHC is manufactured from an electrostatic-charge-dissipative polymer, it is germane to note that precautions were taken in the earlier study to eliminate electrostatic charge, via pre-treatment per manufacturer instructions (with the non-conducting VHC) and the use of charge-dissipative-materials VHCs.

The greatest differences we observed between treatment modalities with the AeroChamber Mini VHC occurred in the mechanical-ventilation scenario, whereas aerosol delivery in the manual-resuscitation scenario and the spontaneous-breathing scenario was substantially equivalent (see Table 2). Apart from the fact that there were differences between the configurations in filter location with respect to the aerosol-generation source, which probably reduced aerosol delivery, particularly with the mechanical-

### Table 3. Estimated Mean Mass of Albuterol Available for Inhalation, Divided by Body Weight*

<table>
<thead>
<tr>
<th>Simulation Scenario</th>
<th>Premature Neonate</th>
<th>Term Neonate</th>
<th>2-Year-Old Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>3.3</td>
<td>0.95</td>
<td>0.33</td>
</tr>
<tr>
<td>Manual resuscitation</td>
<td>5.5</td>
<td>2.68</td>
<td>0.83</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>6.0</td>
<td>2.63</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* All values are μg/kg.
ventilation scenario (see Figs. 2A, 3A, and 4A), the significantly reduced aerosol delivery in these simulations was probably associated with the saturation of the circuit gas (37°C, > 99% relative humidity). The circuit gas was much more humid than in the manual-resuscitation scenario or the spontaneous-breathing scenario, which were all at room ambient conditions (22 ± 1°C, 44 ± 7% relative humidity). It is well known that aerosol delivery is decreased by saturated or near-saturated conditions in adult mechanical ventilation circuits,17,18 and medication delivery can be reduced by as much as 40%, compared to that with a non-humidified circuit at room ambient conditions.19,20 However, although circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in ventilator-supported patients.21 It also follows that in mechanically ventilated patients lower-respiratory-tract aerosol deposition is generally lower with nebulizer than with pMDI,20 which favors pMDI with VHC.

Limitations

First, our study was intended primarily to establish the mass of medication emitted from the distal end of the ETT or mask and thus available to be inhaled. Second, as in all in vitro models, we could not simulate the outcome of patient exhalation in any of the treatment scenarios, which would result in a small loss of particles that did not deposit in the airways during inspiration.3,21 Third, we could not account for patient-related factors such as individual airway geometry, or type, location, or severity of pulmonary disease.22 Fourth, we were not able to evaluate our data in relation to the clinical study with hydrofluoroalkane-propelled albuterol, of the type presented by Tal et al,15 because such data do not yet exist. Fifth, we measured total emitted mass rather than fine-particle mass, which could be deemed more appropriate for assessing lung deposition.23 Measuring the aerosol particle size distribution would have required use of a cascade impactor with the breathing simulator, which would have added substantially to the complexity of the measurement methodology24 and therefore to the variability of each data set.25 In defense of our choice to report just total emitted mass, the use of a VHC (with either ETT or face mask) would be expected to eliminate most, if not all, particles > 5 μm aerodynamic diameter, which deposit in the oropharynx rather than the lungs.26

Finally, although in our simulations of spontaneous breathing we applied the mask to the model face with just sufficient force to achieve the necessary seal,27 we were unable to ensure that the force exerted was constant. Instead, we relied on visual observation that the face mask was mildly compressed on the face, as would be the case in clinical practice. The bench-top studies by Shah et al suggest that it is possible that slightly increased total emitted mass might be possible with greater force applied to the mask, because the greater compression decreases the functional dead space between the mask and the face.28

Conclusions

Our in vitro study demonstrates that delivery of pMDI albuterol via VHC to pre-term and term neonates and small children with obstructive lung disease is possible, via ETT during mechanical ventilation or manual resuscitation, or via mask during spontaneous breathing, which are the most likely scenarios. On a weight-adjusted basis, our measurements of total emitted mass per actuation were comparable to previous in vitro measurements for pMDI albuterol to spontaneously breathing younger pediatric patients, and similar to or somewhat greater than the mean value for total patient-delivered albuterol reported in the benchmark clinical study, which involved chlorofluorocarbon-propelled albuterol to very young pediatric patients,14 most likely because our study could not model either the exhalation portion of each breathing cycle or replicate patient-specific factors such as disease severity and location. As expected, aerosol delivery during mechanical ventilation via ETT was less than during manual resuscitation via ETT or spontaneous breathing, probably because the circuit gas was saturated in the mechanical-ventilation scenario. We conclude that the AeroChamber Mini VHC provides a versatile alternative to existing VHCs. As well as the need to evaluate its performance in the clinical setting, further laboratory investigations are warranted with other pMDI-based formulations that might be delivered to the classes of patients modeled.

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28. Shah SA, Berlinstei A, Ruben BK. Force-dependent static dead space of face masks used with holding chambers. Respir Care 2006;51(2):140-144.