Influence of Moisture Accumulation in Inline Spacer on Delivery of Aerosol Using Metered-Dose Inhaler During Mechanical Ventilation

Hui-Ling Lin MSc RRT RN, James B Fink PhD RRT FAARC, Yue Zhou PhD, and Yung-Sung Cheng PhD

BACKGROUND: A practitioner questioned whether moisture that collected in the ventilator circuit and spacer affected the delivery of aerosol from a pressurized metered-dose inhaler (pMDI). An in vitro model was used to quantify the impact of accumulated humidity in a pMDI spacer and ventilator over time. METHODS: A ventilator with an adult heated-wire ventilator circuit and humidifier was set to deliver adult settings. An impactor was placed between the endotracheal tube and the test lung to determine drug mass and mass median aerodynamic diameter of the aerosol delivered. An AeroVent pMDI spacer was placed in the inspiratory limb of the ventilator circuit and left in an open position. Eight actuations of HFA albuterol pMDI (720 μg) was administered at 1, 2, and 3 hours after the heater had reached equilibrium at 37°C, and < 10 min after turning off the heater/humidifier. The spacer was dried and returned to the heated circuit for additional testing. Samples were analyzed via spectrophotometer. One-way analysis of variance was applied ($P < .05$). RESULTS: The delivered drug as a percent of emitted dose (mean ± SD) was greater at hour one (23 ± 2.1%) and with the dry spacer (21.8 ± 3.3%) than at hours 2 and 3 or with humidifier off (11.4 ± 3.8%, 12.3 ± 0.8%, and 12.7 ± 0.3%, respectively, $P = .002$). Mass median aerodynamic diameters with each comparison did not vary between conditions. Delivery efficiency was similar for the dry spacer and the spacer in the humidified circuit for one hour. However, once visible condensate occurred, drug delivery efficiency decreased by approximately 50%. CONCLUSIONS: Aerosol delivery from a pMDI with spacer during mechanical ventilation was greater with a dry spacer and unchanged for the first hour after initiating heated humidification. Turning off the heated humidifier did not increase drug delivered. *Key words: aerosols, metered-dose inhalers, humidity, mechanical ventilation, drug deposition, condensation.* [Respir Care 2009;54(10):1336–1341. © 2009 Daedalus Enterprises]

Introduction

The pressurized metered-dose inhaler (pMDI) is often used to deliver aerosol therapy to patients receiving mechanical ventilation. Because the standard boot supplied with pMDI cannot be used during mechanical ventilation, a variety of inline adapters and spacers have been developed.[1] To minimize interruptions of mechanical ventilation and positive end-expiratory pressure, and to reduce risk of ventilator-associated pneumonia, the pMDI spacer commonly remains in the circuit to keep the system closed over the course of treatment. As time elapses, moisture accumulates from the heated humidifier in the ventilator

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circuit.[2] The pMDI spacer can collect condensate during use and act as a water trap. To that point, Waugh reported that water accumulation in pMDI spacers increased over 6 hours.[2]

More recently, on the adult acute care section of the American Association for Respiratory Care's e-mail Listserv, a respiratory therapy practitioner questioned whether moisture that collected in the ventilator circuit and spacer affected the delivery of aerosol from pMDI.[3] Studies have shown that the inhaled drug mass delivered through an artificial airway from a pMDI is affected by high relative humidity and temperature within the ventilator circuit, with reduction of up to 50% in delivered dose, compared to ambient conditions.[4,5] This reduction of aerosol drug delivery with heated humidity has prompted some clinicians to suggest turning off the heated humidifier immediately before aerosol administration, to improve aerosol delivery.

Based on published reports of reduced aerosol delivery in heated humidified ventilation circuits, one might expect this reduction would be consistent independent of whether condensate is visible in the spacer or circuit. However, neither the impact of turning off heated humidification prior to aerosol administration nor the impact of water accumulation in the spacer on drug delivery from a pMDI during mechanical ventilation has been reported.

The aim of the present study is to investigate whether accumulated condensate in a pMDI inline spacer and ventilator circuit impact the aerosol mass and particle size of aerosol distribution of albuterol delivered to a heated humidified in vitro model of adult ventilation. A secondary objective is to quantify any improvement in drug delivery, by measuring the mass of albuterol deposited distal to the ETT when heated humidity is turned off prior to aerosol administration.

Methods

This study was performed at the Lovelace Respiratory Research Institute, Albuquerque, New Mexico.

Lung Model

The model of adult mechanical ventilation is illustrated in Figure 1. An Avea ventilator (Viasys Healthcare, Yorba Linda, California) with an adult 22-mm inner diameter heated-wire circuit and active heated humidifier (MR850, Fisher and Paykel Healthcare, Laguna Hills, California) provided volume-control ventilation with adult parameters (tidal volume of 700 mL, respiratory rate 12 breaths/min, inspiratory flow 50 L/min with decelerating pattern, positive end-expiratory pressure 5 cm H_2O, and bias flow 2 L/min). The heated humidifier was set to deliver humidified gas at approximately 37°C at the airway.

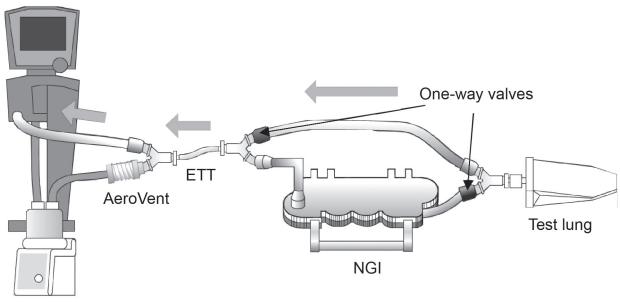

Fig. 1. Schematic of the experimental apparatus.

Gas exiting the ventilator passed from the ventilator circuit through the endotracheal tube (ETT, 8.0 mm inner diameter) and a Y-piece connector into a Next Generation Pharmaceutical Impactor (NGI, MSP, Minneapolis, Minnesota) en route to a mechanical test lung (Siemens, Munich, Germany).

The NGI was designed specifically for pharmaceutical inhaler testing, collecting particles of different sizes in 7 stages, and is intended to operate at any inlet flow rate of 30–100 L/min.[6] Particles are deposited in the throat and collection cups. The ETT was positioned so that the distal tip was superior to the ventilator circuit, preventing condensate and liquid drug from entering the impactor. Exhaled gas from the test lung was routed through 2 one-way valves, an 18-inch corrugated tube, Y connectors, and the ETT, back to the ventilator circuit. The flow of gas passing into the impactor resulted in a mean 30 L/min during each breath, measured between the ETT and the impactor by a DC-1 flow calibrator (Bios International, Pompton Plains, Illinois).

After each set of pMDI actuations, the impactor was left inline for 1 min post-administration. After each run, the impactor was bypassed by connecting the ventilator circuit directly to the test lung while the impactor was opened and the samples were collected; the impactor was cleaned and returned to the test setup for the next measurement. All experiments were performed at an ambient temperature of 22 ± 2°C and a relative humidity of 45 ± 4%, as measured by a thermo-hydrometer (RH411, Omega Engineering, Stamford, Connecticut).

Metered-Dose Inhaler Preparation. Each pMDI of hydrofluoroalkane-formulated albuterol sulfate (GlaxoSmithKline, Research Triangle Park, North Carolina) (manufacturer-estimated emitted dose of 90 μg) was warmed to hand temperature, well shaken, and primed with 4 actuations, using the boot provided by the manufacturer, prior to use. All actuations from each pMDI canister were counted and recorded to avoid use of empty pMDIs during the experiment. During test measurements, each actuation was discharged into a pMDI spacer (AeroVent, Monaghan Med-

ical, Plattsburgh, New York) at the beginning of inspiration. Successive actuations of the pMDI were at ≥ 20-s intervals. Eight actuations (720 μg) of albuterol were administered for each measurement. Because of the relatively low variability found with in vitro aerosol measurements, and its prevalent use in the in vitro pMDI literature, each set of measurements was performed in triplicate ($n = 3$).

Study Design

Experiment 1. The ventilator was run until a stable temperature of 37 ± 1°C was achieved, as measured at the airway. The pMDI spacer was placed between the inspiratory limb of the ventilator circuit and proximal to the Y connector, and left in an open position for 3 hours. Eight actuations of the pMDI were administered at 1, 2, and 3 hours. At the end of the third-hour experiment the heated humidifier was turned off, and an additional set of measurements was taken within 10 min. The spacer was inline continuously, without disconnection or draining the accumulated condensation through the 4 sets of measurements.

Experiment 2. The heated humidifier was turned on and allowed to return to 37 ± 1°C while the spacer was removed from the ventilator circuit, rinsed with tap water, blown dry with air, and returned to the circuit. A set of measurements was taken with the dry spacer in the heated humidified ventilator circuit.

Experiment 3. To compare accumulation of water condensate in the AeroVent spacer when used as directed (closed between dosings) and with the methods used in the present study, a clean dry spacer was weighed using an electronic semi-micro balance (Sartorius, Göttingen, Germany) and placed in a preheated heated humidified ventilator circuit. Eight actuations of albuterol were performed each hour, for 3 hours, both when the spacer was (1) closed between doses, as directed on the label, and (2) left open between doses. To determine water accumulated in the spacer, the spacer was weighed after each hourly dosing.

Measurement

The impactor was disassembled after each trial and drug was eluted from the parts using distilled water (5 mL for the universal standard port, and 3 mL for all stages). The eluted drug was analyzed with a spectrophotometer at 224 nm. The concentration of drug was determined as μg/mL and then multiplied by the volume of fluid to quantify the amount of drug deposited in the throat and at each stage. Inhaled mass was defined as the sum of drug mass from each compartment. Percent of drug deposited was calculated by dividing the inhaled mass by the emitted dose from the pMDI label (720 μg). Drug mass quantified from each part/compartment of the impactor was used to determine mass median aerodynamic diameter (MMAD).

Table 1. Mean Percentage of Drug Mass

Time/Test Condition	Total Mass (mean ± SD %)
Dry chamber*	21.8 ± 3.3
1 h	23 ± 2.1
2 h	11.4 ± 3.8
3 h	12.3 ± 0.8
Heater off	12.7 ± 0.3

* The P values were .004 compared to 2 h, .009 compared to 3 h, and .013 compared to heater off.

Date Analysis

Descriptive statistics (means and standard deviations) for each condition were calculated. All statistical calculations of particle-size distribution (MMAD) and inhaled mass were performed using commercially available software (SigmaPlot, Systat Software, San Jose, California). The comparison of total inhaled drug mass, percent of drug deposited, and MMAD were analyzed with SPSS version 11.5 (SPSS, Chicago, Illinois) with one-way analysis of variance, with a significance level of .05. Each group was compared using a Bonferroni post hoc test.

Results

Table 1 summarizes the percentage of emitted dose of albuterol from the pMDI with spacer (mean ± SD) deposited distal to the ETT over the course of the experiments 1 and 2. The percentage of dose delivered varied between 11.4% and 23% ($P = .002$). The highest delivery efficiency of albuterol from the pMDI was with the dry spacer (21.8 ± 3.3%) and a new spacer left open for one hour in a heated humidified circuit (23 ± 1.2%). In contrast, when the spacer was visibly saturated with moisture for longer than one hour, the delivered drug mass was reduced by approximately 50%. When the heater was turned off, the delivery efficiency did not increase.

The particle-size distributions (MMAD) are summarized in Figure 2. There is no significant difference between experiments. The MMAD appears to be insignificantly decreased when the heater was turned off.

The accumulated condensation in the AeroVent spacer at 1, 2, and 3 hours when used as directed (closing between doses) were 0.49 g, 0.82 g, and 2.33 g, respectively. Water accumulation with the spacer left open between doses was 1.07 g, 3.65 g, and 4.74 g.

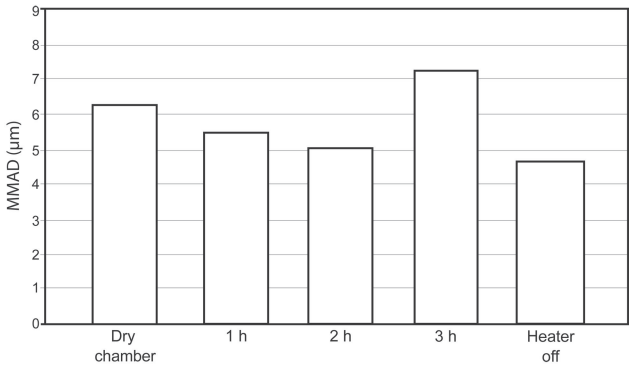

Fig. 2. Particle-size distributions.

Discussion

The current study demonstrates that the presence of heated humidity and water accumulated in a pMDI spacer over time impact delivered drug efficiency, compared to administration with heated humidity alone. This finding is unique in that the heated humidity both at one hour and with a dry spacer did not decrease inhaled mass below levels previously reported in non-humidified ventilator circuits. However, once the spacer was visibly saturated with humidity, the mass decreased by as much as 50%.

Numerous authors have identified a reduction of aerosol delivery efficiency during mechanical ventilation with heated humidification, often with a 40−50% reduction from dry/ambient conditions.[4,5,11] These results have always been presented in terms of heated humidification being on or off, without description of the amount of time that the pMDI spacer or nebulizer was in the heated humidified circuit prior to the experiments being conducted.

The differences in delivered aerosol to the distal tip of the ETT are consistent with reports from Fink et al, in which actuation of albuterol hydrofluoroalkane pMDI with an AeroVent spacer delivered 22.0% under dry, and 12.3% under heated humidified conditions.[4] In the paper the investigators described allowing the ventilator circuit to equilibrate at the desired temperature (35–37°C) but did not describe the length of time that the heated humidifier was operating prior to making measurements. Fink recalled that the ventilator, circuit, and test lung were assembled with the AeroVent left in the open position in the inspiratory limb, and the ventilator/heated humidifier was turned on and left to warm up and equilibrate while other preparations for the experiment were conducted. However, the time between turning on the ventilation and beginning of measurements was not noted. However, the time between turning on the ventilation and the beginning of measurements was not noted, but the heated humidifier system used generally requires up to 30 min in order to reach equilibrium.

When the humidifier was turned off to administer the pMDI in a saturated ventilator circuit, there was no significant increase in drug delivered, compared to drug delivery with heated humidity at hours 2 and 3. The accumulated water and thermal mass of the circuit, when turning the heater off, may have been sufficient to maintain the heat and humidification levels to reduce the drug delivery efficiency.

Although turning the heater off immediately prior to pMDI administration does not improve aerosol delivery, it does increase the risk that the humidifier may not be turned back on post-administration and that the patient will suffer the effects of inadequate humidification over a prolonged period of time. This practice should be discouraged.

We selected the AeroVent for this study because it has been widely characterized in previous reports.[2,4,7-11] It should be noted that the AeroVent was not designed or marketed to be left open between doses, as used in this study. However, numerous pMDI spacers add similar volume to a ventilator circuit as the AeroVent in the open position. The water collected in the open AeroVent (1.07 mL in hour 1, with 3.7–4.7 mL in hours 2 and 3, respectively) supports our observations that a relatively small amount of condensation was observed in the spacer after one hour and that the water appeared to cover the bottom of the spacer by the end of hour 3. Waugh reported up to 5.6 mL in water accumulation in a variety of pMDI spacers.[2] While AeroVent accumulated less water than the fixed internal volume of an ACE spacer and an OptiVent spacer, the condensation increased significantly during 6 hours, from 0.394 g at 2 hours to 0.765 g at 6 hours, using a heated-wire ventilator circuit with temperature at 34.5°C. In contrast with Waugh's study, we found water accumulation of 2.33 mL in the AeroVent, when used as directed, after 3 hours. The difference may be due to the higher delivered temperature at 37°C in the current study. It is possible that over several days of use the water accumulation in the AeroVent, used as directed, could exceed the 3–4 mL found in the open spacer in the course of our study. Our finding of accumulated water in the spacer is within the range reported by Waugh, suggesting that results of this study may be relevant to any spacer that accumulates water during the course of use, be it for hours or for days.

Efforts are made not to break or open the ventilator circuit unnecessarily. Reasons range from avoiding derecruitment of the lung, which may take hours to reestablish, to reducing risk of infectious agents entering or leaving the ventilator circuit. While the accumulation of condensation in the spacer did not seem to further reduce drug delivered to the simulated patient between hour 2 and 3, it seems preferable that the accumulated liquid periodically be drained out of the circuit. By rotating the spacer, most of the visible condensation in the AeroVent spacer can be

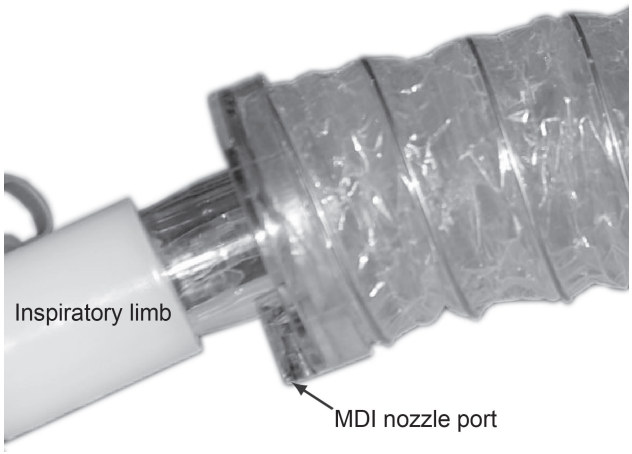

Fig. 3. AeroVent spacer, with the receptacle port downward.

drained without breaking the closed system. Thus the pMDI nozzle port, which is made with a smooth surface, faces downward, and the spacer is below the Y-piece connector. The condensate flows out through the nozzle port without perceptible leak from the ventilator (Fig. 3). The amount of water remaining in the spacer after the water was drained through the actuation port is approximately 0.245 g, which is less than the amount of water accumulated within the first hour in the spacer, regardless of whether the AeroVent is closed or left open in the ventilator circuit after drug dosing. The drainage of accumulated water from the spacer by turning the actuation port downward is efficient and safe, compared to breaking the ventilator circuit system. However, the impact of draining the spacer on aerosol delivery was beyond the scope of this study, and may warrant future evaluation.

Lange and Finlay reported approximately 20% of the total administered dose from a pMDI with 37°C and 100% relative humidity.[11] This suggests that the NGI and the model used was sufficient for quantifying aerosol delivered. However, the particle-size distribution, with humidifier set at 37°C and relative humidity of 100%, was approximately 2.5 μm in Lange and Finlay's study, versus 4.6–7.2 μm in the present study. Lange and Finlay utilized a well controlled climatized chamber, whereas the current study was done with higher absolute humidity and cooler ambient temperatures. When the cold mist was released from the pMDI canister the water condensation on the aerosol particles may have impacted the rate of propellant evaporation: hence, the particle deposition in the stage 2 and 3 of the NGI at cut points of 6.35 μm and 3.97 μm.

Studies have shown that larger particles generated by aerosol therapy are most likely to trap in the ventilator circuit and the ETT during mechanical ventilation.[9,11-14] Bishop et al studied pMDI delivery though different adaptors.[9] The majority of the particles produced are in a small range (< 1.0 μm), and no particles were detected in the large range (> 5.1 μm). It's unclear if the large particle distributions in the present study were due to the humidity, which might influence the rate of propellant evaporation, or due to the measurement method.

In this study MMADs remained similar over the course of the tests, regardless of the duration of humidity and the heater use. This may be an artifact of the method used, which was previously verified for use with a dry ventilator circuit, but not with the presence of humidity.[15] To our knowledge, this is the first research using an alternative method of the NGI in a heated humidified ventilator circuit. An impactor, composed of several stages, separates particles of different sizes, and is the most commonly used equipment to measure particle distribution. Impactors such as the Andersen cascade impactor and the NGI require a negative flow of 28–30 L/min to draw the aerosol through the stages. For use of the NGI with the ventilator in the present study, the ventilator flow pattern entering the impactor was selected to produce a mean flow of 30 L/min exiting the impactor, the flow for which the impactor is calibrated.

Previous validation of use of the NGI during mechanical ventilation was performed using a dry gas at ambient temperatures to deliver nebulized 2.1-μm fluorescing particles through the ventilator and the manufacturer's recommended method to compare particle distribution (unpublished data). Although forcing tidal breaths through the impactor appears to modify peak flow patterns, the measured particle-size distributions were similar to measurements with constant flow through the impactor.

Studies have shown that aerosol delivery through a higher relative humidity environment influences the particle distributions.[16,17] We found no significant difference in MMAD across experiments, whether the heater was turned on or off. This may suggest that high relative humidity was maintained, even with small decreases in temperature and absolute humidity. Because the validation of delivering the pMDI through the NGI was done without heated humidity, the MMAD of the present study may not be reliable in providing an absolute value; changes in MMAD across experimental conditions may or may not be relevant. These findings suggest the need for future validation of particle size with the NGI, when used in a heated humidified ventilator circuit.

Ventilator settings were selected that were typical but not inclusive of all clinical situations. Testing with a broad range of ventilator settings was beyond the scope of this study. Further testing with additional medications, spacer/adapter designs, and other types of aerosol generators may be warranted to confirm that these observation are more widely relevant.

Conclusions

Aerosol delivery from a pMDI with the AeroVent spacer during mechanical ventilation was greater with a dry spacer and unchanged for the first hour after initiating heated humidification. Once condensation occurred, the inhaled drug mass decreased by up to 50%. Turning off the heated humidifier did not increase drug delivered but could increase the risk of forgetting to turn the heater back on.

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