

STUDY SUMMARY

Specialty Chambers

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Trudell Medical International

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Foreword

Trudell Medical International is the global leader in the development and manufacture of aerosol drug delivery devices for patient use. In addition to our flagship **AeroChamber*** brand of Valved Holding Chambers, a full range of specialty application products have been designed to deliver Metered Dose Inhaler (MDI) aerosol medication within the hospital environment. Each device has been engineered to meet the same high standards you have come to expect from Trudell Medical International.

Trudell Medical International offers the following specialty chambers:

- **AeroTrach Plus*** Anti-Static Valved Holding Chamber
Designed for the delivery of MDI medications to spontaneously breathing tracheostomy patients with standard 15mm connections.
- **AeroChamber mini*** Aerosol Chamber
Highly efficient device is designed to maintain various levels of PEEP when being used with pressurized ventilation systems. Small volume chamber includes exhalation channel and one-way valve that preserves aerosol dose and minimizes dead space. Can be used in mechanical ventilation circuits, with manual resuscitation bags or noninvasive ventilation.
- **AeroVent*** Collapsible Holding Chamber / **AeroChamber*** VENT Chamber
Designed to be left in the inspiratory limb of a ventilator circuit, and can be collapsed when not in use without interruption of continuous mechanical ventilation.
- **AeroChamber*** MV Holding Chamber
A proven standard for the delivery of aerosol medications to mechanically ventilated patients. Can be used with a resuscitation bag or placed in the ventilator circuit.

AARC Clinical Practice Guideline:

Selection of Device, Administration of Bronchodilator, and Evaluation of Response to Therapy in Mechanically Ventilated Patients. *Respiratory Care* 1999, 44 (1): 105-113.

- **Metered Dose Inhaler Use:** 1) Use an MDI fitted with a chamber device; 2) actuate the MDI manually and synchronize actuation with the beginning of inspiration; 3) 4 puffs are the usual recommended dose; however, greater doses may be required when clinical monitoring of the patient suggests incomplete or inadequate response.
- **Chamber-style adapter:** Both *in vitro* and *in vivo* have found that the combination of an MDI and a chamber device results in a four-to-six fold increase in delivery of aerosol over MDI actuation into an elbow connector (without chamber) attached directly to the Endotracheal tube or into an inline adapter without chamber. This correlates with clinical response studies showing clinical response with as little as 4 puffs of albuterol whereas an elbow adapter demonstrated no response with 100 actuations of albuterol.

Use of Metered Dose Inhaler and Spacer versus Nebulizer in Mechanically Ventilated Patients

BRONCHODILATOR DELIVERY WITH METERED-DOSE INHALER DURING MECHANICAL VENTILATION. Georgopoulos D, Mouloudi E, Kondili E, Klimathianaki M. Crit Care. 2000; 4 (4): 227-234.

The delivery of bronchodilators with metered-dose inhaler (MDI) in mechanically ventilated patients has attracted considerable interest in recent years. This is because the use of the MDI has several advantages over the nebulizer, such as reduced cost, ease of administration, less personnel time, reliability of dosing and a lower risk of contamination. A spacer device is fundamental in order to demonstrate the efficacy of the bronchodilatory therapy delivered by MDI. Provided that the technique of administration is appropriate, MDIs are as effective as nebulizers, despite a significantly lower dose of bronchodilator given by the MDI.

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

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 h 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 h 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 \pm SD) 169 \pm 129 mg albuterol (38%) was recovered in the urine; with the nebulizer, 409 \pm 515 mg albuterol (16%) was recovered in the urine; and with the MDI port on the right-angle adaptor, 41 \pm 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.

EVALUATING THE DELIVERY OF NEBULIZED AND METERED-DOSE INHALERS IN AN *IN VITRO* INFANT VENTILATOR LUNG MODEL. Avent ML, Gal P, Ransom JL, Brown YL, Hansen CJ, Ricketts WA, Soza F. The Annals of Pharmacotherapy Feb 1, 1999; 33 (2): 144-148.

OBJECTIVE: To evaluate drug delivery to the lungs of nebulized and metered-dose inhalers (MDIs) in an *in vitro* infant lung model. METHODS: An *in vitro* lung model was modified to study drug delivery. A 1000 mL intravenous bag filled with 500 mL deionized water was attached to a 3.5 mm (12 cm length) endotracheal tube. An inline Marquest Whisper Jet infant circuit nebulizer system delivered 2.5 mg/3 mL albuterol sulfate inhalation solution (Ventolin nebulizer) at a flow rate of 5 L/min. An Aerochamber (Monaghan) was placed at the endotracheal tube for the delivery of the MDIs. Albuterol MDI (Ventolin) 10 inhalations and beclomethasone MDI (Beclonase) 20 inhalations were delivered. A Servo 900C (Siemens-Elma) was used at the following ventilator settings: positive inspiratory pressure 30 cm H₂O, intermittent mandatory ventilation 40 breaths/min, positive end expiratory pressure 4 cm H₂O, inspiratory time 0.4 sec. Each formulation was run at least 10 times and assayed in duplicate by HPLC. An unpaired Student's t-test was used

to analyze the statistical significance of the data. RESULTS: There was a significantly greater percentage of drug delivery with MDI albuterol (1.96 +/- 0.50) as compared with nebulized albuterol (1.26 +/- 0.37) ($p = 0.002$) or beclomethasone dipropionate (0.51 +/- 0.24) ($p = 0.001$). CONCLUSIONS: Albuterol MDI provides a more efficient delivery of drug to the lung as compared with nebulized albuterol and MDI beclomethasone dipropionate.

PRESSURIZED AEROSOL VERSUS JET AEROSOL DELIVERY TO MECHANICALLY VENTILATED PATIENTS.

Fuller HD, Dolovich MB, Pomituck G, Wong Pack W, Newhouse MT. Am Rev Respir Dis 1990; 141: 440-444.

The purpose of this study was to compare deposition of aerosol to the lung from a metered-dose inhaler (MDI) and aerosol holding chamber and from a jet nebulizer in ventilator-dependent patients. Twenty-one patients were entered into the study, all receiving assisted ventilation and inhaled bronchodilators because of airflow limitation. The average age was 68 yr; there were 10 men and 11 women. The patients were randomized to receive either 4 puffs (800 micrograms) of radiolabeled fenoterol by MDI of 1.75 ml (1,750 micrograms) of radiolabeled fenoterol solution by nebulizer. Imaging of lung fields was made by a portable scintillation camera at 5-min intervals during the study. Results showed that 20 patients completed the study, 9 receiving fenoterol by MDI, and 11 by jet nebulizer. Four were excluded from analysis because of previous pneumonectomy, two from each group. Lung deposition measured as a percent of given dose from either system was 5.65 +/- 1.09 (mean +/- SEM) for MDI plus extension chamber and 1.22 +/- 0.35 for jet nebulizer (p less than 0.001). Therefore, this trial shows significantly greater efficiency of aerosol deposition to the lung in ventilator-dependent patients when using an MDI plus aerosol holding chamber than when using a jet nebulizer.

***AeroTrach Plus** Anti-Static Valved Holding Chamber**

FACTORS AFFECTING ALBUTEROL DELIVERY VIA MDI IN A SPONTANEOUSLY BREATHING PEDIATRIC TRACHEOSTOMY MODEL. Chavez AI, Berlinski A. Am J Respir Crit Care Med 181; 2010: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™*, AeroChamber Mini™, AeroTrach Plus™, 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™ 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™ (48% efficiency) was 1.7-, 2- and 8-fold more efficient than other non-bagged systems (AeroChamber MV™, AeroChamber Mini™ and Hudson™ respectively). Medibag™ and AeroChamber MV™ were 1.4- and 4.1-fold more efficient than other bagged systems (AeroChamber Mini™ 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™ 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™ was overall the most efficient delivery device.

PERFORMANCE OF A VALVED HOLDING CHAMBER WITH TRACHEOSTOMY ADAPTER: COMPARISON WITH CONVENTIONAL VALVED HOLDING CHAMBER. Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Schmidt JN. ERS Annual Congress, Berlin, Germany, September 2001.

We report the outcome of a study comparing a new valved holding chamber (VHC) with tracheostomy adapter (AeroTrach Plus™, Trudell Medical International, London, Canada) with a conventional VHC (AeroChamber Plus™ 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™ = 38.8 ± 6.2 µg, AeroChamber Plus™ = 32.6 ± 7.3 µg; 12.0 l/min - AeroTrach Plus™ = 49.8 ± 7.0 µg, AeroChamber Plus™ = 46.8 ± 7.4 µg; 28.3 l/min - AeroTrach plus™ = 62.3 ± 1.6 µg, AeroChamber Plus™ = 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 (un-paired 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.

***AeroChamber mini** Aerosol Chamber**

A NOVEL, VERSATILE VALVED HOLDING CHAMBER FOR DELIVERING INHALED MEDICATIONS TO NEONATES AND SMALL CHILDREN: LABORATORY SIMULATION OF DELIVERY OPTIONS. DiBlasi RM, Coppolo DP, Nagel MW, Doyle CC, Avvakoumova VI, Ali RS, Mitchell JP. *Respir 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 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 microg/actuation) during: mechanical ventilation via endotracheal tube (ETT); manual resuscitation via ETT; and spontaneous breathing via face mask. We tested 5 units of the AeroChamber Mini VHC per test. We simulated the tidal breathing of a premature neonate (V(T) 6 mL), a term neonate (V(T) 20 mL), and a child approximately 2 years old (V(T) 60 mL). We collected the aerosol on an electret filter and quantitatively assayed for albuterol. **RESULTS:** The total emitted mass of albuterol per actuation that exited the VHC was marginally greater during spontaneous breathing (12.1 +/- 1.8 microg) than during manual resuscitation (10.0 +/- 1.1 microg) (P = .046). Albuterol delivery via mechanical ventilation, though comparable with the premature-neonate model (3.3 +/- 1.2 microg), the term-neonate model (3.8 +/- 2.1 microg), and the 2-y-old-child model (4.2 +/- 2.3 microg) (P = .63), was significantly lower than in the spontaneous-breathing and manual-resuscitation models (P < .001). In the neonatal models the total emitted mass was similar with the spontaneous-breathing model (6.0 +/- 1.0 microg with the premature-neonate model, 10.5 +/- 0.7 microg with the term-neonate model) and the manual-resuscitation model (5.5 +/- 0.3 microg premature-neonate model, 10.7 +/- 0.9 microg term-neonate model) (P > or = .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 VHC may provide a versatile alternative to VHCs that are designed exclusively for one aerosol treatment modality.

THE NEONATAL EUROPEAN STUDY OF INHALED STEROIDS (NEUROSIS): AN EU-FUNDED INTERNATIONAL RANDOMISED CONTROLLED TRIAL IN PRETERM INFANTS. Bassler D, Halliday HL, Plavka R, Hallman M, Shinwell E, Jareau P, Carnielli V, van den Anker J, Schwab M, Poets CF. *Neonatology* 2010;97: 52-55.

Exerpt: The Neonatal European Study of Inhaled Steroids (NEUROSIS) is a randomized placebo-controlled, international clinical trial. 850 infants of 23-27 weeks' postmenstrual age (either mechanically ventilated or on CPAP) will be randomized during the first 12 h of life to budesonide or placebo. Study drugs will be administered via a spacer device and continued until infants no longer need either supplemental oxygen or positive pressure support or have reached a postmenstrual age of 32 0/7 weeks regardless of ventilator status. The primary outcome of survival without BPD will be determined at 36 weeks' postmenstrual age, and BPD will be defined according to the physiological definition. Study patients will be followed and neurodevelopmental outcomes assessed at a corrected age of 18-22 months. The severity of BPD according to 3 different definitions will be determined as an exploratory analysis. Candidate genes related to absorption, distribution, metabolism, and excretion of budesonide will be investigated including pharmacokinetic data. Moreover, a sub-study on genetic susceptibility to BPD will be performed. NEUROSIS is funded by the European Union in its 7th framework program. Infants are planned to be randomized starting from September 2009, and units are invited to participate. The results of NEUROSIS will provide useful indications about the efficacy and safety of inhaled steroids in very preterm infants.

CHANGE IN PRACTICE IMPROVES VENTILATOR ASSOCIATED PNEUMONIA IN NEONATAL PATIENTS RECEIVING AEROSOL DELIVERY. Hattan L, Polito A. Respiratory Care 2010. Open Forum Abstract.

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 Aug 10 2009 to Jun 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 Aug 2009 and Jun 2010 that were ventilated and receiving aerosol therapy using the Aeroneb® Pro and/ or the AeroChamber® mini during their course of ventilation. All patients were less than one year of age. From Aug 10 to Jan 10 there were 7 patients of 17 (41%) that met criteria for VAP. Following implementation of an expanded VAP bundle from Jan 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.

IN VITRO EVALUATION OF A NOVEL VENTILATION CHAMBER (VC) FOR DELIVERY OF AEROSOLIZED MEDICATION TO THE MECHANICALLY VENTILATED PREMATURE INFANT. Nagel M, Foley M, Mitchell J, Ali R, MacKay H, Coppolo D. Eur. Respir. J., 2009; 34(S53): P2036.

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. 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*, 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 (ASL5000; 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 pre-term infant (Vt = 5 ml; 20% duty cycle, 60 breaths/min). Aerosol reaching the distal end of the ET was captured on a filter and assayed afterwards for deposited albuterol by HPLC-UV spectrophotometry. The mass of albuterol recovered after 6 breathing cycles using the AeroChamber mini* VCs 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). 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). Coppolo D, Mitchell JP, Avvakoumova V, MacKay H, Ali R, Nagel MW. Am J Respir Crit Care Med 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™ spacers (Monaghan Medical Corp., n=5 devices) used out of package were compared with a similar number of Airlife™ dual spray Mini Spacer (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_{4.7µm} for In-Circuit Spacer Devices

Formulation	pMDI alone	AeroChamber mini Spacer	Airlife Dual Spray Mini Spacer
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_{4.7µm} from the AeroChamber Mini spacers was substantially equivalent (within ±20%) of FPM_{4.7µm} emitted by the pMDI alone, and significantly exceeded fine particle mass provided by the bi-directional 'T'-piece spacer [un-paired t-test, p < 0.001].

INHALED MEDICATIONS FOR NEONATES AND SMALL CHILDREN VIA A NOVEL AEROSOL CHAMBER (VHC): LABORATORY SIMULATION OF DELIVERY OPTIONS. DiBlasi R, Coppolo DP, Mitchell JP, Doyle CC, Avvakoumova VA. *Resp 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 beta₂-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™, 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, through measureable and comparable for each model (3.3 ± 1.2 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.

AeroChamber* MV Holding Chamber

EFFECTS OF INHALED FORMOTEROL COMPARED WITH SALBUTAMOL IN VENTILATED PRETERM INFANTS.

Rieger-Fackeldey E, Reinhardt D, Schulze A. *Pulm Pharmacol Ther* 2004; 17 (5): 293-3000.

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 microg every 6 h) or formoterol (12 microg every 12 h) 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 h 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. Mitchell JP, Nagel MW, Wiersema KJ, Doyle CC, Migounov VA. *Respir 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 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/min, inspiratory-expiratory ratio of 1:2.1, peak inspiratory pressure = 20 cm H₂O. 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 microg/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 microg/actuation) compared with CFC-BDP (2.4 +/- 0.8 microg/actuation) (paired t test, p < 0.001). More HFA-BDP (2.7 +/- 0.2 microg/actuation) was lost from the delivery system during exhalation (0.9 +/- 0.4 microg/actuation for CFC-BDP) (p < 0.001). The mass median aerodynamic diameter (MMAD) increased from 1.2 microm (room ambient) to 2.8 microm (higher temperature and humidity conditions) for HFA-BDP. In contrast, MMAD for CFC-BDP remained close to 4.6 microm under either condition, but particles finer than about 4.0 microm 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. Garner SS, Wiest DB, Bradley JW, Habib DM. Arch Dis Child 2002; 87:49-53.

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 (AUC₀₋₄) was 5.86 for MDI plus spacer versus 4.93 ng/ml x h 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. Halliday HL, Patterson CC, Halahakoon C. 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. Wildhaber JH, Hayden MJ, Dore ND, Devadason SG, LeSouëf PN. CHEST 1998;113 (1): 181-191.

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 inline nonchamber device (Baxter MDI Adapter) and a small (Aerochamber MV) and a large (Nebuhaler) inline 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 nonchamber 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 inline 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 nonchamber device.

COMPARISON OF TWO SMALL-VOLUME HOLDING CHAMBERS FOR AEROSOL-BASED DRUG DELIVERY TO THE VENTILATED PATIENT. Mitchell JP, Nagel MW. Presented at ACAA 1997.

The delivery of albuterol from a pressurized metered-dose inhaler (pMDI (Ventolin[®]: total unit dose 90 µg ex actuator, GlaxoSmithKline)) via an AeroChamber* HC for mechanical ventilation (Monaghan Medical Corp. (MV-AC)) was compared with an OptiVent™ HC (HealthScan Products Inc.). Each device was located upstream of the 'wye' of a 'Universal' ventilator circuit (Hudson RCI[®]) equipped with a 7.0 mm bore endo-tracheal (E-T) tube, connected to an AdultStar 1500 ventilator (Infrasonics Inc.). The ventilator was set to provide a duty cycle of 700 ml tidal volume, 8 breaths/min and I/E of 50/50. An in-line respiratory filter (Marquest Medical Products Inc.) was connected directly at the distal end of the E-T tube with its far side coupled to an anesthesia bag to enable the exhalation portion of each breathing cycle to be simulated. 5 actuations from the pre-primed pMDI were administered at the start of every other inhalation via the MV-AC. Afterwards the filter was removed from the circuit and the collected albuterol assayed by HPLC. The procedure was repeated with the OptiVent™ HC. The AC-MV delivered significantly more drug to the filter (48.4 ± 0.6 µg/dose (n = 5 replicates)) whereas the Optivent™ provided only 22.6 ± 0.6 µg/dose (n = 5 replicates) (unpaired t-test, p <0.001). The smaller OptiVent™ is more prone to impaction of the drug-laden aerosol particles on the interior chamber walls. The low output from this HC may be an issue in the effective delivery of bronchodilators to patients on ventilator support.

COMPARISON OF MDI ALBUTEROL DOSE DELIVERY IN A HEATED, HUMIDIFIED ADULT VENTILATOR CIRCUIT WITH THE MV-AEROCHAMBER AND ACE RESERVOIR SYSTEMS. DeKler R, Rau JL. Respiratory Care 1996.

Introduction: No data exist to compare the dose delivery of the prototype MD spacer, MV-Aerochamber (Monaghan Medical Corp), and the ACE (Diemolding Healthcare Corp) Spacer device. Purpose: This study examined the dose delivery of MDI albuterol through an adult, heated, humidified ventilator circuit using the MV-Aerochamber and ACE spacer devices. Methods: Albuterol sulfate (Proventil, Schering) was delivered using 6 samples each of the MV-Aerochamber and ACE spacer devices. An MA-1 ventilator set to deliver a V_{T} of 800 mL, of 10/min, and flowrate of 60 L/min. Ventilation was delivered to a Manley test lung (Ohmeda Corp) set on C_{L} 50, R_{AW} 0 through a size 8.0

endotracheal tube (ETT). A servo-controlled Fisher- Paykel heated humidifier (model MR-480) was used to provide approximate saturation of inspired gas between 30-35°C. Each test dose measurement used 5 MDI actuations, and each actuation was spaced 5 breaths apart. Cotton filter material placed at the distal end of the ETT collected the aerosolized drug. The filter was then washed in a glass vial containing 20 mL of ethanol. Spectrophotometric assay at a wavelength of 278 nm was used to measure each sample solution. Statistical analysis was then applied to the collected data. Results:

AeroChamber* MV Holding Chamber		ACE	
Dose (mcg)	Dose (%)	Dose (mcg)	Dose (%)
37.6	41.7	41.0	45.5
47.0	52.2	42.3	47.0
39.5	43.8	30.9	34.3
43.2	48.0	35.2	39.1
31.8	35.3	44.4	49.3
36.9	40.9	39.0	43.3
Mean = 39.3	Mean = 43.7	Mean = 38.8	Mean = 43.1
SD = 5.28	SD = 5.88	SD = 4.98	SD = 5.53

Conclusions: The MV-Aerochamber performed equally as well as the ACE under the outlined study methodology. There was no statistical difference (p=0.8728) detected in the measure of the 6 units tested for the 2 brands using a Mean Whitney U test.

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

The aim of this randomized, double-blind, placebo-controlled trial was to assess the short-term effect of a topical glucocorticoid (budesonide 600 µg twice daily) vs. placebo administered by metered dose inhaler (MDI) and spacer (Aerochamber 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 produces clinical improvement in ventilated preterm infants, without glucocorticoid side effects.

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

The best means for optimal delivery of drugs into lungs of infants with bronchopulmonary dysplasia (BPD) is uncertain. We aimed to measure radio-aerosol deposition of salbutamol by jet nebulizer and metered dose inhalers (MDI) in ventilated and non-ventilated BPD infants. In a randomized, crossover sequence, salbutamol lung deposition was measured using an MDI (2 puffs or 200 micrograms) or sidestream jet nebulizer (5 minutes of nebulization with 100 micrograms/kg) in 10 ventilated (mean birth weight, 1,101 g) and 13 non-ventilated (mean birth weight, 1,093 g) prematurely born infants. Non-ventilated infants inhaled aerosol through a face mask, connected to a nebulizer or an MDI and spacer (Aerochamber). Ventilated infants received aerosol from an MDI + MV15 Aerochamber 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 inter-subject variability in lung deposition and a tendency for the aerosol to be distributed to the central lung regions.

DETERMINANTS OF AEROSOLIZED ALBUTEROL DELIVERY TO MECHANICALLY VENTILATED INFANTS.

Coleman DM, Kelly HW, McWilliams BC. Chest 1996; 110 (4): 1130.

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 and Aerovent, Diemolding Healthcare Div, Canastota, NY; ACE, Monaghan Medical Corp, Plattsburgh, NY; and an in-line MDI adapter, Instrumentation Industries Inc, Pittsburgh). CNA delivered significantly more aerosol to the lung model ($4.8 \pm 0.6\%$ of the starting dose) than INA ($3.8 \pm 0.3\%$; $p < 0.01$). There was a significant stepwise decrease in aerosol delivery with increasing nebulizer flow ($4.8 \pm 1.3\%$ at 5.0 L/min; $3.7 \pm 1.1\%$ at 6.5 L/min; and $2.7 \pm 1.1\%$ 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, demonstrated a marked degree of variability. Most of the starting dose of albuterol either remained in the nebulizer ($30.4 \pm 6.0\%$ at 5.0 L/min and $25.3 \pm 4.1\%$ at 8.0 L/min) or was deposited in the inspiratory tubing ($34.7 \pm 0.7\%$ at 5.0 L/min and $43.7 \pm 4.9\%$ 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.

AeroVent* Collapsible Holding Chamber (AeroChamber* VENT Chamber)

IN VITRO PERFORMANCE OF A NEW COLLAPSIBLE HOLDING CHAMBER FOR THE DELIVERY OF AEROSOLIZED MEDICATION BY PRESSURIZED METERED-DOSE INHALER TO PATIENTS ON MECHANICAL VENTILATION. Nagel MW, Avvakoumova V, Doyle C, Ali R, Mitchell JP, Coppolo DC. Accepted for presentation at American Thoracic Society Annual Conference, May 2012.

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 Corp., 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[®]), 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, Fischer & 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/min) 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 (Fischer & Paykel). Assay of recovered salbutamol was undertaken by HPLC-UV spectrophotometry. Results: Total mass of salbutamol/actuation via each of the devices (mean ± S.D.) 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 [®] 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
	22 mm coupled directly to wye connector	10.9 ± 1.1
RTC 24-V ventilator adapter	15 mm with adapter direct to ETT	10.4 ± 1.7
	Coupled direct to ETT	3.4 ± 1.1
Ballard suction catheter with pMDI port		
Hudson ventilator adapter	22 mm coupled directly to wye connector	14.3 ± 1.9
Fischer & 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 (un-paired 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. Nagel MW, Avvakoumova VA, Ali R, Doyle C, Mitchell J. Proc. 21st ERS Annual Congress, Berlin, Germany, in Eur. Respir. J., 2011; 38S55: 346s.

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*, 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- μ g/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/min) 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 \pm S.D.) from the AeroVent Plus and Spirale CHCs was 22.7 \pm 3.1 and 4.7 \pm 0.7 μ g/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. Ari A, Areabi H, Fink JB. Respir 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/min, peak inspiratory flow 60 L/min, and PEEP 5 cm H₂O). 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 \pm 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 \pm 1.0%, 24.7 \pm 4.4%, and 27.8 \pm 3.3%, respectively) and heated/humidified circuits (16.8 \pm 2.6%, 16.5 \pm 4.3%, and 17 \pm 1.0%, respectively). In contrast, the jet nebulizer was most efficient in position 3 under both non-humidified (14.7 \pm 1.5%) and heated/humidified (6.0 \pm 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 < .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 INLINE SPACER ON DELIVERY OF AEROSOL USING METERED-DOSE INHALER DURING MECHANICAL VENTILATION. Lin HL, Fink JB, Zhou Y, Cheng YS. Respir 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. An AeroVent pMDI spacer was placed in the inspiratory limb of the ventilator circuit and left in an open

position. Eight actuations of HFA albuterol pMDI (720 µg) was administered at 1, 2, and 3 hours after the heater had reached equilibrium at 37°C, and < 10 min after turning off the heater/humidifier. The spacer was dried and returned to the heated circuit for additional testing. Samples were analyzed via spectrophotometer. One-way analysis of variance was applied (P < .05). RESULTS: The delivered drug as a percent of emitted dose (mean ± SD) was greater at hour one (23 ± 2.1%) and with the dry spacer (21.8 ± 3.3%) than at hours 2 and 3 or with humidifier off (11.4 ± 3.8%, 12.3 ± 0.8%, and 12.7 ± 0.3%, respectively, P = .002). Mass median aerodynamic diameters with each comparison did not vary between conditions. Delivery efficiency was similar for the dry spacer and the spacer in the humidified circuit for one hour. However, once visible condensate occurred, drug delivery efficiency decreased by approximately 50%. CONCLUSIONS: Aerosol delivery from a pMDI with spacer during mechanical ventilation was greater with a dry spacer and unchanged for the first hour after initiating heated humidification. Turning off the heated humidifier did not increase drug delivered.

AEROSOL DELIVERY WITH METERED-DOSE INHALER DURING ADULT MECHANICAL VENTILATION: INFLUENCE OF INSPIRATORY FLOW RATE, TIDAL VOLUME, AND ACTUATION ADAPTORS. Lin HL, Zhou Y, Cheng YS, Fink JB. *Resp Care* 2008; 53 (11): 1520.

Background: The deposition of aerosol medications may be influenced by various factors. An *in vitro* model was used to determine the influence of tidal volume, inspiratory flow, and adaptor type on drug delivery and particle size distribution distal to the ETT. Methods: HFA albuterol pMDI (Key Pharmaceuticals) was actuated 8 times using an Aerovent® chamber (Monaghan Medical), a MiniSpacer® dual-spray nozzle (Cardinal Health Corp), and unidirectional nozzle built into the "Y" of the heated-wire ventilator circuit (Fisher & Paykel Inc). An AVEA ventilator (VIASYS Inc) with 2L/min bias flow and 5 cmH₂O PEEP set to deliver: (1) 700 mL VT, 12 breaths/min, 50 L/min IFR; (2) 700 mL VT, 12 b/min, 70 L/min IFR; (3) 400 mL VT, 15 b/min, 50 L/min IFR; (4) 400 mL VT, 15 breaths/min, 30 L/min IFR; and (5) 250 mL VT, 20 b/min, 30 L/min IFR. An Impactor (NGI; MSP) was placed between the ETT and test lung to determine inhaled mass and mass median aerodynamic diameter (MMAD) (n=3). Samples were analyzed via spectrophotometer (224 nm) and a factorial ANOVA was performed (p<0.05). Results: The % of emitted dose (±SE) deposited distal to the endotracheal tube is shown in the figure below. Discussion: Aerosol delivery through an AeroVent spacer yielded significantly higher inhaled mass (p < 0.01). Using this model the changes in volume and inspiratory flow did not significantly change inhaled mass or MMAD. Conclusion: Based on this model, changes in drug delivery do not support changing ventilator flow rate or tidal volumes for administration of albuterol with an HFA pMDI.

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. Coppolo D, Mitchell J, Avvakoumova V, Nagel M. *ATS International Conference, Toronto, 2008; in ARJCCM; 177 (abstracts issue): A383.*

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. We report a laboratory study in which a CHC (AeroVent*; Monaghan Medical Corp., 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*; 90µg/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. 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

ALBUTEROL DELIVERY VIA TRACHEOSTOMY TUBE. Piccuito CM, Hess Dr. *Respir 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/min, 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 semi-circular 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 s). 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. Goode ML, Fink JB, Dhand R, Tobin MJ. *American Journal of Respiratory and Critical Care Medicine* 2001; 163 (1): 109-114.

In mechanically ventilated patients with airway obstruction, helium–oxygen (He–O₂) mixtures reduce airway resistance and improve ventilation, but their influence on aerosol delivery is unknown. Accordingly, we determined the effect of various He–O₂ mixtures on albuterol delivery from metered-dose inhalers (MDIs) and jet nebulizers in an *in vitro* model of mechanical ventilation. Albuterol delivery from a MDI was increased when the ventilator circuit contained 80% helium and 20% oxygen (He–O₂ 80/20) versus O₂: 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–O₂ 80/20 than O₂, and the amount of nebulized drug was inversely correlated with gas density ($r = 0.94$, $p < 0.0001$). When the nebulizer was operated with O₂, greater albuterol delivery was achieved when the ventilator circuit contained He–O₂ rather than O₂. In summary, He–O₂ 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–O₂ 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. Duarte AG, Momii K, Bidani A. *Respir 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 $14.4 \pm 3.8\%$ after 4 MDI puffs, $18.3 \pm 1.8\%$ after 10 MDI puffs, or $13.7 \pm 2.6\%$ 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. Waugh JB. Heart Lung 2000;29 (6): 424-8.

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, quasiexperimental, and random assignment. SETTING: The study was conducted in a university laboratory. MATERIALS: Three brands of MDI spacers (OptiVent, ACE, AeroVent) 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 posttest (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 degrees C-22.8 degrees C (71 degrees -73 degrees F) and a relative humidity range of 57%-65%. RESULTS: Multivariate repeated measures analysis demonstrated a difference between brands ($P < .001$). The amount of water accumulated during 6 hours (time variable) was significantly different ($P < .001$), as was the interaction between time and "spacer brand" (with Greenhouse-Geisser adjustment). The interaction of time and position was also significantly different ($P = .001$). Water accumulations at a 45 degrees angle were: AeroVent 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.

RECONCILING IN VITRO AND IN VIVO MEASUREMENTS OF AEROSOL DELIVERY FROM A METERED-DOSE INHALER DURING MECHANICAL VENTILATION AND DEFINING EFFICIENCY – ENHANCING FACTORS. Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. 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 s; $p < 0.02$) increased aerosol delivery, whereas use of a hydrofluoroalkane (HFA)-propelled MDI decreased aerosol delivery compared with the CFC-propelled MDI. A 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.

A COMPARISON OF BRONCHODILATOR THERAPY DELIVERED BY NEBULIZATION AND METERED-DOSE INHALER IN MECHANICALLY VENTILATED PATIENTS. Marik P, Hogan J, Krikorian J. *Chest* 1999; 115: 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 h and who had normal renal function were randomized to receive the following: (1) five puffs (450 µg) 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 h 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 µg albuterol (38%) was recovered in the urine; with the nebulizer, 409 ± 515 µg albuterol (16%) was recovered in the urine; and with the MDI port on the right-angle adaptor, 41 ± 61 µg 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.

SERUM ALBUTEROL LEVELS IN MECHANICALLY VENTILATED PATIENTS AND HEALTHY SUBJECTS AFTER METERED-DOSE INHALER ADMINISTRATION. Duarte A, Dhand R, Reid R, Fink J, Fahey P, Tobin M, Jenne J. *Am J Respir Crit Care Med.* 1996; 154: 1658-63.

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 a 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 min, 0.98 +/- 0.10 at 10 min, 0.56 +/- 0.08 at 15 min, and 0.37 +/- 0.03 at 30 min in mechanically ventilated patients versus zero at baseline, 0.89 +/- 0.12 at 5 min, 1.27 +/- 0.13 at 10 min, 0.84 +/- 0.09 at 15 min, and 0.53 +/- 0.07 at 30 min in control subjects (p > or = 0.07 at 5, 10, and 30 min; p < or = 0.05 at baseline and at 15 min). Area under the curve (AUC₀₋₃₀) 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 (AUC₀₋₃₀) 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. Coleman DM, Kelly HW, McWilliams BC. *Chest* 1996; 109 (6): 1607-13.

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 and Aerovent, 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, 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. Manthous CA, Chatila W, Schmidt GA, Hall JB. *Chest* 1995; 107: 210-213.

β_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 H₂O 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) at 30-min intervals, while measuring resistive pressure (defined as $P_{\text{peak}} - P_{\text{pause}}$) 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 H₂O ($p < 0.12$). 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. Dhand R, Jubran A, Tobin MJ. *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-min intervals after administration of albuterol for 60 min. Significant decreases in maximum (Rrsmax; $p < 0.01$) and minimum inspiratory resistance (Rrsmin; $p < 0.01$) were present at 5 min and persisted for 60 min after administration of albuterol ($p < 0.01$ for both parameters). Rrsmax indicates maximal inspiratory resistance while Rrsmin represents the ohmic flow resistance. Intrinsic positive end-expiratory pressure decreased significantly ($p < 0.05$) 15 min 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.

PREDICTION AND ASSESSMENT OF BRONCHODILATOR RESPONSE IN MECHANICALLY VENTILATED PATIENTS. Wollam PJ, Kasper CL, Bishop MJ, Pierson DJ. *Respiratory Care* 1994; 39 (7): 730-735.

BACKGROUND: Bronchodilators are commonly prescribed for mechanically ventilated patients, yet uniform indications for and objective assessment of the efficacy of aerosolized bronchodilator use in this population are generally lacking. In this prospective study of consecutive mechanically ventilated patients, we asked, Can we identify a priori those patients who are most likely to respond to inhaled bronchodilators? **MATERIALS & METHODS:** 54 consecutive mechanically ventilated patients in acute respiratory failure participated in the study. We recorded auto-PEEP, PIP, and whether wheezing was present on auscultation before and 15 minutes after the first dose of bronchodilator. Evidence for the presence of reversible airway obstruction (RAO)-diagnosis of COPD or asthma and/or use of inhaled corticosteroids or bronchodilators-was obtained from the patient's chart. The bronchodilator was delivered via metered-dose inhaler with an Aerovent chamber as prescribed by the primary physician. The therapy was deemed indicated if the patient had a history of RAO or if auto-PEEP or wheezing was present. A positive response to bronchodilator was defined as a decrease in wheezing, > 2 cm H₂O decrease in auto-PEEP, or > 4 cm H₂O decrease in PIP. **RESULTS:** 42/54 (78%) patients had at least one indication for bronchodilator. Of these 42, 27 were positive on at least 1 of the 3 response criteria. Of the 12 patients without an indication, only 1 had a positive response (xsquared, p 0.05). **CONCLUSIONS:** Using the information often available to the clinician (eg, limited patient history, physical exam, PIP, and auto-PEEP), it is not possible to predict reliably which patients will benefit from bronchodilator treatment. Based on the results of this study, we recommend an empirical trial of bronchodilator in mechanically ventilated patients for whom a potential indication exists. In the absence of such an indication or if objective measurements fail to document a response, continued bronchodilator administration may not be clinically useful or cost-effective.

ALBUTEROL DELIVERY BY METERED-DOSE INHALER WITH A PEDIATRIC MECHANICAL VENTILATORY CIRCUIT MODEL. Garner SS, Wiest DB, Bradley JW. *Pharmacotherapy*, 1994; 14(2): 210-4.

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 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 2000 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 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 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. Rau JL, Harwood RJ, Groff JL. *Chest* 1992; 102 (3): 924-30.

We investigated the use of a reservoir device for delivery of a 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 reservoir was placed on the inspiratory limb of the ventilator circuit just before the patient Y connector. In method 3, the AeroVent was placed between the patient Y connector and the ETT. Standardized ventilator settings with a Servo 900C were used for all three methods (VE = 9.6 L; respiratory rate = 12

breaths per minute; TI = 20 percent of 1 s). 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 on the inspiratory limb increased this to 32.1 percent and the AeroVent 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 reservoir chamber significantly increased bronchodilator delivery by aerosol with an MDI in an adult lung model of an intubated patient on ventilatory support.

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