TRUDELL MEDICAL INTERNATIONAL

Specialty Chambers

Study Summary

Updated: January 2024

AeroChamber* MV
Holding Chamber

AeroChamber* mini
Anti-Static Holding Chamber

AeroTrach Plus*
Anti-Static Valved Holding Chamber

AeroChamber* VENT
Holding Chamber

CONTENTS

PRODUCT OVERVIEW

The following range of chambers has been designed for designed for specialized aerosol drug delivery.

AeroChamber* VENT Holding Chamber‡
Collapsible chamber designed for delivery of metered dose inhaler (MDI) medications to mechanically ventilated patients. It is placed in the inspiratory limb of a ventilator circuit without any additional flow and can be left in the circuit in the collapsed position.

AeroChamber* MV Holding Chamber‡‡
Designed for delivery of MDI medications in mechanical ventilation circuits or with a manual resuscitation bag.

AeroChamber* mini Anti-Static Holding Chamber
Small volume chamber designed for the delivery of MDI medications in mechanical ventilation circuits or with a manual resuscitation bag. Compact, the chamber minimizes dead space.

AeroTrach Plus* Anti-Static Valved Holding Chamber
Specifically designed for delivery of MDI medications to tracheostomy patients in hospital and home environments. It can be easily and comfortably connected to standard 15mm tracheotomy tubes.

‡ ***AeroChamber* VENT*** Holding Chamber is also marketed as ***AeroVent Plus**** Collapsible Holding Chamber.
‡‡ ***AeroChamber* MV*** Holding Chamber is also marketed as ***AeroChamber**** Holding Chamber for Mechanical Ventilation (HC MV).

AEROCHAMBER VENT* HOLDING CHAMBER

NEW **DOES SPACER/ADAPTER DEVICE CHOICE AFFECT DELIVERY OF A PRESSURIZED METERED DOSE INHALER (pMDI) THROUGH A HUMIDIFIED CIRCUIT TO A SIMULATED PATIENT ON MECHANICAL VENTILATION.** M Nagel, J Suggett, C Doyle, R Ali. Thorax 2023;78:A128-A129.

Introduction: Delivery of aerosolized medication to mechanically ventilated patients is a key element of their treatment. It is desirable to not break the ventilation circuit during aerosol therapy to reduce the risk of infection or derecruitment. This study evaluates the effect pressurized metered dose inhaler (pMDI) delivery devices that stay in line have on drug delivery in a simulated adult ventilator setting. **Methods:** An adult mechanical ventilation circuit (Fisher & Paykel RT210) was humidified (T = 37ºC, 100% RH), and a simulated ventilated adult model (tidal volume = 500 mL, duty cycle = 33%, rate = 13 breaths/minute) was generated using a Dräger Infinity† C500 ventilator. An aerosol collection filter was located at the distal end of the 8.0 mm diameter endotracheal tube (ETT) and the far-side of the filter was coupled to a Dräger SelfTestLung† simulating the patient. 5 actuations of a Ventolin† pMDI were delivered through the device on test, each time followed by 6 complete breathing cycles, shaking the canister between actuations. This procedure (*n* = 5/device) was performed with four devices: the ***AeroChamber* VENT*** Holding Chamber (HC) (also marketed as ***AeroVent Plus**** Collapsible Holding Chamber), the Spirale† drug delivery system (DDS), the Hudson RCI† MDI Adapter (these three devices were placed in the inspiratory limb), and via the built-in pMDI port adapter within the wye connector of the ventilator circuit. Assay of recovered salbutamol was undertaken by HPLC-UV spectrophotometry.

Results:

Device	Total Mass of Salbutamol/Actuation (mean ± SD) (µg)
AeroChambe*r* **VENT*** Holding Chamber	28.1 ± 5.4
Spirale† DDS	7.5 ± 3.6
Hudson RCI† MDI Adapter	9.5 ± 2.7
Fisher & Paykel Built-In pMDI Port Adapter	18.1 ± 2.6

The ***AeroChamber* VENT*** Holding Chamber delivered significantly more medication to the distal end of the ETT compared with the other devices (un-paired t-test, $p < 0.001$). **Conclusions:** In this study, we have shown device type influences aerosolized drug delivery during simulated adult mechanical ventilation. Although Spirale† DDS closely resembles ***AeroChamber* VENT*** Holding Chamber, the Spirale† bellows had difficulties keeping a spacer-like shape when expanded for aerosol delivery. This study highlights the variability in drug delivery using a pMDI and that spacer/adapter choice are critical factors to be considered when using these devices as a treatment option.

NEW **HOW DO DIFFERENT METHODS OF HUMIDIFICATION AFFECT DRUG DELIVERY TO A SIMULATED PATIENT RECEIVING MECHANICAL VENTILATION.** M Nagel, J Schloss, C Doyle, R Ali, JA Suggett, DP Coppolo. CHEST 2023;164(4):A6165-A6166.

Purpose: Humidity can be introduced to the ventilation circuit via a traditional heated humidifier or a heat and moisture exchange (HME) filter that uses the patient's own moisture from exhalation to maintain humidity during mechanical ventilation. Traditional HMEs remove medication during aerosol delivery and therefore need to be removed from the circuit before providing aerosol therapy. It is desirable to not break the ventilation circuit to reduce the risk of infection or derecruitment. Therefore, more recently, HMEs have been developed that allow for aerosol delivery without removing the HME from the circuit. By turning a dial on the HME the filter media is bypassed and aerosol can transfer through. This results in a more complicated aerosol transport path and as such will have an effect on the amount of medication delivered to the patient. The purpose of this study was to evaluate how the type of humidification might impact aerosol delivery in a simulated adult ventilator setting and provide information to clinicians when determining dosing. **Methods:** An adult mechanical ventilation circuit (Fisher & Paykel RT210) was humidified with either a traditional heated humidifier (Fisher & Paykel MR850) or using a Gibeck† Humid-Flo† HME (Teleflex Medical) to simulate a ventilated adult model (tidal volume = 500 mL, duty cycle = 33%, rate = 13 breaths/minute) generated using a Dräger Infinity† C500 ventilator. An aerosol collection filter was located at the

distal end of the 8.0 mm diameter endotracheal tube (ETT) and coupled to a Dräger SelfTestLung†, simulating the patient. 5 actuations of a Ventolin† pressurized metered dose inhaler (pMDI) were delivered through the device on test, each time followed by 6 complete breathing cycles, shaking the canister between actuations. This procedure (*n* = 5/device) was performed with either the ***AeroVent Plus****** Collapsible Holding Chamber (CHC) (also marketed as ***AeroChamber**** ***VENT*** Holding Chamber) or Hudson RCI† MDI Adaptor, placed in the inspiratory limb or via the built-in pMDI port adapter within the wye connector of the circuit. Assay of albuterol recovered from the collection filter was undertaken by HPLC-UV spectrophotometry. **Results:** The ***AeroVent Plus****** CHC delivered values of 33.1 ± 2.7 µg and 28.1 ± 5.4 µg for the HME and heated humidifier respectively. In comparison, the Hudson RCI† MDI Adaptor delivered 20.2 ± 3.9 µg and 9.5 ± 2.7 µg, and the built-in ventilator circuit pMDI port delivered 22.9 ± 1.2 µg and 18.1 ± 2.6 µg. The ***AeroVent Plus****** CHC delivered significantly more medication to the distal end of the ETT compared with the other devices (unpaired t-test, $p < 0.001$). **Conclusions:** The ***AeroVent Plus****** CHC delivered the largest dose of albuterol using either humidification option. Delivery from the Hudson RCI† MDI Adaptor was most affected by the humidifier option and was reduced by more than 50% when the heated humidifier was used. **Clinical Implications:** This study demonstrates that the type of delivery device and humidification supplied to the mechanically ventilated patient will influence drug delivery. These data should help support decision making where the intent is to maximize aerosol delivery during mechanical ventilation.

LUNG DEPOSITION AND SYSTEMIC BIOAVAILABILITY OF DIFFERENT AEROSOL DEVICES WITH AND WITHOUT HUMIDIFICATION IN MECHANICALLY VENTILATED PATIENTS. IOF Moustafa, MRA-A Ali, M Al Hallag, H Rabea, JB Fink, P Dailey, MEA Abdelrahim. Heart & Lung 2017;46(6):464-467.

Background: During mechanical ventilation medical aerosol delivery has been reported to be up to two-fold greater with dry inhaled gas than with heated humidity. Urine levels at 0.5 hours post dose (URSAL0.5%) has been confirmed as an index of lung deposition and 24 hours (URSAL24%) as index of systemic absorption. Our aim was to determine the effect of humidification and aerosol device type on drug delivery to ventilated patients using urine levels. **Methods:** In a randomized crossover design, 36 (18 female) mechanically ventilated patients were assigned to one of three groups. Groups 1 and 2 received 5,000 mg salbutamol using vibrating mesh (VM) and jet nebulizers (JN), respectively, while group 3 received 1,600 mg (16 puffs) of salbutamol via metered dose inhaler with ***AeroChamber**** ***VENT*** Holding Chamber (MDI-AV). All devices were placed in the inspiratory limb of ventilator downstream from the humidifier. Each subject received aerosol with and without humidity at > 24 hour intervals with > 12 hour washout periods between salbutamol doses. Patients voided urine 15 minutes before each study dose and urine samples were collected at 0.5 hour post dosing and pooled for the next 24 hours. ***Results:*** The MDI-AV and VM resulted in a higher percentage of urinary salbutamol levels compared to the JN ($p < 0.05$). Urine levels were similar between humidity and dry conditions. ***Conclusions:*** Our findings suggest that *in vitro* reports overestimate the impact of dry vs. heated humidified conditions on the delivery of aerosol during invasive mechanical ventilation.

IN VITRO **PERFORMANCE OF A NEW COLLAPSIBLE HOLDING CHAMBER (CHC) FOR THE DELIVERY OF AEROSOLIZED MEDICATION BY PRESSURIZED METERED DOSE INHALER (pMDI) TO PATIENTS ON MECHANICAL VENTILATION.** D Coppolo, J Mitchell, M Nagel, V Avvakoumova, C Doyle, R Ali. American Journal of Respiratory and Critical Care Medicine 2012;185:A5629.

Rationale: It is desirable not to break the ventilation circuit during the delivery of aerosols to patients receiving inhalation therapy whilst on mechanical ventilation. The ***AeroVent**** Collapsible Holding Chamber (CHC) (Monaghan Medical Corporation, Plattsburgh, NY) was developed several years ago to combine the benefit of a holding chamber when expanded with the convenience of being able to collapse the device when not in use, thereby minimizing water trapping. The present *in vitro* evaluation of a new version ***(AeroVent Plus**** Collapsible Holding Chamber (CHC)), in which the pMDI canister receptacle has been offset from the CHC axis to reduce internal impaction, and which can also accept GSK† pMDI canisters having a dose counter provides comparative data with other in-line adapters. **Methods:** The ***AeroVent Plus**** CHC (*n* = 5) was inserted in the inspiratory limb of an adult mechanical ventilation circuit with humidifier (Model MR850JHU, Fisher & Paykel, Auckland, NZ). The distal end of the CHC coupled to the wye connector to which a 7.0 mm diameter endotracheal tube (ETT) was attached. An aerosol collection filter was located at the distal end of the ETT, and the far side of the filter was coupled to an adult test lung (Michigan

Instruments, Grand Rapids, MI) simulating the patient. The circuit was humidified near to body conditions (T = 37°C, 100% RH), and tidal breathing (600 mL, duty cycle = 33%, 10 breaths/minute) was simulated by a Servo ventilator (Siemens, Sweden, model 900C). 5 actuations of Ventolin† (GSK† Canada, 100 µg salbutamol ex-valve) were delivered, each time followed by 6 complete breathing cycles, shaking the canister between actuations. Similar measurements (*n* = 5/device) were also performed, replacing the CHC with the: (a) AirLife† Dual Spray MiniSpacer† (Cardinal Health, Dublin, OH); (b) OptiVent† (Philips Healthcare, Andover, MA); (c) adult universal in-line pMDI adapter (model RTC 24-V, Instrumentation Industries Inc., Bethel Park, PA); (d) Ballard† suction catheter with pMDI port (Kimberly-Clark Healthcare, Roswell, GA); (e) Hudson ventilator adapter (Hudson RCI†, Research Triangle Park, NC); (f) pMDI adapter (Fisher & Paykel). Assay of recovered salbutamol was undertaken by HPLC-UV spectrophotometry. **Results:** Total mass of salbutamol/actuation via each of the devices (mean ± SD) is summarized in the Table.

Device	Ventilator Circuit Tubing Outside Diameter (mm)	Mass Salbutamol/ Actuation (µg)
AeroVent Plus* CHC	22 mm in-line, coupled directly to wye connector	22.7 ± 3.1
AirLife† Dual Spray MiniSpacer†	22 mm in-line coupled directly to wye connector	14.5 ± 2.3
	15 mm with adapter direct to ETT	12.0 ± 0.9
OptiVent† VHC	22 mm coupled directly to wye connector	16.2 ± 2.0
RTC 24-V ventilator adapter	22 mm coupled directly to wye connector	10.9 ± 1.1
	15 mm with adapter direct to ETT	10.4 ± 1.7
Ballard† suction catheter with pMDI port	Coupled direct to ETT	3.4 ± 1.1
Hudson ventilator adapter	22 mm coupled directly to wye connector	14.3 ± 1.9
Fisher & Paykel (F&P) pMDI adapter	Coupled to wye connector with F&P adapter	16.6 ± 2.8

Conclusions: The ***AeroVent Plus**** CHC delivered significantly more medication to the distal end of the ETT compared with the other adapters (unpaired t-test, $p < 0.001$).

IN VITRO **PERFORMANCE OF AN IMPROVED COLLAPSIBLE HOLDING CHAMBER (CHC) FOR THE DELIVERY OF BRONCHODILATORS TO PATIENTS RECEIVING MECHANICAL VENTILATION.** M Nagel, V Avvakoumova, R Ali, C Doyle, J Mitchell. European Respiratory Journal 2011;38:P1986.

Bronchodilator delivery by pressurized metered dose inhaler (pMDI) to patients on mechanical ventilation is best achieved without breaking the breathing circuit. We describe an evaluation of an improved CHC (***AeroVent Plus**** Collapsible Holding Chamber, Trudell Medical International, London, Canada (*n* = 5 devices, 1 measurement/device)), in which the pMDI canister receptacle is offset from the CHC axis to reduce internal impaction, and can also accept GSK† pMDI canisters having a dose counter. Delivery of 3 actuations of salbutamol (HFA Ventolin†, GSK† (Canada); 100 µg/actuation) was assessed with the expanded CHC inserted in the inspiratory limb of an adult breathing circuit equipped with a 7 mm diameter endotracheal tube (ETT). An adult test lung (Michigan Instruments) was used to simulate the patient. The circuit was humidified near to body conditions (T = 36°C, 100% RH), and tidal breathing (600 mL, duty cycle = 33%, 10 breaths/minute) was simulated by a Servo ventilator (Siemens, model 900C). A filter was located between the distal end of the ETT and test lung to collect the aerosol. Total mass (TM) of salbutamol after 6 respiratory cycles was determined by HPLC-UV spectrophotometry. Similar measurements were undertaken with a Spirale† CHC (Armstrong Medical), providing benchmark data from a CHC having the pMDI receptacle in line with the axis of the device. TM (mean ± SD) from the ***AeroVent Plus**** and Spirale† CHCs was 22.7 ± 3.1 and 4.7 ± 0.7 µg/actuation respectively. Placing the canister receptacle off-axis with respect to the CHC substantially improved medication delivery. Clinicians using these devices should be aware of the implications of this change.

EVALUATION OF AEROSOL GENERATOR DEVICES AT 3 LOCATIONS IN HUMIDIFIED AND NON-HUMIDIFIED CIRCUITS DURING ADULT MECHANICAL VENTILATION. A Ari, H Areabi, JB Fink. Respiratory Care 2010;55(7):837-844.

Background: The position of the jet or ultrasonic nebulizer in the ventilator circuit impacts drug delivery during mechanical ventilation, but has not been extensively explored, and no study has examined all of the commonly used nebulizers. **Methods:** Drug delivery from jet, vibrating mesh, and ultrasonic nebulizers and pressurized metered dose inhaler (pMDI) with spacer was compared in a model of adult mechanical ventilation, with heated/humidified and non-humidified ventilator circuits. Albuterol sulfate was aerosolized at 3 circuit positions: (1) between the endotracheal tube and the Y-piece; (2) 15 cm from Y-piece; and (3) 15 cm from the ventilator, with each device (n = 3) using adult settings (tidal volume 500 mL, ramp flow pattern, 15 breaths/minute, peak inspiratory flow 60 L/min, and PEEP 5 cm H(2)O). The drug deposited on an absolute filter distal to an 8.0 mm inner diameter endotracheal tube was eluted and analyzed via spectrophotometry (276 nm), and is reported as mean ± SD percent of total nominal or emitted dose. **Results:** The vibrating mesh nebulizer, ultrasonic nebulizer, and pMDI with spacer were most efficient in position 2 with both non-humidified (30.2 ± 1.0%, 24.7 ± 4.4%, and 27.8 ± 3.3%, respectively) and heated/humidified circuits (16.8 ± 2.6%, 16.5 ± 4.3%, and 17 ± 1.0%, respectively). In contrast, the jet nebulizer was most efficient in position 3 under both non-humidified (14.7 ± 1.5%) and heated/humidified (6.0 ± 0.1%) conditions. In positions 2 and 3, all devices delivered approximately 2-fold more drug under non-humidified than under heated/humidified conditions ($p < 0.01$). At position 1 only the pMDI delivered substantially more drug than with the non-humidified circuit. **Conclusion:** During mechanical ventilation the optimal drug delivery efficiency depends on the aerosol generator, the ventilator circuit, and the aerosol generator position.

INFLUENCE OF MOISTURE ACCUMULATION IN IN-LINE SPACER ON DELIVERY OF AEROSOL USING METERED DOSE INHALER DURING MECHANICAL VENTILATION. H-L Lin, JB Fink, Y Zhou, Y-S Cheng. Respiratory Care 2009;54(10):1336-1341.

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. A pMDI spacer ***AeroVent**** Collapsible Holding Chamber 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 minutes 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 ($p < 0.05$). **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, $p = 0.002$). 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.

COMPARATIVE EVALUATION OF A COLLAPSIBLE HOLDING CHAMBER (CHC) FOR USE BY PATIENTS ON MECHANICAL VENTILATION MODIFIED TO ACCEPT GSK† PRESSURIZED METERED DOSE INHALER (pMDI) PRODUCTS HAVING A DOSE COUNTER. D Coppolo, J Mitchell, V Avvakoumova, M Nagel. American Thoracic Society International Conference, Toronto, 2008.

Background: GSK† Inc. have recently introduced an integrated dose counter with their pressurized metered dose inhaler (pMDI) products, making them physically incompatible with current spacers/holding chambers used for ventilators. **Study Design and Measurement Equipment:** We report a laboratory study in which a CHC (***AeroVent****) Collapsible Holding Chamber; Monaghan Medical Corporation, Syracuse, NY), modified to accept the GSK† dose counter was evaluated against the original CHC with two GSK† formulations (FloVent† HFA; 44 µg/actuation fluticasone propionate (FP) and Ventolin† HFA; 90 µg/actuation albuterol base equivalent (ALB)) likely to be used in the care of patients on mechanical ventilation. Measurements of total emitted mass (TEM) of FP or ALB were made sampling the aerosol from the CHC (n = 5 devices/group; 3 replicates/device) at 28.3 L/min, collecting the medication on an electret filter located at the exit of the CHC. Assay for FP or ALB was subsequently undertaken by HPLC-UV spectrophotometry. **Results:** Values of TEM from the old and new CHCs were substantially equivalent with both formulations (Table 1).

TEM (mean SD) via *AeroVent** **CHCs**

TEM (µg/actuation)	Original CHC	Modified CHC
FP	16.2 ± 1.8	14.9 ± 1.1
ALB	36.1 ± 2.4	34.8 ± 2.4

Conclusions: The modified CHC readily accepts the new style of valve stem. Values of TEM from the original and modified CHCs were substantially equivalent. Differences between the two devices were < 10%.

ALBUTEROL DELIVERY VIA TRACHEOSTOMY TUBE. CM Piccuito, DR Hess. Respiratory Care 2005;50(8):1071-1076.

Hypothesis: Albuterol delivery through a tracheostomy tube is affected by device (nebulizer vs. metered dose inhaler), interface (mask vs. T-piece), bias flow, and humidification. **Methods:** A lift bar was placed between the chambers of a dual chambered lung model such that a ventilator triggered simulated spontaneous breathing at a rate of 20 breaths/minute, tidal volume of 0.4 L, and inspiratory:expiratory ratio of 1:2. An 8 mm inner diameter cuffed tracheostomy tube was placed through a semicircular model that simulated a patient's neck. Four conditions of gas flow and humidification were used for the nebulizer experiments: heated aerosol (approximately 30 L/min, approximately 30°C), heated humidity (approximately 30 L/min, approximately 30°C), high flow without added humidity (approximately 30 L/min), or a nebulizer attached to the tracheostomy tube without additional flow. The nebulizer was filled with 4 mL that contained 2.5 mg of albuterol, and operated at 8 L/min. The nebulizer was tested with a T-piece or tracheostomy mask. For the metered dose inhaler experiments, a spacer was used and actuation of the inhaler (100 µg per actuation) was synchronized with inhalation (4 actuations separated by > 15 seconds). When the spacer was used without additional flow, a valved T-piece was used with a 1-way valve placed either proximal or distal to the spacer. A filter was attached between the lung model and the distal end of the tracheostomy tube. Albuterol washed from the filter was measured by ultraviolet spectrophotometry. **Results:** For the nebulizer, the most efficient delivery was with no flow other than that to power the nebulizer and with a T-piece (p < 0.001). The most efficient method for aerosol delivery was metered dose inhaler with a valved T-piece and placement of the 1-way valve in the proximal position (p < 0.001). The effect of humidity was unclear from the results of this study. **Conclusions:** Albuterol delivery via tracheostomy was affected by the delivery device (nebulizer vs. inhaler), bias gas flow, and the patient interface.

IMPROVEMENT IN AEROSOL DELIVERY WITH HELIUM – OXYGEN MIXTURES DURING MECHANICAL VENTILATION. ML Goode, JB Fink, R Dhand, MJ Tobin. American Journal of Respiratory and Critical Care Medicine 2001;163(1):109-114.

In mechanically ventilated patients with airway obstruction, helium-oxygen ($He-O_2$) mixtures reduce airway resistance and improve ventilation, but their influence on aerosol delivery is unknown. Accordingly, we determined the effect of various $He-O_2$ mixtures on albuterol delivery from metered dose inhalers (MDIs) and jet nebulizers in an *in vitro* model of mechanical ventilation. Albuterol delivery from an MDI was increased when the ventilator circuit contained 80% helium and 20% oxygen ($He-O_2$ 80/20) versus O_2: 46.7 ± 3.3 versus 30.2 ± 1.3 (SE)% of the nominal dose ($p < 0.001$) – the difference was mainly due to decreased drug deposition in the spacer chamber, mean 39.2% and 55.2%, respectively ($p < 0.001$). Nebulizer efficiency at a flow rate of 6 L/min was five times lower with $He-O_2$ 80/20 than O_2, and the amount of nebulized drug was inversely correlated with gas density ($r = 0.94$, $p < 0.0001$). When the nebulizer was operated with O_2, greater albuterol delivery was achieved when the ventilator circuit contained $He-O_2$ rather than O_2. In summary, $He-O_2$ mixtures in the circuit increased aerosol delivery for both MDIs and nebulizers in the mechanically ventilated model by as much as 50%. In conclusion, at appropriate flow rates and concentrations, $He-O_2$ in the ventilator circuit may improve aerosol delivery in mechanically ventilated patients with severe airway obstruction.

BRONCHODILATOR THERAPY WITH METERED DOSE INHALER AND SPACER VERSUS NEBULIZER IN MECHANICALLY VENTILATED PATIENTS: COMPARISON OF MAGNITUDE AND DURATION OF RESPONSE. AG Duarte, K Momii, A Bidhani. Respiratory Care 2000;45(7):817-823.

Objective: Four hour comparison of the bronchodilator response of albuterol administered via metered dose inhaler (MDI) with spacer versus small volume nebulizer (SVN) to mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). **Design:** Prospective randomized clinical trial. **Setting:** Medical intensive care unit in a university hospital. **Patients:** Thirteen mechanically ventilated COPD patients. **Intervention:** Albuterol administration of 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via MDI with spacer or 2.5 mg via SVN to mechanically ventilated patients in order to assess the bronchodilator response over 4 hours. **Measurements and Results:** Mechanically ventilated patients were enrolled in a randomized crossover study wherein one group received 4 puffs (0.4 mg) or 2.5 mg of albuterol and another group received 10 puffs (1.0 mg) or 2.5 mg of albuterol on separate days. Respiratory mechanics measurements were obtained over 4 hours. Total airway resistance declined by 14.4 ± 3.8% after 4 MDI puffs, 18.3 ± 1.8% after 10 MDI puffs, or 13.7 ± 2.6% after 2.5 mg via SVN, compared to baseline ($p < 0.01$). After albuterol delivery, airway resistance remained improved for 90 - 120 minutes ($p < 0.05$) and returned to baseline by 4 hours with all treatments. **Conclusion:** The airway response to albuterol administration via MDI and SVN to mechanically ventilated patients was similar in magnitude and duration, returning to baseline by 240 minutes. In stable, mechanically ventilated COPD patients, albuterol may be administered via MDI with spacer or via SVN every 4 hours.

WATER ACCUMULATION IN METERED DOSE INHALER SPACERS UNDER NORMAL MECHANICAL VENTILATION CONDITIONS. JB Waugh. Heart & Lung: The Journal of Critical Care 2000;29(6):424-428.

Objective: The purpose of this study was to compare the water accumulation in 3 types of metered dose inhaler (MDI) spacer shapes in-line in a ventilator circuit, in 2 positions over 2, 4, and 6 hour time periods through the use of heated and nonheated wire ventilator circuits. **Design:** The study design was prospective, quasi-experimental, and random assignment. **Setting:** The study was conducted in a university laboratory. **Materials:** Three brands of MDI spacers (OptiVent†, ACE†, ***AeroVent***** Collapsible Holding Chamber) were tested. **Outcome Measures:** Grams of water accumulation were measured. **Intervention:** Distilled water accumulation was measured in 3 brands of MDI spacers in 0 degrees and 45 degrees positions at 2, 4, and 6 hour time intervals. Water accumulation was measured in each spacer by calculating the differences between pretest (dry) weights and post test (wet) weights through the use of an analytical balance. A Marquest SCT-3000 Servo controlled humidifier with heated wire ventilator circuit was used with a room temperature range of 21.7°C - 22.8°C (71°F - 73°F) and a relative humidity range of 57% - 65%. **Results:** Multivariate repeated measures analysis demonstrated a difference between brands ($p < 0.001$). The

amount of water accumulated during 6 hours (time variable) was significantly different ($p < 0.001$), as was the interaction between time and "spacer brand" (with Greenhouse-Geisser adjustment). The interaction of time and position was also significantly different ($p = 0.001$). Water accumulations at a 45 degrees angle were: ***AeroVent****** Collapsible Holding Chamber 0.765 ± 0.152 g; OptiVent† 1.894 ± 0.228 g; and ACE† 4.043 ± 0.665 g through 6 hours of use. **Conclusions:** We found that water accumulation was a result of the type of spacer, position of the spacer, and time that the spacer was left in-line. All 3 brands of spacer collected less than 5 mL of water over 6 hours in either position. Heated wire circuits accumulated less water than nonheated wire circuits and may be safer when using MDI spacers.

A COMPARISON OF BRONCHODILATOR THERAPY DELIVERED BY NEBULIZATION AND METERED DOSE INHALER IN MECHANCIALLY VENTILATED PATIENTS. P Marik, J Hogan, J Krikorian. CHEST 1999;115(6):1653-1657.

Background: The optimal method of delivering bronchodilators in mechanically ventilated patients is unclear. The purpose of this study was to compare the pulmonary bioavailability of albuterol delivered by the nebulizer, the metered dose inhaler (MDI) and spacer, and the right angle MDI adaptor in ventilated patients using urinary analysis of drug levels. **Methods:** Mechanically ventilated patients who had not received a bronchodilator in the previous 48 hours and who had normal renal function were randomized to receive the following: (1) five puffs (450 mg) of albuterol delivered by the MDI with a small volume spacer; (2) five puffs of albuterol delivered by the MDI port on a right angle adaptor; or (3) 2.5 mg albuterol delivered by a nebulizer. Urine was collected 6 hours after the administration of the drug, and the amounts of albuterol and its sulfate conjugate were determined in the urine by a chromatographic assay. **Results:** Thirty patients were studied, 10 in each group: their mean age and serum creatinine level were 62 years and 1.3 mg/dL, respectively. With the MDI and spacer, (mean ± SD) 169 ± 129 mg albuterol (38%) was recovered in the urine; with the nebulizer, 409 ± 515 mg albuterol (16%) was recovered in the urine; and with the MDI port on the right angle adaptor, 41 ± 61 mg albuterol (9%) was recovered in the urine ($p = 0.02$ between groups). The level of albuterol in the urine was below the level of detection in four patients in whom the drug was delivered using the right angle MDI adaptor. **Conclusion:** The three delivery systems varied markedly in their efficiency of drug delivery to the lung. As previous studies have confirmed, this study has demonstrated that using an MDI and spacer is an efficient method for delivering inhaled bronchodilators to the lung. The pulmonary bioavailability was poor with the right angle MDI port. This port should not be used to deliver bronchodilators in mechanically ventilated patients.

RECONCILING *IN VITRO* AND *IN VIVO* MEASEUREMENTS OF AEROSOL DELIVERY FROM A METERED DOSE INHALER DURING MECHANICAL VENTILATION AND DEFINING EFFICIENCY-ENHANCING FACTORS. JB Fink, R Dhand, J Grychowski, PJ Fahey, MJ Tobin. American Journal of Respiratory and Critical Care Medicine 1999;159(1):63-68.

We attempted to resolve the discrepancies in reported data on aerosol deposition from a chlorofluorocarbon (CFC) propelled metered dose inhaler (MDI) during mechanical ventilation, obtained by *in vivo* and *in vitro* methodologies. Albuterol delivery to the lower respiratory tract was decreased in a humidified versus a dry circuit (16.2 versus 30.4%, respectively; $p < 0.01$). In 10 mechanically ventilated patients, 4.8% of the nominal dose was exhaled. When the exhaled aerosol was subtracted from the *in vitro* delivery of 16.2% achieved in a humidified ventilator circuit, the resulting value (16.2 - 4.8 = 11.4%) was similar to *in vivo* estimates of aerosol deposition. Having reconciled *in vitro* with *in vivo* findings, we then evaluated factors influencing aerosol delivery. A lower inspiratory flow rate (40 versus 80 L/min; $p < 0.001$), a longer duty cycle (0.50 versus 0.25; $p < 0.04$), and a shorter interval between successive MDI actuations (15 versus 60 seconds; $p < 0.02$) increased aerosol delivery, whereas use of a hydrofluoroalkane (HFA) propelled MDI decreased aerosol delivery compared with the CFC propelled MDI. An MDI and actuator combination other than that designed by the manufacturer altered aerosol particle size and decreased drug delivery. In conclusion, aerosol delivery in an *in vitro* model accurately reflects *in vivo* delivery, providing a means for investigating methods to improve the efficiency of aerosol therapy during mechanical ventilation.

SERUM ALBUTEROL LEVELS IN MECHANICALLY VENTILATED PATIENTS AND HEALTHY SUBJECTS AFTER METERED DOSE INHALER ADMINISTRATION. AG Duarte, R Dhand, R Reid, JB Fink, PJ Fahey, MJ Tobin, JW Jenne. American Journal of Respiratory and Critical Care Medicine 1996;154(6):1658-1663.

In mechanically ventilated patients, systemic blood levels of inhaled drugs reflect absorption from the lower respiratory tract alone since, unlike nonintubated patients, oropharyngeal and gastrointestinal absorption cannot occur. To determine the efficiency of aerosol administration by a metered dose inhaler (MDI), we measured serum albuterol levels after administration by an MDI and spacer to nine mechanically ventilated patients (10 puffs) and to 10 healthy subjects (six puffs). Serum albuterol levels (± SEM) quantitated by high performance liquid chromatography and electrochemical detection were: 0.09 ± 0.04 mg/mL/puff at baseline, 0.66 ± 0.10 at 5 minutes, 0.98 ± 0.10 at 10 minutes, 0.56 ± 0.08 at 15 minutes, and 0.37 ± 0.03 at 30 minutes in mechanically ventilated patients versus zero at baseline, 0.89 ± 0.12 at 5 minutes, 1.27 ± 0.13 at 10 minutes, 0.84 ± 0.09 at 15 minutes, and 0.53 ± 0.07 at 30 minutes in control subjects (p > or = 0.07 at 5, 10, and 30 minutes; p < or = 0.05 at baseline and at 15 minutes). Area under the curve (AUC_{0-30}) in the mechanically ventilated patients was 16.8 ± 1.4 versus 23.4 ± 1.9 mg/mL/puff x min in control subjects (p = 0.014). In summary, administration of albuterol with a MDI achieved a profile of serum levels in mechanically ventilated patients similar to that in healthy control subjects, but the peak serum level and systemic bioavailability (AUC_{0-30}) were lower in the patients. In conclusion, serum levels reliably assess lower respiratory tract deposition of albuterol, and show that MDIs are more efficient for aerosol delivery in mechanically ventilated patients than was previously reported in studies using radiolabeled aerosols.

DETERMINANTS OF AEROSOLIZED ALBUTEROL DELIVERY TO MECHANICALLY VENTILATED INFANTS. DM Coleman, HW Kelly, BC McWilliams. CHEST 1996;109(6):1607-1613.

An *in vitro* lung model and a volume ventilator were used to evaluate the delivery of aerosolized albuterol through an infant ventilator circuit. We compared the following: continuous nebulization (CNA) and intermittent nebulization (INA); various nebulizer gas flows, 5.0, 6.5, and 8.0 L/min; and duty cycle of 33% and 50%. The efficiency and consistency of aerosol delivery by metered dose inhaler (MDI) with four different spacer devices and by nebulizer positioned at the manifold and at the same position as the MDI were also evaluated. A volume ventilator (Servo 900B) was used with settings selected to reflect those of a moderately to severely ill 4 kg infant. A 3.5 mm endotracheal tube was used in all experiments. A specific type of nebulizer used (AirLife† Misty Neb; Baxter; Valencia, Calif) and several spacers were studied (***AeroChamber***** Valved Holding Chamber (VHC) and ***AeroVent***** Collapsible Holding Chamber, Monaghan Medical Corporation in Plattsburgh, NY [corrected]; ACE†, Diemolding Healthcare Division in Canastota, NY [corrected]; and an in-line MDI adapter, Instrumentation Industries Inc, Pittsburgh). CNA delivered significantly more aerosol to the lung model (4.8 ± 0.6% of the starting dose) than INA (3.8 ± 0.3%; p < 0.01). There was a significant stepwise decrease in aerosol delivery with increasing nebulizer flow (4.8 ± 1.3% at 5.0 L/min; 3.7 ± 1.1% at 6.5 L/min; and 2.7 ± 1.1% at 8.0 L/min). Increasing duty cycle did not significantly affect delivery. Overall the spacers with MDI were more efficient than the nebulizer in either position delivering about twice the percentage of the starting dose than the nebulizers. All modes of delivery, except the ***AeroChamber***** VHC, demonstrated a marked degree of variability. Most of the starting dose of albuterol either remained in the nebulizer (30.4 ± 6.0% at 5.0 L/min and 25.3 ± 4.1% at 8.0 L/min) or was deposited in the inspiratory tubing (34.7 ± 0.7% at 5.0 L/min and 43.7 ± 4.9% at 8.0 L/min) in our system. In conclusion, we have confirmed that aerosol delivery depends on the mode of delivery and the operating conditions. Although delivery with an MDI and spacer is more efficient than a nebulizer, both methods may produce high variability depending on the method or spacer used.

TREATMENT OF BRONCHOSPASM BY METERED DOSE INHALER ALBUTEROL IN MECHANICALLY VENTILATED PATIENTS. CA Manthous, W Chatila, GA Schmidt, JB Hall. CHEST 1995;107:210-213.

ß$_2$-agonist bronchodilators delivered by metered dose inhalers (MDI) are commonly used in the treatment of bronchospasm in both intubated and nonintubated patients. Substantial data support the effectiveness of MDI delivery systems in nonintubated patients. However, few studies have examined the effectiveness of MDIs in intubated, mechanically ventilated patients. MDIs are often used in conjunction with a spacing device that may enhance delivery of drug to the airways, but few *in vivo* data have demonstrated efficacy of this delivery method in ventilated patients. We studied ten critically ill patients who had a peak (P_{peak}) to pause (P_{pause}) gradient of more than 15 cm H_2O during sedated, quiet breathing on assist control ventilation. We administered 5, 10, and 15 puffs (90 micrograms per puff) of MDI albuterol through a specific spacer (***AeroVent****** Collapsible Holding Chamber) at 30 minute intervals, while measuring resistive pressure (defined as P_{peak} - P_{pause}) before and after treatments. Resistive airway pressure after 5 puffs decreased in nine of ten patients, from 25.1 ± 7.2 to 20.8 ± 5.6 cm H_2O ($p < 0.12$). The addition of 10 more puffs further reduced resistive pressure in nine of nine patients from 20.8 ± 5.6 to 19.0 ± 4.4 ($p < 0.01$). Fifteen more puffs (30 cumulative puffs) did not result in further improvement ($p > 0.5$). A toxic reaction occurred in one patient (systolic blood pressure decreased 20 mm Hg) after 5 puffs of albuterol. We conclude that MDI administered through this specific spacer is effective in mechanically ventilated patients in doses up to 15 puffs, and that therapy should be titrated to effectiveness and toxicity.

BRONCHODILATOR DELIVERY BY METERED DOSE INHALER IN VENTILATOR SUPPORTED PATIENTS. R Dhand, A Jubran, MJ Tobin. American Journal of Respiratory and Critical Care Medicine 1995;151(6):1827-1833.

The optimal dose and technique for administration of bronchodilators with a metered dose inhaler (MDI) in mechanically ventilated patients have not been established. We studied the efficacy and safety of 10 puffs (90 micrograms/puff) of albuterol administered by an MDI in seven mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). Rapid airway occlusions at constant flow inflation were performed before and at 5 minute intervals after administration of albuterol for 60 minutes. Significant decreases in maximum (R_{rs}max; $p < 0.01$) and minimum inspiratory resistance (R_{rs}min; $p < 0.01$) were present at 5 minutes and persisted for 60 minutes after administration of albuterol ($p < 0.01$ for both parameters). R_{rs}max indicates maximal inspiratory resistance while R_{rs}min represents the ohmic flow resistance. Intrinsic positive end expiratory pressure decreased significantly ($p < 0.05$) 15 minutes after albuterol administration. Heart rate, blood pressure, and arterial oxygenation did not show significant change after albuterol. In summary, 10 puffs of albuterol given by an MDI and spacer produced significant bronchodilation in ventilator supported patients with COPD, without producing side effects. In conclusion, higher doses of albuterol given by an MDI and spacer could be used routinely in mechanically ventilated patients with COPD.

ALBUTEROL DELIVERY BY METERED DOSE INHALER WITH A PEDIATRIC MECHANICAL VENTILATORY CIRCUIT MODEL. SS Garner, DB Wiest, JW Bradley. Pharmacotherapy 1994;14(2):210-214.

Study Objective: To determine albuterol delivery by metered dose inhaler (MDI) in an *in vitro* pediatric mechanical ventilatory circuit model. The influence of a spacing device, endotracheal tube (ETT) diameter and length, and air humidity was also investigated. **Design:** An albuterol MDI canister was connected to an ***AeroVent****** Collapsible Holding Chamber spacer or AirLife† MDI adapter and ETT 4.0, 5.0, or 6.0 mm at commercially available and equal lengths. The ETT tip was attached to an in-line filter holder with a 1 microns type A/E glass fiber filter. Ventilator settings were fractional concentration of inspired oxygen 50%, tidal volume 250 mL, inspiratory:expiratory (I:E) ratio 1:3, rate 25 breaths/minute, temperature 35 degrees C, and a decelerating flow pattern. Ten albuterol canisters were activated two times each (total 2,000 micrograms) into dry (4.0, 5.0, and 6.0 mm ETT) and humidified air (4.0 and 6.0 mm ETT) and repeated in triplicate. Percentage MDI output was determined by weighing the filter before and after drug administration (balance sensitivity 10 micrograms). Significant differences ($p <$ or $= 0.05$) among the groups with and without a spacer and in dry and humidified air were determined by ANOVA with Scheffe's multiple comparison test. Multiple regression was used to determine significant associations between ETT diameter and length and delivery. **Main Results:** With the ***AeroVent****** Collapsible Holding Chamber spacer in humidified air, delivery with the 4.0 and 6.0 mm ETT was approximately 2.3% and 5%, respectively. The spacer and dry air

significantly improved delivery. **Conclusions:** In humidified air, the dose of albuterol by MDI with an ***AeroVent****** Collapsible Holding Chamber spacer should be doubled for children intubated with 6.0 mm ETT, and four puffs administered for every one puff desired for 4.0 mm ETT. The results of this investigation should prove useful in initial clinical trials of albuterol MDI in ventilator dependent infants and children.

EVALUATION OF A RESERVOIR DEVICE FOR METERED DOSE BRONCHODILATOR DELIVERY TO INTUBATED ADULTS. AN *IN VITRO* STUDY. JL Rau, RJ Harwood, JL Groff. CHEST 1992;102(3):924-930.

We investigated the use of a reservoir device for delivery of an MDI bronchodilator aerosol using a lung model of an intubated, mechanically ventilated adult. **Methods:** Albuterol (Proventil†) was delivered with a MDI using three methods. In method 1, the MDI was attached directly onto the ETT using a commercially available actuator/adapter. In method 2, the Monaghan ***AeroVent****** Collapsible Holding Chamber reservoir was placed on the inspiratory limb of the ventilator circuit just before the patient Y connector. In method 3, the ***AeroVent****** Collapsible Holding Chamber was placed between the patient Y connector and the ETT. Standardized ventilator settings with a Servo 900C were used for all three methods (V_E = 9.6 L; respiratory rate = 12 breaths per minute; T_I = 20 percent or 1 second). Aerosol drug delivery was measured at the distal tip of the ETT using a spectrophotometric technique. Percentage of amount delivered was calculated from measured delivery of the MDI. **Results:** The MDI directly on the ETT delivered 7.3 percent of the total dose to the end of the ETT. The ***AeroVent****** Collapsible Holding Chamber on the inspiratory limb increased this to 32.1 percent and the ***AeroVent****** Collapsible Holding Chamber between the Y connector and the ETT delivered 29 percent. Both reservoir delivery methods delivered significantly more drug than direct placement of the MDI on the ETT (*p* less than 0.01) but did not differ from each other (*p* greater than 0.05). **Conclusions:** Use of the ***AeroVent****** Collapsible Holding Chamber reservoir chamber significantly increased bronchodilator delivery by aerosol with an MDI in an adult lung model of an intubated patient on ventilatory support.

AEROCHAMBER MV* HOLDING CHAMBER

INHALED SALBUTAMOL DOSE DELIVERED BY JET NEBULIZER, VIBRATING MESH NEBULIZER AND METERED DOSE INHALER WITH SPACER DURING INVASIVE MECHANICAL VENTILATION. MHE El Hansy, ME Boules, AFM El Essawy, MB Al-Kholy, MM Abdelrahman, ASA Said, RRS Hussein, ME Abdelrahim. Pulmonary Pharmacology and Therapeutics 2017;45(August):159-163.

Background: Patient receiving invasive mechanical ventilation (IMV) may benefit from medical aerosol, but guidance on dosing with different aerosol devices is limited to *in vitro* studies. The study was designed to compare aerosol delivery with five different types of aerosol generators during IMV. **Method:** In randomized design, 60 (30 female) mechanically ventilated chronic obstructive pulmonary disease (COPD) patients were assigned to one of 5 groups. Groups 1 - 4 received 5,000 mg salbutamol using Aerogen† Pro (PRO), Aerogen† Solo (SOLO), NIVO vibrating mesh and jet nebulizers (JN), respectively, while group 5 received 800 mg (8 puffs) of salbutamol via metered dose inhaler with ***AeroChamber* MV*** Holding Chamber (MDI-AC). All devices were place in the inspiratory limb of ventilator downstream from humidifier which was switched off while delivery. Patients received the inhaled dose on day 1 and provided urine 30 post dosing. They also received the same inhaled dose with a filter before the endotracheal tube on day 2. Amount of salbutamol excreted in urine 30 minutes post inhalation and the amount deposited on the filter from all the COPD patients were determined as indices of pulmonary deposition and systemic absorption, respectively. **Results:** No significant difference was found between the 3 vibrating mesh nebulizers (VMNs). The *in vivo* and *ex vivo* testing showed that all the VMNs resulted in better aerosol delivery compared to JN ($p < 0.01$). However, MDI-AC resulted in better aerosol delivery to VMNs but must be accompanied with careful attention and proper delivery of MDI-AC doses by healthcare provider. **Conclusions:** VMNs can be exchanged with each other, with no dose adjustment. However, dose adjustment is a must when replacing VMNs by JN or MDI-AC. This similarity and difference between the 5 aerosol delivery methods suggest that for IMV patients, aerosol delivery methods should be chosen or substituted with care.

***IN VITRO* / *IN VIVO* COMPARISON OF INHALED SALBUTAMOL DOSE DELIVERED BY JET NEBULIZER, VIBRATING MESH NEBULIZER AND METERED DOSE INHALER WITH SPACER DURING NON-INVASIVE VENTILATION.** A Hassan, RS Eldin, MM Abdelrahman, ME Abdelrahim. Experimental Lung Research 2017;43(1):19-28.

Background: Patients receiving non-invasive ventilation (NIV) may benefit from medical aerosol, but most guidance on dosing with different aerosol devices is limited to *in vitro* studies. The study was designed to *in vitro*, *ex vivo*, and *in vivo* compare aerosol delivery during bilevel NIV with three types of aerosol generators: metered dose inhaler with ***AeroChamber* MV*** Holding Chamber spacer (AC), Aerogen† Pro vibrating mesh nebulizer (PRO), and SideStream† jet nebulizer (Philips Respironics, UK) (SIDE). **Materials and Method:** A bilevel ventilator with dry single limb circuit and fixed expiratory port was set in spontaneous mode with initial inspiratory and expiratory pressures of 20 and 5 cm H_2O, 1:3 inspiratory:expiratory ratio, and 15 breaths.minute^{-1}. Aerosol generators were placed proximal to facial mask of NIV chronic obstructive pulmonary disease (COPD) patients. 1 mL salbutamol nebulizer solution (5 mg/mL) was nebulized using PRO and SIDE. 12 MDI doses, containing 100 µg salbutamol each, were delivered using AC. *In vitro* aerosol fate and aerodynamic droplet characteristics, *in vivo* amount of salbutamol excreted 30 minutes and pooled up to 24 hours post inhalation in urine from 12 COPD patients (as indices of pulmonary deposition and systemic absorption, respectively) and amount of salbutamol deposited on *ex vivo* filters (expected inhalable amount) was determined. **Results:** The *in vitro*, *in vivo* and *ex vivo* testing showed that PRO had better aerosol delivery compared to SIDE ($p < 0.01$). However, with smaller nominal dose MDI with AC resulted in similar aerosol delivery to PRO suggesting better aerosol delivery stress on careful attention and proper delivery by health care provider. **Conclusions:** These similarities and differences between the three aerosol generators tested suggest that aerosol delivery methods should be carefully chosen or substituted in non-invasive ventilated patients.

EFFECTS OF INHALED FORMOTEROL COMPARED WITH SALBUTAMOL IN VENTILATED PRETERM INFANTS. E Rieger-Fackeldey, D Reinhardt, A Schulze. Pulmonary Pharmacology Therapy 2004;17(5):293-300.

Background: Short acting beta-2 agonists have shown beneficial effects in preterm infants, but data on long acting beta-2 agonists are still lacking. **Objectives:** To compare the effects of inhaled formoterol with salbutamol in preterm infants. **Methods:** Randomized, double blind, crossover design of salbutamol (100 microgram every 6 hours) or formoterol (12 microgram every 12 hours) delivered by metered dose inhaler on two consecutive days to very low birth weight infants on assisted mechanical ventilation (n = 12; gestational age 25.7 ± 2 weeks; birth weight 720 ± 254 g; postnatal age 25 ± 9 days; mean ± SD). Treatment with the second drug was administered until day 7 in eight infants. Outcome variables were minute volume MV, respiratory mechanics, heart rate HR, blood pressure, serum potassium and blood glucose levels. **Results:** Mean MV increased by maximal 26% (salbutamol) and by 22% (formoterol) differing from baseline values until 6 and 8 hours through increased mean tidal volume (Vt) in both groups (max. 14%). Mean static compliance (Crs) increased by 26% (salbutamol) and by 32% (formoterol) until 60 min post-administration. There was no tachyphylaxis. **Conclusion:** Inhaled salbutamol and formoterol equally increase MV, Vt, Crs and HR in mechanically ventilated infants with a longer lasting systemic effect of formoterol.

THE DELIVERY OF CHLOROFLUOROCARBON PROPELLED VERSUS HYDROFLUOROALKANE PROPELLED BECLOMETHASONE DIPROPIONATE AEROSOL TO THE MECHANICALLY VENTILATED PATIENT: A LABORATORY STUDY. JP Mitchell, MW Nagel, KJ Wiersama, CC Doyle, VA Migounov. Respiratory Care 2003;48(11):1025-1032.

We describe a laboratory investigation comparing the delivery of chlorofluorocarbon (CFC) and hydrofluoroalkane (HFA) formulated beclomethasone dipropionate (BDP) by metered dose inhaler and holding chamber (***AeroChamber* MV*** Holding Chamber (HC MV) in a simulation of a mechanically ventilated adult patient. **Methods:** We equipped each HC MV (n = 5) with an 8.0 mm diameter endotracheal tube (ETT), locating the HC MV in the inspiratory limb of a breathing circuit linked to a mechanical ventilator set to simulate tidal breathing at tidal volume = 830 mL, respiratory rate = 15 breaths/minute, inspiratory:expiratory ratio of 1:2.1, peak inspiratory pressure = 20 cm H_2O. Temperature and humidity settings were 35 ± 1 degrees C and 100% relative humidity (close to body conditions). We compared delivery of 5 actuations of CFC and HFA BDP (both 50 microgram/actuation), measuring total emitted mass captured by a filter at the distal end of the ETT. In a separate study, we inserted the distal end of the ETT within the entry cone of a cascade impactor so that the aerosol particle size distribution could be determined with the circuit at similar environmental conditions as described previously. We made benchmark measurements with circuit temperature and humidity at room ambient conditions (21 ± 1 degrees C and 54 ± 5% RH respectively). **Results:** Total emitted mass (5 measurements/device) was significantly greater for HFA BDP (14.1 ± 1.1 microgram/actuation) compared with CFC BDP (2.4 ± 0.8 microgram/actuation) (paired t-test, $p < 0.001$). More HFA BDP (2.7 ± 0.2 microgram/actuation) was lost from the delivery system during exhalation (0.9 ± 0.4 microgram/actuation for CFC BDP) ($p < 0.001$). The mass median aerodynamic diameter (MMAD) increased from 1.2 micrometer (room ambient) to 2.8 micrometer (higher temperature and humidity conditions) for HFA BDP. In contrast, MMAD for CFC BDP remained close to 4.6 micrometer under either condition, but particles finer than about 4.0 micrometer increased in size when the circuit was saturated. **Conclusions:** Total emitted mass for HFA BDP was increased by a factor of 5.8 compared with CFC BDP, due largely to the finer particle size distribution of the HFA based solution formulation. Additional water vapor required to operate the breathing circuit at close to body conditions resulted in fine particle growth with both formulations.

TWO ADMINISTRATION METHODS FOR INHALED SALBUTAMOL IN INTUBATED PATIENTS. SS Garner, DB Wiest, JW Bradley, DM Habib. Archives of Disease in Childhood 2002;87(1):49-53.

Aims: To compare serum concentrations and effects on respiratory mechanics and haemodynamics of salbutamol administered by small volume nebuliser (SVN) and metered dose inhaler (MDI) plus spacer. **Methods:** Blinded, randomised, crossover study in 12 intubated infants and children (mean age 17.8 months) receiving inhaled salbutamol therapy. Subjects received salbutamol as 0.15 mg/kg by SVN and four puffs (400 µg) by MDI plus spacer at a four hour interval in random order. Passive respiratory mechanics were measured by a single breath/single occlusion technique, and serum salbutamol concentrations by liquid chromatography-mass spectrometry at 30 minutes, 1, 2, and 4 hours after each dose. Haemodynamics (heart rate and blood pressure) were recorded at each measurement time. **Results:** There was no difference in percentage change in respiratory mechanics or haemodynamics between the two methods of administration. Mean area under the curve (AUC_{0-4}) was 5.86 for MDI plus spacer versus 4.93 ng/mL x hour for SVN. **Conclusions:** Serum concentrations and effects on respiratory mechanics and haemodynamics of salbutamol were comparable with the two administration methods under the conditions studied. Future studies are needed to determine the most effective and safe combination of dose and administration method of inhaled salbutamol in mechanically ventilated infants and children.

A MULTICENTER, RANDOMIZED OPEN STUDY OF EARLY CORTICOSTEROID TREATMENT (OSECT) IN PRETERM INFANTS WITH RESPIRATORY ILLNESS: COMPARISON OF EARLY AND LATE TREATMENT AND OF DEXAMETHASONE AND INHALED BUDESONIDE. HL Halliday, CC Patterson, CWNL Halahakoon. Pediatrics 2001;107(2):232-240.

Aim: To compare early (< 3 days) with late (> 15 days) steroid therapy and dexamethasone with inhaled budesonide in very preterm infants at risk of developing chronic lung disease. **Methods:** Five hundred seventy infants from 47 neonatal intensive care units were enrolled. Criteria for enrollment included gestational age < 30 weeks, postnatal age < 72 hours, and need for mechanical ventilation and inspired oxygen concentration > 30%. Infants were randomly allocated to 1 of 4 treatment groups in a factorial design: early (< 72 hours) dexamethasone, early budesonide, delayed selective (> 15 days) dexamethasone, and delayed selective budesonide. Dexamethasone was given in a tapering course beginning with 0.50 mg/kg/day in 2 divided doses for 3 days reducing by half until 12 days of therapy had elapsed. Budesonide was administered by metered dose inhaler and a spacing chamber in a dose of 400 microg/kg twice daily for 12 days. Delayed selective treatment was started if infants needed mechanical ventilation and > 30% oxygen for > 15 days. The factorial design allowed 2 major comparisons: early versus late treatment and systemic dexamethasone versus inhaled budesonide. The primary outcome was death or oxygen dependency at 36 weeks and analysis was on an intention-to-treat basis. Secondary outcome measures included death or major cerebral abnormality, duration of oxygen treatment, and complications of prematurity. Adverse effects were also monitored daily. **Results:** There were no significant differences among the groups for the primary outcome. Early steroid treatment was associated with a lower primary outcome rate (odds ratio [OR]: 0.85; 95% confidence interval [CI]: 0.61,1.18) but even after adjustment for confounding variables the difference remained nonsignificant. Dexamethasone treated infants also had a lower primary outcome rate (OR: 0.86; 95% CI: 0.62,1.20) but again this difference remained not significant after adjustment. For death before discharge, dexamethasone and early treatment had worse outcomes than budesonide and delayed selective treatment (OR: 1.42; 95% CI: 0.93,2.16; OR: 1.51; 95% CI: 0.99,2.30 after adjustment, respectively) with the results not quite reaching significance. Duration of supplementary oxygen was shorter in the early dexamethasone group (median: 31 days vs. 40 - 44 days). Early dexamethasone was also associated with increased weight loss during the first 12 days of treatment (52 g vs. 3 g) compared with early budesonide, but over 30 days there was no difference. In the early dexamethasone group, there was a reduced incidence of persistent ductus arteriosus (34% vs. 52% - 59%) and an increased risk of hyperglycemia (55% vs. 29% - 34%) compared with the other 3 groups. Dexamethasone was associated with an increased risk of hypertension and gastrointestinal problems compared with budesonide but only the former attained significance. **Conclusions:** Infants given early treatment and dexamethasone therapy had improved survival without chronic lung disease at 36 weeks compared with those given delayed selective treatment and inhaled budesonide, respectively, but results for survival to discharge were in the opposite direction; however, none of these findings attained statistical significance. Early dexamethasone treatment reduced the risk of persistent ductus arteriosus. Inhaled budesonide may be safer than dexamethasone, but there is no clear evidence that it is more or less effective.

SALBUTAMOL DELIVERY FROM A HYDROFLUOROALKANE PRESSURIZED METERED DOSE INHALER IN PEDIATRIC VENTILATOR CIRCUITS: AN *IN VITRO* STUDY. JH Wildhaber, MJ Hayden, ND Dore, SG Devadason, PN LeSouëf. CHEST 1998;113(1):186-191.

Study Objective: The aim of our study was to determine the *in vitro* delivery of salbutamol from a pressurized metered dose inhaler (pMDI) containing hydrofluoroalkane (HFA) propellant through various delivery devices to four models of a pediatric lung. **Design:** To determine the effect of electrostatic charge, delivery of salbutamol was initially assessed with a multistage liquid impinger (MSLI) through an in-line non-chamber device (Baxter MDI Adapter) and a small (***AeroChamber*** **MV*** Holding Chamber) and a large (Nebuhaler†) in-line chamber device. Following this, the delivery was assessed to four lung models appropriate for a child of 70 kg, 50 kg, 15 kg, and 4 kg, with the same three reduced static devices inserted directly into a pediatric ventilator circuit. **Measurements and Results:** Reduction of electrostatic charge improved small particle delivery through holding chambers to the MSLI by 12 to 14%. In the ventilator model, the mean delivery was between 1.9% and 5.4% for the non-chamber device, between 14.3% and 27.2% for the small holding chamber, and between 7.2% and 25.7% for the large holding chamber. Delivery was the least efficient in the 4 kg model compared to the 70 kg, 50 kg, and 15 kg models. **Conclusions:** Salbutamol from an HFA pMDI is delivered efficiently through in-line holding chambers with reduced static in pediatric ventilator settings. A large holding chamber has no advantage over a small holding chamber. In addition, salbutamol delivery is more efficient through a holding chamber than through a non-chamber device.

EFFICIENCY OF AEROSOL MEDICATION DELIVERY FROM A METERED DOSE INHALER VERSUS JET NEBULIZER IN INFANTS WITH BRONCHOPULMONARY DYSPLASIA. TF Fok, S Monkman, M Dolovich, S Gray, G Coates, B Paes, F Rashid, M Newhouse, H Kirpalani. Pediatric Pulmonology 1996;21(5):301-309.

The best means for optimal delivery of drugs into lungs of infants with bronchopulmonary dysplasia (BPD) is uncertain. We aimed to measure radioaerosol deposition of salbutamol by jet nebulizer and metered dose inhalers (MDI) in ventilated and nonventilated BPD infants. In a randomized, crossover sequence, salbutamol lung deposition was measured using an MDI (2 puffs or 200 micrograms) or Sidestream† jet nebulizer (MedicAid UK) (5 minutes of nebulization with 100 micrograms/kg) in 10 ventilated (mean birth weight, 1,101 g) and 13 nonventilated (mean birth weight, 1,093 g) prematurely born infants. Nonventilated infants inhaled aerosol through a face mask, connected to a nebulizer or an MDI and spacer (***AeroChamber**** Valved Holding Chamber). Ventilated infants received aerosol from an MDI + MV15 ***AeroChamber*** **MV*** Holding Chamber or a nebulizer inserted in the ventilator circuit. Lung deposition by both methods was low: mean (SEM) from the MDI was 0.67 (0.17)% of the actuated dose, and from the nebulizer it was 1.74 (0.21)% and 0.28 (0.04)% of the nebulized and initial reservoir doses, respectively. Corresponding figures for the ventilated infants were 0.98 (0.19)% from the MDI and 0.95 (0.23)% and 0.22 (0.08)% from the nebulizer. In both groups, and for both methods of delivery, there was marked intersubject variability in lung deposition and a tendency for the aerosol to be distributed to the central lung regions.

EFFECTIVENESS OF BUDESONIDE AEROSOL IN VENTILATOR-DEPENDENT PRETERM BABIES: A PRELIMINARY REPORT. S Arnon, J Grigg, M Silverman. Pediatric Pulmonology 1996;21(4):231-235.

Summary The aim of this randomized, double blind, placebo controlled trial was to assess the short term effect of a topical glucocorticoid (budesonide 600 mu g twice daily) vs. placebo administered by metered dose inhaler (MDI) and spacer (***AeroChamber*** **MV*** Holding Chamber (MV15) directly into endotracheal tube of intubated infants for 7 days. Twenty preterm infants (mean birth weight, 1,030 g; mean gestational age, 27.3 weeks) who still needed assisted ventilation at 14 days of age were randomly assigned to receive budesonide (n = 9) or placebo (n = 11) and completed the study. The primary outcome was the need for mechanical ventilation after 7 days of treatment. Other outcome variables included ventilator settings, blood gases, serum cortisol levels, and bronchoalveolar lavage inflammatory cell counts. No ventilated infant was extubated during the study period. The treatment group showed significant improvements in mean peak inspiratory pressure, ventilator efficiency index, and (A-a) oxygen difference. There were no changes in the placebo group. Serum cortisol levels and bronchoalveolar lavage cell counts did not change significantly during study period. There was no difference in side effects between the groups. This trial demonstrates that topical budesonide administered by MDI and ***AeroChamber*** **MV*** Holding Chamber produces clinical improvement in ventilated preterm infants, without glucocorticoid side effects.

DETERMINANTS OF AEROSOLIZED ALBUTEROL DELIVERY TO MECHANICALLY VENTILATED INFANTS. DM Coleman, HW Kelly, BC McWilliams. CHEST 1996;109(6):1607-1613.

An *in vitro* lung model and a volume ventilator were used to evaluate the delivery of aerosolized albuterol through an infant ventilator circuit. We compared the following: continuous nebulization (CNA) and intermittent nebulization (INA); various nebulizer gas flows, 5.0, 6.5, and 8.0 L/min; and duty cycle of 33% and 50%. The efficiency and consistency of aerosol delivery by metered dose inhaler (MDI) with four different spacer devices and by nebulizer positioned at the manifold and at the same position as the MDI were also evaluated. A volume ventilator (Servo 900B) was used with settings selected to reflect those of a moderately to severely ill 4 kg infant. A 3.5 mm endotracheal tube was used in all experiments. A specific type of nebulizer used (AirLife† Misty Neb; Baxter; Valencia, Calif) and several spacers were studied (***AeroChamber***** Valved Holding Chamber (VHC) and ***AeroVent***** Collapsible Holding Chamber, Monaghan Medical Corporation in Plattsburgh, NY [corrected]; ACE†, Diemolding Healthcare Division in Canastota, NY [corrected]; and an in-line MDI adapter, Instrumentation Industries Inc, Pittsburgh). CNA delivered significantly more aerosol to the lung model (4.8 ± 0.6% of the starting dose) than INA (3.8 ± 0.3%; $p < 0.01$). There was a significant stepwise decrease in aerosol delivery with increasing nebulizer flow (4.8 ± 1.3% at 5.0 L/min; 3.7 ± 1.1% at 6.5 L/min; and 2.7 ± 1.1% at 8.0 L/min). Increasing duty cycle did not significantly affect delivery. Overall the spacers with MDI were more efficient than the nebulizer in either position delivering about twice the percentage of the starting dose than the nebulizers. All modes of delivery, except the ***AeroChamber***** VHC, demonstrated a marked degree of variability. Most of the starting dose of albuterol either remained in the nebulizer (30.4 ± 6.0% at 5.0 L/min and 25.3 ± 4.1% at 8.0 L/min) or was deposited in the inspiratory tubing (34.7 ± 0.7% at 5.0 L/min and 43.7 ± 4.9% at 8.0 L/min) in our system. In conclusion, we have confirmed that aerosol delivery depends on the mode of delivery and the operating conditions. Although delivery with an MDI and spacer is more efficient than a nebulizer, both methods may produce high variability depending on the method or spacer used.

AEROCHAMBER MINI* ANTI-STATIC HOLDING CHAMBER

NEW **EARLY INHALED BUDESONIDE FOR THE PREVENTION OF BRONCHOPULMONARY DYSPLASIA.** D Bassler, R Plavka, ES Shinwell, M Hallman, P-H Jarreau, V Carnielli, JN Van den Anker, C Meisner, C Engel, M Schwab, HL Halliday, CF Poets for the NEUROSIS Trial Group. New England Journal of Medicine 2015;373:1497-1506.

Background: Systemic glucocorticoids reduce the incidence of bronchopulmonary dysplasia among extremely preterm infants, but they may compromise brain development. The effects of inhaled glucocorticoids on outcomes in these infants are unclear. **Methods:** We randomly assigned 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) to early (within 24 hours after birth) inhaled budesonide or placebo until they no longer required oxygen and positive pressure support or until they reached a postmenstrual age of 32 weeks 0 days. The primary outcome was death or bronchopulmonary dysplasia, confirmed by means of standardized oxygen saturation monitoring, at a postmenstrual age of 36 weeks. **Results:** A total of 175 of 437 infants assigned to budesonide for whom adequate data were available (40.0%), as compared with 194 of 419 infants assigned to placebo for whom adequate data were available (46.3%), died or had bronchopulmonary dysplasia (relative risk, stratified according to gestational age, 0.86; 95% confidence interval [CI], 0.75 to 1.00; p = 0.05). The incidence of bronchopulmonary dysplasia was 27.8% in the budesonide group versus 38.0% in the placebo group (relative risk, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; p = 0.004); death occurred in 16.9% and 13.6% of the patients, respectively (relative risk, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; p = 0.17). The proportion of infants who required surgical closure of a patent ductus arteriosus was lower in the budesonide group than in the placebo group (relative risk, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; p = 0.004), as was the proportion of infants who required reintubation (relative risk, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96; p = 0.03). Rates of other neonatal illnesses and adverse events were similar in the two groups. **Conclusions:** Among extremely preterm infants, the incidence of bronchopulmonary dysplasia was lower among those who received early inhaled budesonide than among those who received placebo, but the advantage may have been gained at the expense of increased mortality. (Funded by the European Union and Chiesi Farmaceutici; ClinicalTrials.gov number, NCT01035190.)

CHANGE IN PRACTICE IMPROVES VENTILATOR ASSOCIATED PNEUMONIA IN NEONATAL PATIENTS RECEIVING AEROSOL DELIVERY. L Hattan, A Polito. Respiratory Care 2010;55(11):1599.

Background: Ventilator associated pneumonia (VAP) is a concern with all patients receiving mechanical ventilation. Much has been reported on reducing risks of in the adult population, little is known in the pediatric and neonatal population, especially those receiving aerosol delivery. **Method:** Retrospective analysis of patients receiving mechanical ventilation and aerosol delivery from August 10, 2009 to June 10, 2010 were reviewed. Criteria used to determine nosocomial infection was adapted from The Centers for Disease Control and Prevention criteria for diagnosis of ventilator associated pneumonia. In January 2010 a new more extensive VAP bundle was implemented for both RN's and RRT's and a comparison was made between the groups. All ventilated patients receiving MDI and aerosol treatments were included, with the exception of long term trach patients. **Results:** 33 NICU patients met our inclusion criteria between August 2009 and June 2010 that were ventilated and receiving aerosol therapy using the Aeroneb† Pro and/ or the ***AeroChamber* mini*** Anti-Static Holding Chamber during their course of ventilation. All patients were less than one year of age. From August 10 to January 10 there were 7 patients of 17 (41%) that met criteria for VAP. Following implementation of an expanded VAP bundle from January to June there were 4 patients of 16 (25%) that met criteria for VAP. **Conclusions:** The improved VAP bundle shows a favorable trend in reducing VAP in neonatal patients on mechanical ventilation and receiving aerosol delivery. Further study to include more patients is needed to establish clinical significance, and a separation of types of delivery methods will be a next step in evaluating a difference in VAP rates in this population of patients.

A NOVEL, VERSATILE VALVED HOLDING CHAMBER FOR DELIVERING INHALED MEDICATIONS TO NEONATES AND SMALL CHILDREN: LABORATORY SIMULATION OF DELIVERY OPTIONS. RM DiBlasi, DP Coppolo, MW Nagel, CC Doyle, VI Avvakoumova, RS Ali, JP Mitchell. Respiratory Care 2010;55(4): 419-426.

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*** Anti-Static Holding Chamber (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 microgram/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*** Anti-Static Holding Chamber 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 ± 1.8 microgram) than during manual resuscitation (10.0 ± 1.1 microgram) (p = 0.046). Albuterol delivery via mechanical ventilation, though comparable with the premature neonate model (3.3 ± 1.2 microgram), the term neonate model (3.8 ± 2.1 microgram), and the 2 year old child model (4.2 ± 2.3 microgram) (p = 0.63), was significantly lower than in the spontaneous breathing and manual resuscitation models (p < 0.001). In the neonatal models the total emitted mass was similar with the spontaneous breathing model (6.0 ± 1.0 microgram with the premature neonate model, 10.5 ± 0.7 microgram with the term neonate model) and the manual resuscitation model (5.5 ± 0.3 microgram premature neonate model, 10.7 ± 0.9 microgram term neonate model) (p > or = 0.46 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 degrees C, relative humidity > 99%), compared to the ambient air (22 ± 1 degrees C, 44 ± 7% relative humidity). The ***AeroChamber* mini*** Anti-Static Holding Chamber may provide a versatile alternative to VHCs that are designed exclusively for one aerosol treatment modality.

INHALED MEDICATIONS FOR NEONATES AND SMALL CHILDREN VIA A NOVEL AEROSOL CHAMBER (VHC): LABORATORY SIMULATION OF DELIVERY OPTIONS. R DiBlasi, D Coppolo, J Mitchell, C Doyle, V Avvakoumova, R Ali, M Nagel. Respiratory Care 2009;54(11):1523.

Background: Delivery of bronchodilators to infants and small children by pressurized metered dose inhaler - holding aerosol valved holding chamber (pMDI-VHC) is limited by airway narrowness, short respiratory cycle times, and low tidal volumes. There is a need for a versatile, efficient VHC, given the variety of treatment modalities. Experiments with such a VHC were undertaken to answer the question: “Are differences in the delivery of inhaled beta-2 agonist medication associated with the simulated delivery options”: mechanical ventilation (MV) via endotracheal tube (ETT); manual resuscitation (MR) via ETT; spontaneous breathing (SB) via face mask? **Methods:** VHCs with internal geometry optimized for aerosol delivery and capable of accepting GSK† pMDI canisters with dose counter (***AeroChamber* mini*** Anti-Static Holding Chamber, n = 5 devices/test) were evaluated for the delivery of HFA albuterol (90 µg/actuation). Tidal breathing of a premature neonate with tidal volume (6 mL), designated NEO-P; term neonate with tidal volume (20 mL), designated NEO-T; and a small child (~ 2 year) with tidal volume (60 mL), designated CH-S, were simulated. Aerosol collection was obtained by electret filter with quantitative assay for albuterol. **Results:** Total emitted mass albuterol/actuation (TEM) ex VHC was marginally greater for the SB (12.1 ± 1.8 µg) than the MR (10.0 ± 1.1 µg) child model (p = 0.046). Albuterol delivery by MV, though measurable and comparable for each model (3.3 ± l.2 µg NEO-P; 3.8 ± 2.1 µg NEO-T; 4.2 ± 2.3 µg CH-S (p = 0.63)), was significantly lower than via the other simulated delivery options (p < 0.001). Similar TEM was measured for the SB (6.0 ± 1.0 µg NEO-P; 10.5 ± 0.7 µg NEO-T), or MR (5.5 ± 0.3 µg NEO-P; 10.7 ± 0.9 µg NEO-T) neonate (1-way ANOVA, p ≥ 0.46). **Discussion And Conclusion:** Reduced delivery of medication for MV was likely associated with the saturated atmosphere within the breathing circuit (T = 37°C/> 99% RH) compared with conditions (T = 22 ± 1°C/44 ± 7% RH) for the other modalities. The new VHC may provide a versatile alternative to existing devices designed exclusively for each treatment modality.

***IN VITRO* EVALUATION OF A NOVEL VENTILATION CHAMBER (VC) FOR DELIVERY OF AEROSOLIZED MEDICATION TO THE MECHANICALLY VENTILATED PREMATURE INFANT.** M Nagel, M Foley, J Mitchell, R Ali, H MacKay, D Coppolo. European Respiratory Journal 2009;34(S53):2036.

Introduction: Delivery of inhaled medication for bronchodilatation of the mechanically ventilated premature infant is difficult because of the small size of the airway access as well as the very low tidal volumes (Vt) that are encountered. **Study Purpose/Materials and Methods:** We report a study in which the delivery of 100 µg albuterol/actuation by pressurized metered dose inhaler (HFA Ventolin†, GSK† Canada) was assessed using the newly designed small volume (100 mL) VC optimized for HFA based products (***AeroChamber* mini*** Anti-Static Holding Chamber, Trudell Medical International, London, Canada; *n* = 5 devices, 3 replicates/device). Benchmark data were obtained with a similar number of a larger (150 mL) VCs (ACE†, DHD Healthcare, Wampsville, NY, USA). Each VC was attached via a 2.5 mm inner diameter neonatal endotracheal tube (ET) to a lung model (ASL 5000; IngMar Medical, Pittsburgh, PA, USA) operated in passive mode and driven by a Servo Ventilator 900C (Siemens-Elma, Sweden), simulating a mechanically ventilated, tidal breathing preterm infant (Vt = 5 mL; 20% duty cycle, 60 breaths/minute). Aerosol reaching the distal end of the ET was captured on a filter and assayed afterwards for deposited albuterol by HPLC-UV spectrophotometry. **Results:** The mass of albuterol recovered after 6 breathing cycles using the ***AeroChamber* mini*** Anti-Static Holding Chambers was 8.8 ± 3.1 µg/actuation, significantly greater than 4.5 ± 2.2 µg/actuation from the ACE† VCs (unpaired t-test, $p < 0.001$). **Conclusions:** The novel VC offers the potential for improving treatment of premature infants by aerosol based drug therapies.

A NOVEL SPACER FOR IN-VENTILATOR CIRCUIT USE PROVIDES EFFICIENT MEDICATION DELIVERY FROM PRESSURIZED METERED DOSE INHALERS (pMDI). DP Coppolo, JP Mitchell, V Avvakoumova, H MacKay, R Ali, MW Nagel. American Journal of Respiratory and Critical Care Medicine 2009;179:A3074.

Rationale: Optimal delivery of aerosol medication to the ventilated patient is difficult to achieve efficiently. Although 'T'-piece actuators are small and can stay in circuit, their efficiency is questionable because of the tendency for the spray formed on actuation to be lost to interior surfaces by impaction. We report a study in which a new spacer with internal geometry optimized for aerosol delivery was evaluated against a commonly used 'T'-piece actuator. **Methods:** Measurements of fine particle mass < 4.7 mm aerodynamic diameter ($FPM_{4.7mm}$) of HFA formulations [albuterol (Ventolin†), fluticasone propionate (FloVent†-50) and ipratropium bromide (Atrovent†)] were made at 28.3 L/min by Andersen 8 stage cascade impactor equipped with USP induction port in accordance with <601> of the US Pharmacopeia. ***AeroChamber* mini*** Anti-Static Holding Chamber (Monaghan Medical Corporation, *n* = 5 devices) used out of package were compared with a similar number of AirLife† Dual Spray MiniSpacer† (Cardinal Health). In each case, collected active pharmaceutical ingredient was assayed by HPLC-UV spectrophotometry. **Results:** Measures of $FPM_{4.7mm}$ are reported in the table, in which equivalent benchmark data for the pMDI alone are provided.

$FPM_{4.7\mu m}$ for In Circuit Spacer Devices

Formulation	pMDI alone	*AeroChamber* mini* Anti-Static Holding Chamber	AirLife† Dual Spray MiniSpacer†
Ipratropium Bromide	6.7 ± 0.4	5.2 ± 0.2	2.4 ± 0.3
Fluticasone Propionate	19.0 ± 2.3	15.3 ± 1.6	10.5 ± 0.6
Albuterol	34.8 ± 1.4	40.8 ± 2.9	27.0 ± 2.9

Conclusions: For all three formulations, $FPM_{4.7\mu m}$ from the ***AeroChamber* mini*** Anti-Static Holding Chambers was substantially equivalent (within ± 20%) of $FPM_{4.7\mu m}$ emitted by the pMDI alone, and significantly exceeded fine particle mass provided by the bidirectional 'T'-piece spacer [unpaired t-test, $p < 0.001$].

*AEROTRACH PLUS** ANTI-STATIC VALVED HOLDING CHAMBER

NEW **EVALUATION OF A VALVED HOLDING CHAMBER FOR THE DELIVERY OF AEROSOL-BASED MEDICATION VIA TRACHEOSTOMY TUBE TO A TIDAL BREATHING MODEL.** M Nagel, JA Suggett, CC Doyle, R Ali, J Schloss, DP Coppolo. CHEST 2023;164(4):A6162.

Purpose: Patients with asthma or obstructive airways disease who have a tracheostomy tube (TT) require aerosolized medication. We report the outcome of a study that investigated aerosol delivery from ***AeroTrach Plus**** (AT) Anti-Static Valved Holding Chamber (VHC) and Misty Max 10† nebulizer (SVN) to a breathing tracheostomy model. **Methods:** Albuterol was delivered to the model via either the AT VHC (Ventolin†, 2 actuations) or SVN (2mL - 1mg/mL) via 4.5 mm or 8.0 mm TTs. The tracheostomy adapter of the AT VHC was attached to the 15 mm adapter of the TT. When the SVN was evaluated, it was coupled to either a small or large tracheostomy mask depending on the size of the TT used. Tidal breathing (155 cc, 25 breaths per minute (bpm), 1:2 inspiratory:expiratory (I:E) ratio or 500 cc, 13 bpm, 1:2 I:E ratio) was simulated using an ASL 5000 breathing simulator. Aerosol particles were captured on a filter located at the distal end of the TT and the contents were assayed for albuterol by HPLC-UV spectrophotometry. In a parallel series of measurements, respirable droplet fraction <4.7 µm ($RDF_{<4.7\mu m}$) was determined and the clinically relevant respirable mass ($RM_{<4.7\mu m}$) was calculated as total mass x $RDF_{<4.7\mu m}$ and represented as mean ± SD in the results. **Results:** The AT VHC produced $RM_{<4.7\mu m}$ values of 36.0 ± 3.2µg and 57.0 ± 6.1µg for the 4.5mm/155cc Vt and 8.0mm/500cc Vt respectively. In comparison, the SVN produced 90.6 ± 16.0 µg and 107.1 ± 5.6 µg for the equivalent conditions. The AT VHC delivered 2 doses in approximately 1 minute whereas the SVN required 4 minutes to deliver the medication to sputter. **Conclusions:** The AT VHC was easier to use (no mask required) and much less time consuming than SVN with mask. In terms of dose per unit time, albuterol delivery via ***AeroTrach Plus**** Anti-Static Valved Holding Chamber was more efficient than a small volume nebulizer. **Clinical Implications:** Further research is required to determine the clinical relevance of these *in vitro* findings.

PERFORMANCE OF A VALVED HOLDING CHAMBER (VHC) WITH TRACHESTOMY ADAPTER: AEROSOL DELIVERY FROM SOFT MIST INHALERS (SMIs). M Nagel, R Ali, C Doyle, DP Coppolo, J Suggett. American Journal of Respiratory and Critical Care Medicine 2019;199:A3299.

Rationale: Patients with asthma or obstructive airways disease who have a tracheostomy tube (TT) or tracheal stoma have difficulty using Metered Dose Inhalers (MDIs) because of a failure to achieve a good seal between the TT and delivery device. We report the outcome of a study that investigated aerosol delivery from soft mist Inhalers (SMI) to a breathing tracheostomy model via a valved holding chamber (VHC) with tracheostomy adapter (***AeroTrach Plus**** Anti-Static Valved Holding Chamber, Trudell Medical International, London, Canada). **Methods:** Five VHC (*n* = 5 replicates/devices) were evaluated for active pharmaceutical ingredients (API) from the 2 different SMI formulations. The tracheostomy adapter of the VHC was attached to the 15 mm adapter of the adult tracheostomy tube (6 mm I.D., 70 mm long Portex†) connected to a breathing simulator (ASL 5000 IngMar Medical, Pittsburgh, PA) which was operated to simulate tidal breathing (Vt = 500 mL; 13 cycles/minute; inspiratory:expiratory ratio 1:2). The SMI was placed in the adapter of the VHC and following actuation of the SMI, 5 breathing cycles were undertaken following which the test apparatus was disassembled, and the mass of API deposited on the filter assayed by HPLC.

Results:

Soft Mist Inhaler Formulation	Active Ingredient (label claim, µg)	Dose Delivered to Distal End of Tracheostomy Tube (µg)
Spiriva† Respimat†	Tiotropium bromide monohydrate (2.5 µg)	1.3 ± 0.2
Inspiolto† Respimat†	Olodaterol hydrochloride (2.5 µg)	1.1 ± 0.2
	Tiotropium bromide monohydrate (2.5 µg)	1.1 ± 0.2
Combivent† Respimat†	Salbutamol (100 µg)	27.2 ± 5.3
	Ipratropium bromide (20 µg)	4.9 ± 1.0

Conclusions: Based on these laboratory data, the VHC with tracheostomy adaptor appears to provide a reliable means of delivering SMI aerosols to patients with a tracheostomy tube (TT) or tracheal stoma. Further research is required to determine the clinical relevance of these *in vitro* findings.

ALBUTEROL DELIVERY VIA METERED DOSE INHALER IN A SPONTANEOUSLY BREATHING PEDIATRIC TRACHEOSTOMY MODEL. A Berlinski, A Chavez. Pediatric Pulmonology 2013;48(10):1026-1034.

Rationale: Little data are available regarding efficiency of drug delivery devices and techniques despite their widespread use in spontaneously breathing tracheostomized patients. We compared patient dose achieved with different devices, inhalation techniques, tracheostomy tube sizes and breathing patterns using a spontaneously breathing tracheostomized pediatric model. **Methods:** A tracheostomy model was connected in series to a breathing simulator with a filter interposed (patient dose). Breathing patterns of a 16 month old and a 6 and 12 year old child with tracheostomy with internal diameters (mm) of 3.5, 4.5, and 5.5 were used. Albuterol HFAp MDI was used. ***AeroTrach Plus**** Anti-Static Valved Holding Chamber, MediBag†, ***AeroChamber*** **MV*** Holding Chamber, ***AeroChamber*** **mini*** Anti-Static Holding Chamber, and in-line adapter with 6 inch tubing were tested. The latter 3 devices were also tested with assisted technique. Albuterol was analyzed via spectrophotometry. **Results:** ***AeroTrach Plus**** Anti-Static Valved Holding Chamber outperformed almost all devices tested. ***AeroChamber*** **MV*** Holding Chamber with unassisted technique was the second best and the adapter was the worst. Comparison of efficiency between best and worst performer ranged from 3- to 17.2-fold. The 16 month old breathing pattern and the 3.5 mm tracheostomy tube had the lowest patient dose. The use of assisted technique decreased patient dose by 18 - 67% for the 4.5 and 5.5 mm but not for 3.5 mm tracheostomy tubes. A median of 7.4% of the nominal dose was deposited in the tracheostomy tubes. **Conclusions:** ***AeroTrach Plus**** Anti-Static Valved Holding Chamber and the adapter were the most and least efficient devices respectively. Tracheostomy size and breathing pattern affected drug delivery. The use of assisted technique reduced aerosol delivery.

FACTORS AFFECTING ALBUTEROL DELIVERY VIA MDI IN A SPONTANEOUSLY BREATHING PEDIATRIC TRACHEOSTOMY MODEL. Al Chavez, A Berlinski. American Journal of Respiratory and Critical Care Medicine 2010;181:A3918.

Introduction: Pediatric patients with tracheostomy are often prescribed inhaled albuterol. Different devices and administration techniques are used but little data are available comparing their efficiency. We evaluated the effect of tracheostomy tube (TRACH) size, breathing pattern, and delivery device on the amount of albuterol reaching the carina (ARC) in a spontaneously breathing pediatric tracheostomy model. **Methods:** We compared: ***AeroChamber*** **MV*** Holding Chamber‡, ***AeroChamber*** **mini*** Anti-Static Holding Chamber‡, ***AeroTrach Plus**** Anti-Static Valved Holding Chamber‡, MediBag†‡, 6 inch tubing + Hudson adapter‡ to deliver albuterol MDI through 3.5 and 4.5 mm TRACHs. Devices marked with ‡ were also tested with synchronized bagging. ***AeroChamber*** **MV*** Holding Chamber experiments were repeated with asynchronous bagging. Three different breathing patterns were tested (16 months and 6 and 12 years old). The TRACH was inserted into a tracheal model that was connected in series to a filter holder, at the level of the carina, and a breathing simulator. Each experiment comprised of 10 puffs run for 6 respiratory cycles each and was repeated 5 times for each scenario. Efficiency was defined as [(drug in the filter/emitted dose) * 100]. ARC was quantified via spectrophotometry at 276 nm. Data were analyzed by ANOVA followed by Tukey ($p < 0.05$). **Results:** ***AeroTrach Plus**** Anti-Static Valved Holding Chamber (48% efficiency) was 1.7-, 2- and 8-fold more efficient than other non-bagged systems (***AeroChamber*** **MV*** Holding Chamber, ***AeroChamber*** **mini*** Anti-Static Holding Chamber and Hudson respectively). MediBag† and ***AeroChamber*** **MV*** Holding Chamber were 1.4- and 4.1-fold more efficient than other bagged systems (***AeroTrach Plus**** Anti-Static Valved Holding Chamber and Hudson respectively). Best non-bagged system was 2.4-fold more efficient than the best bagged system. ARC [mean (95%CI)] varied -24% (-31% to -18%) and +27% (+14% to +40%) when the breathing pattern was changed from 6 years old to 16 months old and 12 years old respectively ($p < 0.05$). Decreasing TRACH size from 4.5 to 3.5 lead to a reduction in ARC of -22% (-39% to -5%); -18% (-30% to -7%) and -25% (-34% to -16%) for breathing patterns of 16 months, 6 years and 12 years old respectively ($p < 0.05$). Synchronized bagging decreased ARC -45% (-50% to -41%); -45% (-52% to -37%) and -31% (-40% to -22%) for breathing patterns of 16 months, 6 and 12 years old respectively ($p < 0.05$). Asynchronous bagging for ***AeroChamber*** **MV*** Holding Chamber further decreased ARC by 33%, 30% and 67% for breathing patterns of 16

months, 6 and 12 years old respectively ($p < 0.01$) **Conclusion:** Manual bagging, a smaller TRACH and the breathing pattern of a younger child decrease ARC. ***AeroTrach Plus**** Anti-Static Valved Holding Chamber was overall the most efficient delivery device.

PERFORMANCE OF A VALVED HOLDING CHAMBER WITH TRACHEOSTOMY ADAPTER: COMPARISON WITH CONVENTIONAL VALVED HOLDING CHAMBER. JP Mitchell, MW Nagel, KJ Wiersema, SL Bates, JN Schmidt. European Respiratory Journal 2001;16(31):904.

We report the outcome of a study comparing a new valved holding chamber (VHC) with tracheostomy adapter (***AeroTrach Plus**** Anti-Static Valved Holding Chamber, Trudell Medical International, London, Canada) with a conventional VHC (***AeroChamber Plus**** Valved Holding Chamber with medium mask, Trudell Medical International) for the delivery of 125 µg/dose fluticasone propionate (FloVent†-125, GlaxoWellcome Canada Inc.). Measurements ($n = 5$ VHCs/group, 1 measurement/VHC) were made by cascade impactor at 4.9, 12.0 and 28.3 L/min in accordance with <601> of the US Pharmacopeia. Values of fine particle dose (< 4.7 µm aerodynamic diameter were as follows: 4.9 L/min - ***AeroTrach Plus**** Anti-Static Valved Holding Chamber = 38.8 ± 6.2 µg, ***AeroChamber Plus**** VHC = 32.6 ± 7.3 µg; 12.0 L/min - ***AeroTrach Plus**** Anti-Static Valved Holding Chamber = 49.8 ± 7.0 µg, ***AeroChamber Plus**** VHC = 46.8 ± 7.4 µg; 28.3 L/min - ***AeroTrach Plus**** Anti-Static Valved Holding Chamber = 62.3 ± 1.6 µg, ***AeroChamber Plus**** VHC = 61.0 ± 5.7 µg. Values of fine particle fraction for both devices were close to 90% irrespective of flow rate. The performance of both devices was equivalent based on FPD (unpaired t-test, $p = 0.18$). Based on these data, the tracheostomy adaptor is likely to have negligible impact on clinical performance compared with the ***AeroChamber Plus**** VHC over a wide range of breathing conditions.

GUIDANCE

NEW **AEROSOL THERAPY IN ADULT CRITICALLY ILL PATIENTS: A CONSENSUS STATEMENT REGARDING AEROSOL ADMINISTRATION STRATEGIES DURING VARIOUS MODES OF RESPIRATORY SUPPORT.** J Li, K Liu, S Lyu, G Jing, B Dai, R Dhand, H-L Lin, P Pelosi, A Berlinski, J Rello, A Torres, C-E Luyt, J-B Michotte, Q Lu, G Reychler, L Vecellio, A Dornelas de Andrade, J-J Rouby, JB Fink, S Ehrmann. Annals of Intensive Care 2023;13(463):1-25.

Background: Clinical practice of aerosol delivery in conjunction with respiratory support devices for critically ill adult patients remains a topic of controversy due to the complexity of the clinical scenarios and limited clinical evidence. **Objectives:** To reach a consensus for guiding the clinical practice of aerosol delivery in patients receiving respiratory support (invasive and noninvasive) and identifying areas for future research. **Methods:** A modified Delphi method was adopted to achieve a consensus on technical aspects of aerosol delivery for adult critically ill patients receiving various forms of respiratory support, including mechanical ventilation, noninvasive ventilation, and high-flow nasal cannula. A thorough search and review of the literature were conducted, and 17 international participants with considerable research involvement and publications on aerosol therapy, comprised a multi-professional panel that evaluated the evidence, reviewed, revised, and voted on recommendations to establish this consensus. **Results:** We present a comprehensive document with 20 statements, reviewing the evidence, efficacy, and safety of delivering inhaled agents to adults needing respiratory support, and providing guidance for healthcare workers. Most recommendations were based on *in vitro* or experimental studies (low-level evidence), emphasizing the need for randomized clinical trials. The panel reached a consensus after 3 rounds anonymous questionnaires and 2 online meetings. **Recommendation I:** During mechanical ventilation, VMN or pMDI with spacer are recommended for aerosol delivery, with no preference between the devices. The use of an inline continuous JN results in changes in tidal volume, inspiratory flow patterns, and fraction of inspired oxygen, and aerosol delivery efficiency is low, thus continuous JN is not preferred for aerosol delivery in this setting. **Recommendation III:** When pMDI is utilized during invasive ventilation, it is recommended to be used with a spacer with a volume > 150 mL and placed in the inspiratory limb before the Y-piece. The pMDI is recommended to be actuated at the beginning of inspiratory flow from the ventilator. **Conclusions:** We offer a multinational expert consensus that provides guidance on the optimal aerosol delivery techniques for patients receiving respiratory support in various real-world clinical scenarios.
[Note: Only recommendations I and III have been listed here due to their relevance to spacer use in a mechanical ventilator circuit.]

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