Rugrats in the Mist: Challenges in Aerosol Therapy to Infants and Pediatric Patients

James B. Fink, PhD, RRT, FAARC, FCCP
Chief Clinical Officer, Aerogen
Adjunct Professor Respiratory Therapy, Georgia State University and
Rush Medical School, Chicago
Fink.jim@gmail.com

Suncoast Pulmonary Symposium Ft. Myers, FL September 2014

Disclosures

- **Chief Clinical Officer**
  - Aerogen,Ireland
- **Consultant**
  - Dance Biopharm
  - Parion
  - Aridis
  - Novartis
  - Bayer
  - Boerhinger Ingleheim
  - Aerogen
  - WHO
- **Opinions expressed are not those of Georgia State University, Rush or Aerogen**

Optimizing aerosol therapy in pediatrics and neonates

depends on 7 steps:

1. Evaluating the patient
2. Selecting the right aerosol generator.
3. Selecting the right interface.
4. Knowing what to do with crying/distressed children
5. Using the right technique
6. Educating the clinician, patient and their parents
7. Assuring patient compliance

Aerosol Challenges Change with Age

- Preterm newborn infants 28 – 32 wk gest age
- Term newborn infants 1 - 27 days
- Infants 28 days- 5 mos
- Older Infants/ Toddler 6 - 23 mos
- Preschool-Children 2 - 5 years
- School-Children 6 - 11 years
- Adolescents 12 -18 years
- Adults 20 - 90+ years

Weight and V_t @ 50th percentile

Preterm infants	2.5 kg	15.7 mL
Term newborn infants	3.5 kg	22 mL
Infants	6.0 kg	37.8 mL
Toddlers	12.0 kg	75.6 mL
Preschool-Children	20 kg	126 mL
School-Children	36 kg	226.8 mL
Adolescents	41 kg	258.3 mL
Adults	65 kg	409.5 mL

Anatomical Differences with Age

	Infant	Child 8 – 12	Adult
Body Weight, Kg	3	Variable	70
Lung Weight, g	50	350	800
Lung Tissue, % total	28	15	9
Alveoli, million	20 – 150	300	600
Diameter Alveoli, micron	50	150	300N
Resp Airways, million	1.5	14	14
A/C Surface Area, m^2	3	32	70

Anatomical Differences with Age

	Infant	Adult
Tidal volume, mL	6	6
Resp Rate, bpm	35	15
Vital Capacity, mL/kg	35	70
FRC, mL/kg	30	35
TLC, mL/kg	63	86
Lung Compliance, mL/cmH2O	7.9	150
Specific Lung Comp, Ct/FRC	0.038	0.05

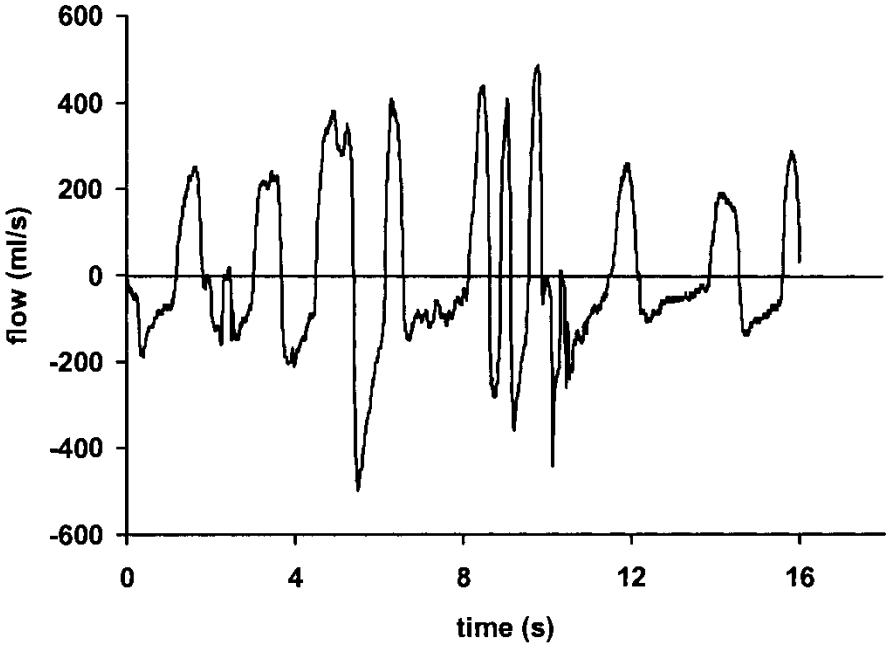
Variability with Age

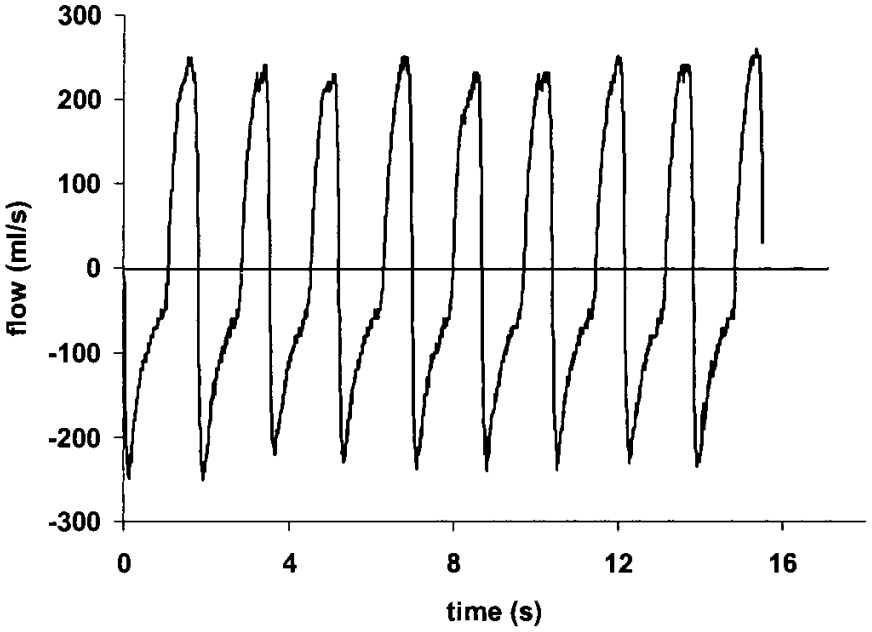
- Airway size
- Respiratory rate
- Flow
- Breathing pattern
- Lung volumes
- Physical and cognitive ability to use device/interface
- Extrathoracic and Inhaled Dose

Aerosol therapy in young children

- Lower aerosol lung deposition than adults
- Young children cannot perform an inhalation manuever
- Can not reliably use a mouthpiece until 3 years
- Often breathe through their nose
- Small volumes with rapid, irregular breathing
- May be distressed during administration
- Can not generate sufficient inspiratory flow to use a DPI until age 5 – 6 years

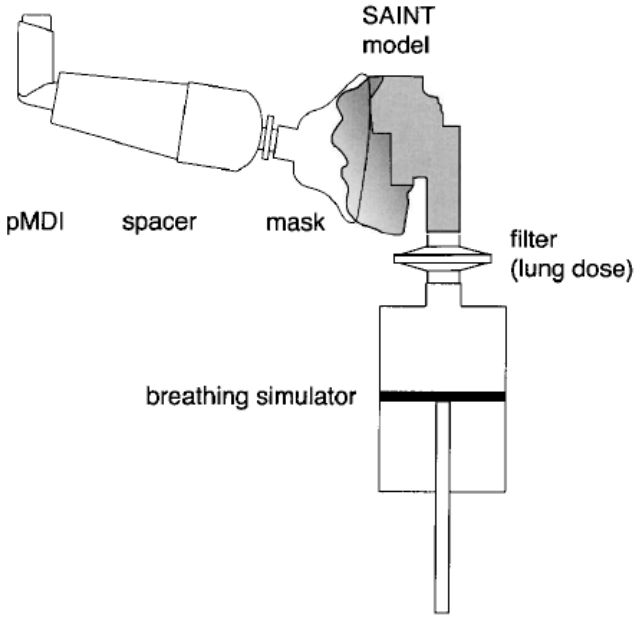
*Example of breathing pattern of a 10-month-old child while **awake** (left) and **asleep** (right)*

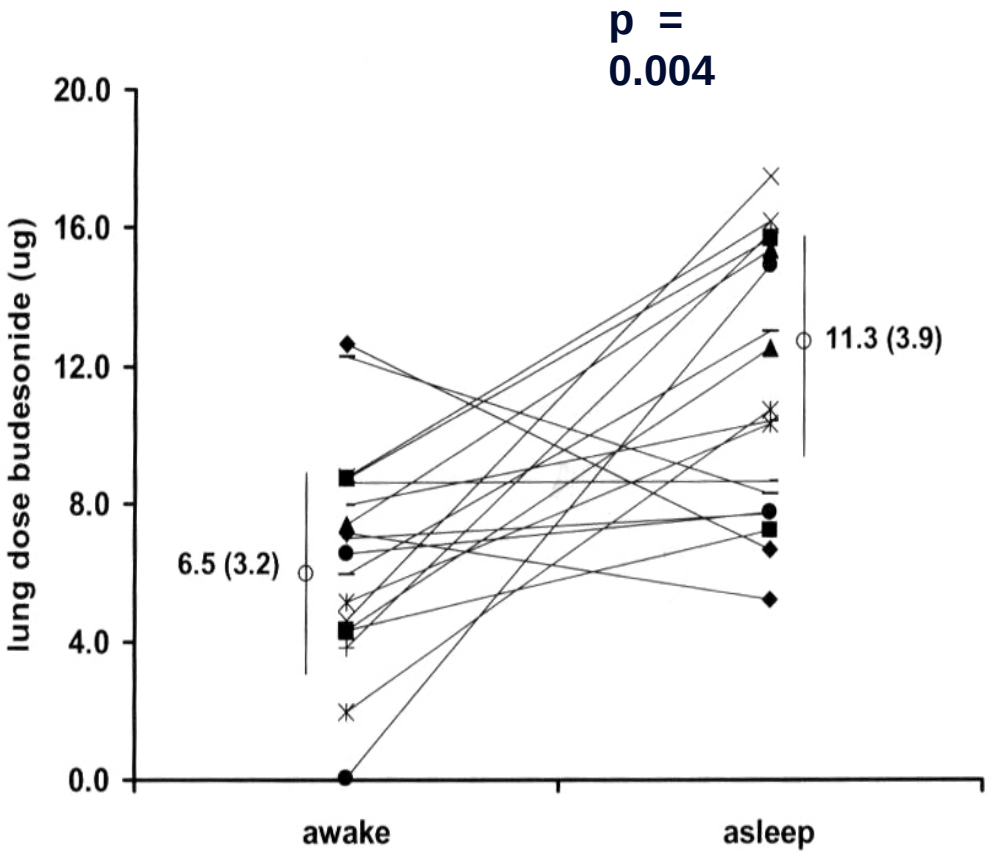




Janssen JM et al. Aerosol therapy and the fighting toddler: Is administration during sleep an alternative? J Aerosol Med 2003, 16: 4: 395-400

In Vitro Method with Sophia Anatomical Infant Nose-Throat (SAINT) model





Face masks are primary interface for infants and small children

- **Face masks can be attached to most nebulizers and valved holding chambers**
- **A good seal is crucial**
- **A small leak can make a big difference in delivered lung dose**
- **Up to 47% of children do not tolerate therapy via face mask and become agitated**
- **During crying dose to the lungs is minimal**

Small Facemask Leak Reduces Lung Dose

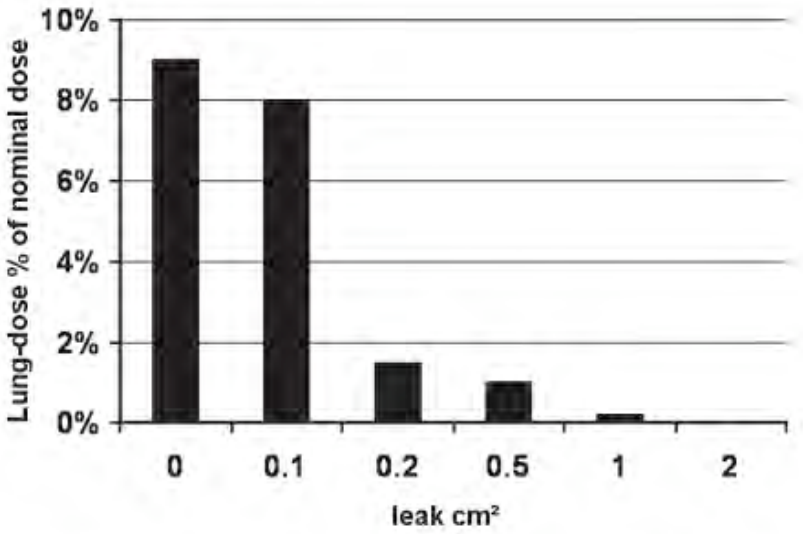
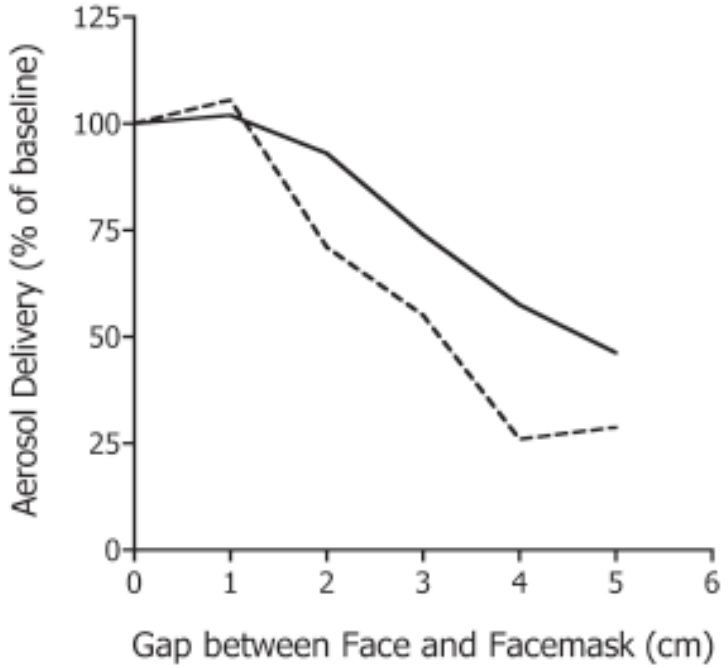


FIG. 1. Effect of facemask leak (cm^2) on lung dose (% of nominal dose) in SAINT model. (Reprinted, with permission, from Esposito et al.[10])

Janssens HM, Tiddens HAWM. JAM 2007, 20: Suppl1: S59-S65



Nikander K et al. JAM 2007. 20:Supp;1:S46 – S58

Agitation Reduces Lung Deposition

- Murakami et al *Ann Allergy 1990; 64*: 383-7

Facemask and Aerosol Delivery In Vivo

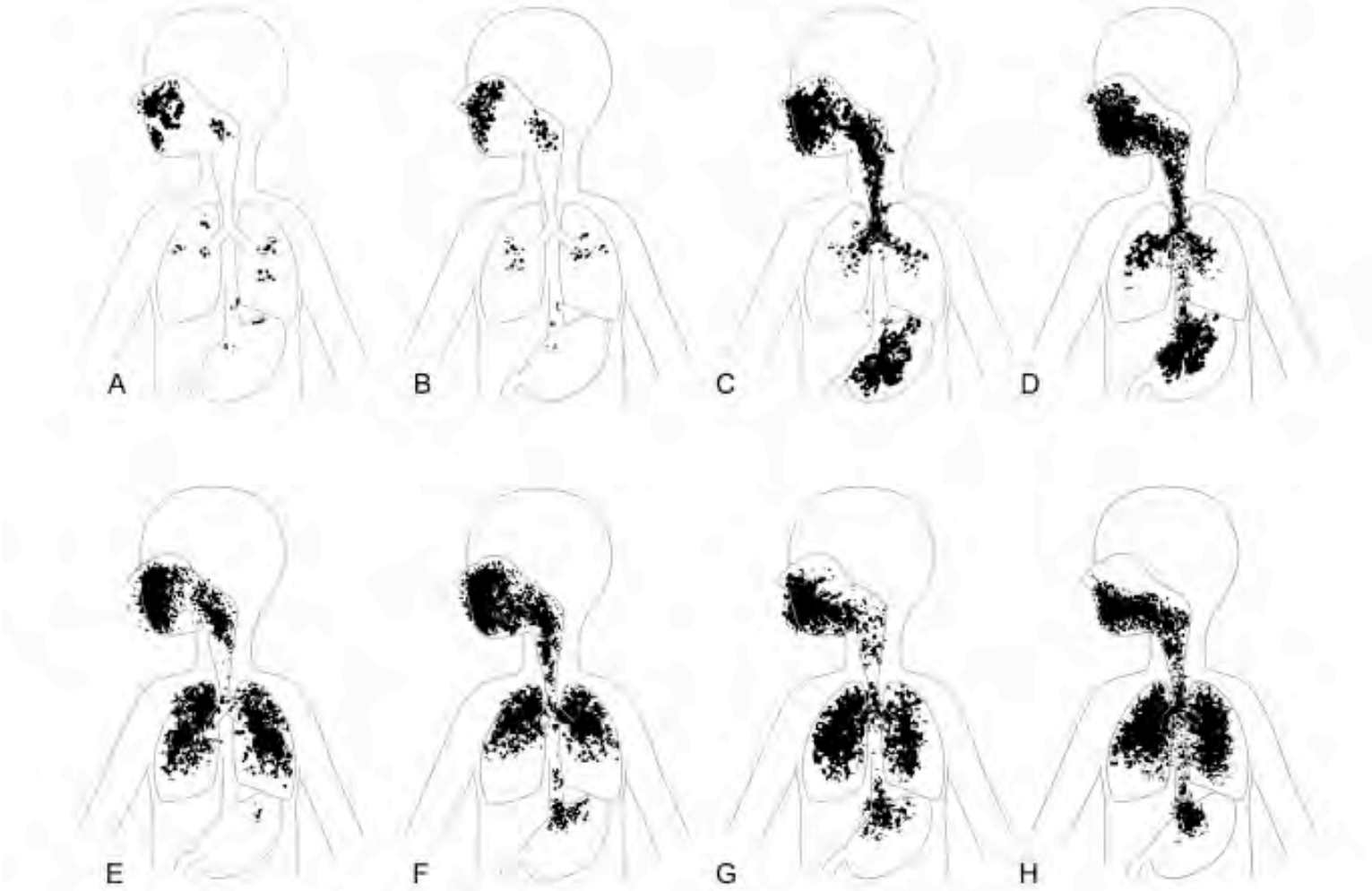


FIG. 1. Drug deposition of radiolabeled Salbutamol in a young child (A) inhaling with a pMDI/spacer through a non-tightly fitted facemask, (B) inhaling with a nebulizer through a non-tightly fitted facemask, (C) inhaling with a pMDI/spacer through a tightly fitted facemask, screaming during inhalation, (D) inhaling with a nebulizer through a tightly fitted facemask, screaming during inhalation, (E,F) inhaling with a pMDI/spacer through a tightly fitted facemask, quietly inhaling, and (G,H) inhaling from a nebulizer through a tightly fitted facemask, quietly inhaling.

Erzinger S et al. JAM 2007 Suppl S78 – S84.

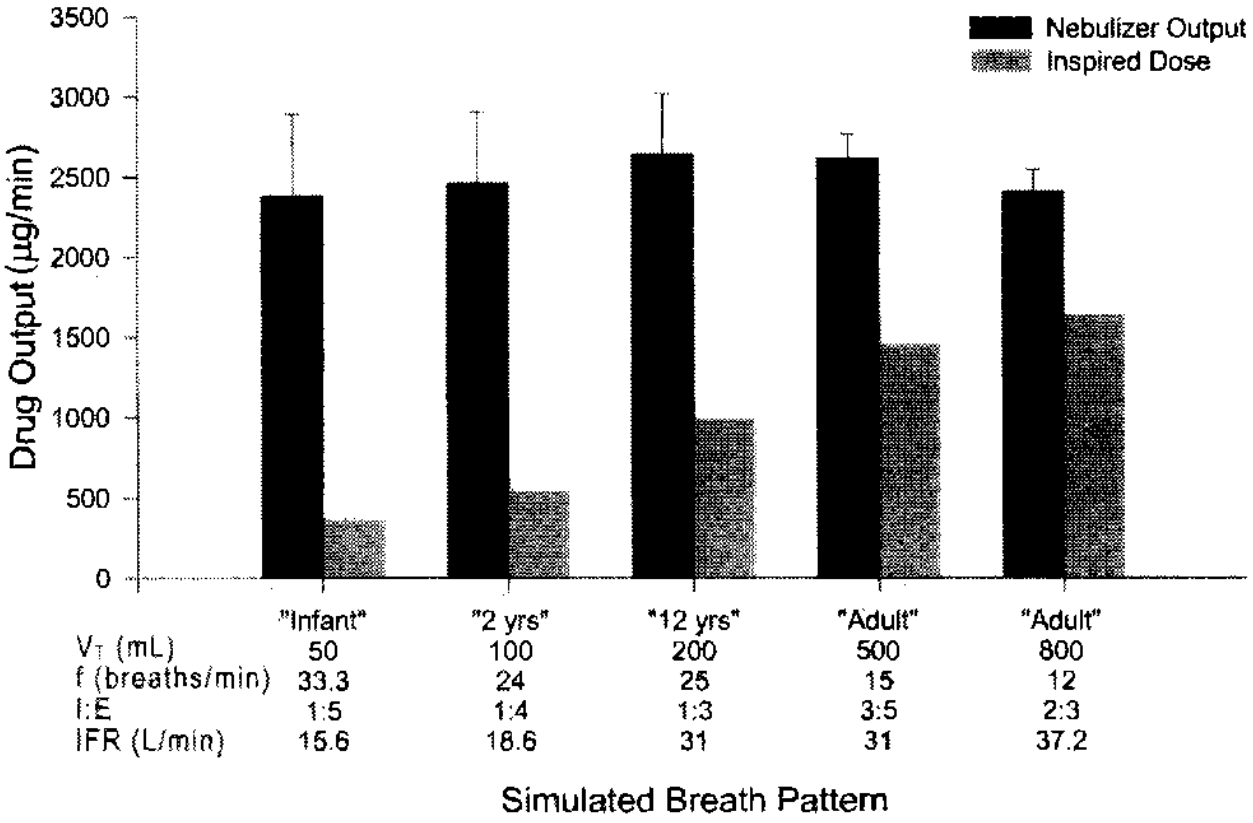
Device requirements change with age and individuals

- **Prescribing clinicians should be aware of the advantages and disadvantages of available inhalation devices for best match of each individual patient.**
- **Proper device selection is critical to adherence and effective therapy.**
- **Optimum device selection changes with patient age, size and abilities**
- **Many clinicians are ill prepared to make proper device selection**

Selecting Appropriate Devices

- **Small volume nebulizers (SVN)**
  - Jet nebulizer (JN)
  - Breath-actuated nebulizers (BAN)
  - Vibrating mesh nebulizer (VMN)
  - Ultrasonic nebulizer (UN)
- **Large volume nebulizers (LVN)**
- **Pressurized metered-dose inhalers (pMDI)**
  - Traditional pMDIs
  - pMDIs with Valved Holding Chambers
  - Breath-actuated pMDI
- **Dry powder inhalers (DPI)**

Breathing Pattern Impact on Inspired Dose In Vitro



Dolovich MB. Assessing nebulizer performance. Respir Care 2002; 47(11): 1290 – 1301.Fig 12

Flow Limits the Ability of Children to Use Passive DPI

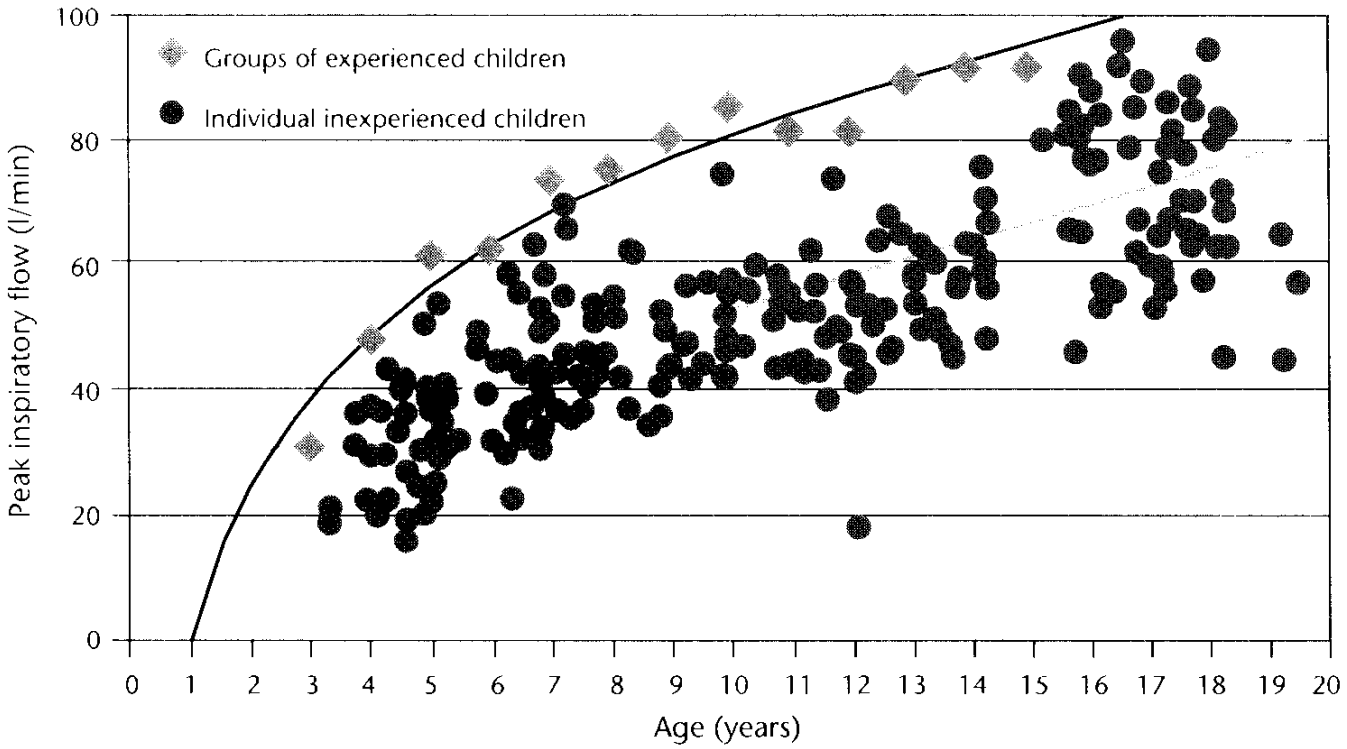


Figure 1. *Peak inspiratory flows in individual inexperienced children (Pedersen* et al, *1990) and groups of experienced children (Agertoft* et al, *1995).*

Selecting Appropriate Interface

Types of Interfaces Used with Aerosol Generators:

- Mouthpiece
- Face Mask
- Blow-by
- Hood
- High Flow Nasal Cannula
- pMDI Accessory Devices
  - Spacer
  - Valved Holding Chamber (VHC)

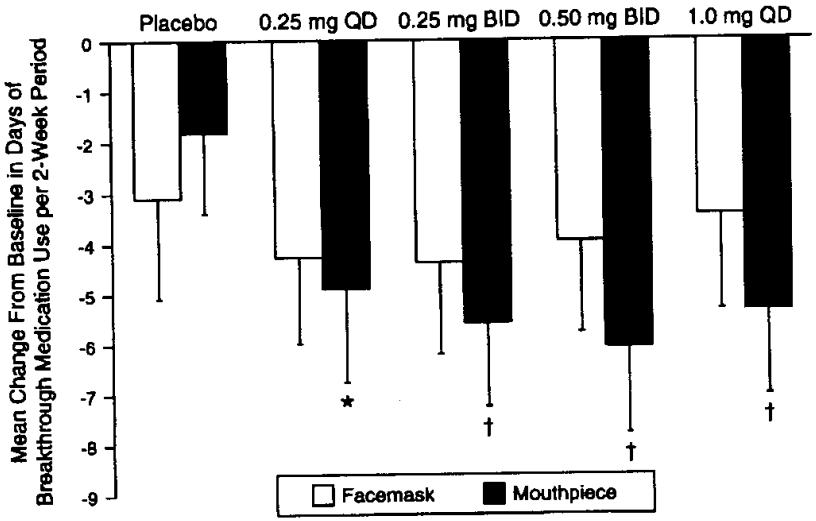
Rau JL. & Smaldone GC. J Aerosol Med 2007; 20(1): 1-2.

Selecting Appropriate Interface

CHOOSING AN AEROSOL GENERATOR & INTERFACE FOR CHILDREN OF DIFFERENT AGES				
	AGE			
	< 4 Years	**≥ 4 Years**	**≥ 5 years**	**≥ 9 years**
Aerosol Generator	Nebulizer or pMDI + VHC	pMDI + VHC or DPI	pMDI, BAN , Breath actuated pMDI All Devices	All Devices
Interface	Mask, Hood, or HFNC	Mask Mouthpiece	Mouthpiece	Mouthpiece

Ari and Fink. Expert Rev Respir Med. 2011 Aug;5(4):561-72.

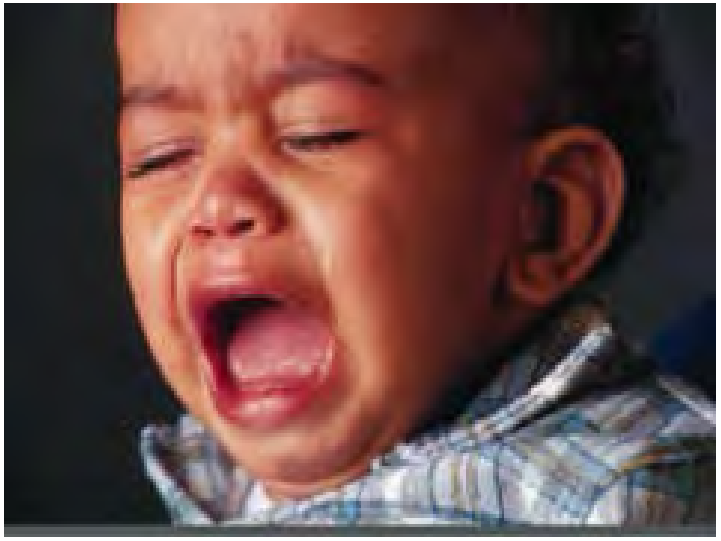
Mask vs Mouthpiece Yield Similar Clinical Outcomes



Adjusted mean changes from baseline in days per 2 wk interval of breakthrough medication use. *p=0.0008 for budesonide at 0.25 mg daily versus placebo; †p<0.001 For budesonide at 0.25 mg twice daily, 0.5 mg twice daily and 1.0 daily versus placebo. Facemask and mouthpiece were similar at each dose.

Mellon AJRCCM 2000. 162: 593-598.

Alternatives to Facemasks:



- **Hoods**
- **Blow by**
  - Less fuss
  - Less aerosol inhaled
  - Unreliable method for dosing

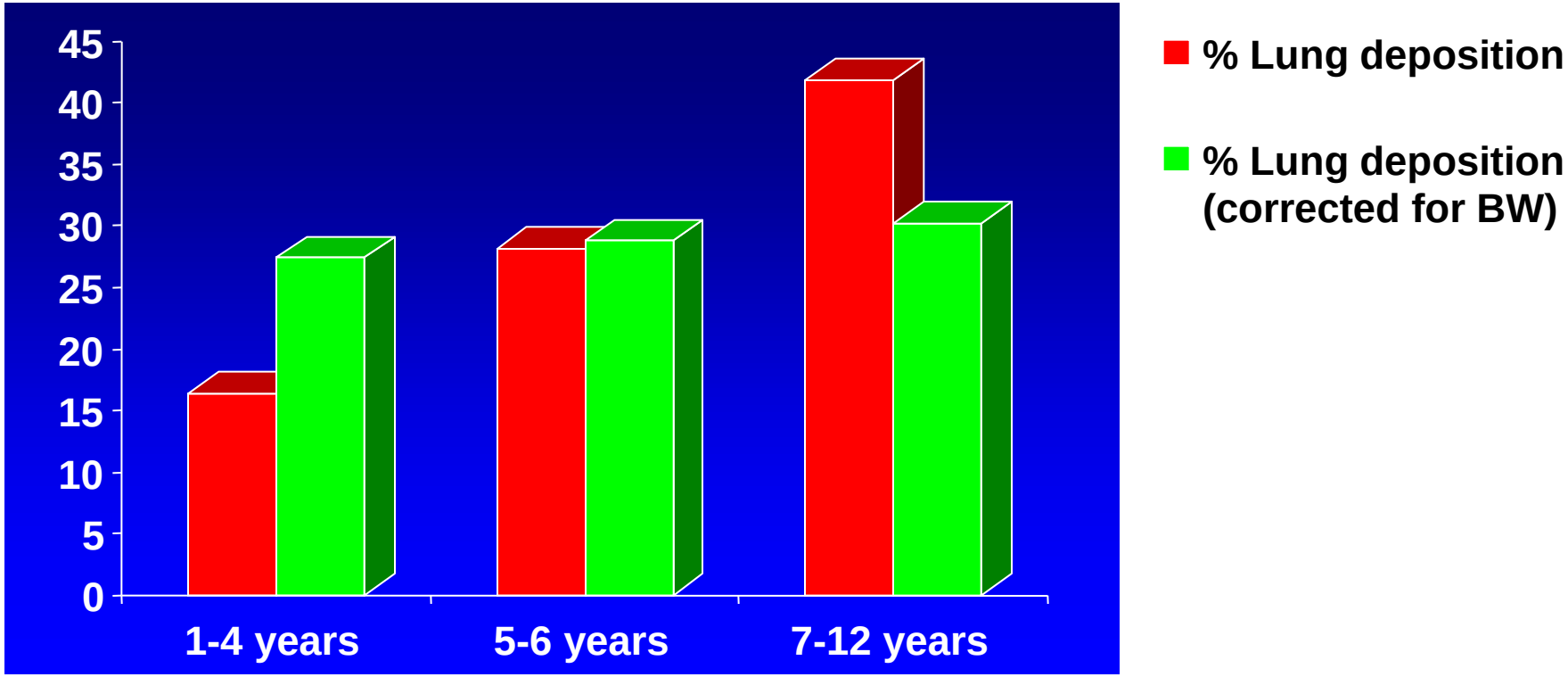
Pediatric Aerosols
Indication and Use

- **Indication for pediatric use of drugs is generally based on extrapolation from adults with supportive pediatric data**
  - Identify appropriate dose
  - Establish Safety of the dose
- **Safety Assessment**
  - During Clinical Trials
    - Monitoring of Adverse Events
    - Lab Parameters
  - Direct assessment of systemic effects
  - Assessment of linear growth
  - Monitoring post marketing AE reports
- **Since Ribavirin, no inhaled drug and few aerosol devices were primarily designed and approved for use with infants and small children**

Do Adult Doses Work with Infants and Children?

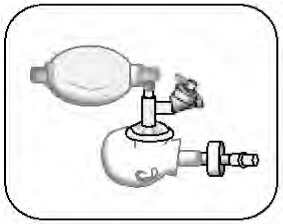
- **Inadequate clinical trials in infants and small children < 2 years**
- **Dose/kg of body weight appears similar across ages**
- **Requirements for plan and testing of drugs in pediatric populations create real issues for industry**
- **Especially when the primary drug/device combination is not suitable for the younger range of peds population**

Lung deposition of Aerosol from pMDI with holding chamber: Corrected for BW

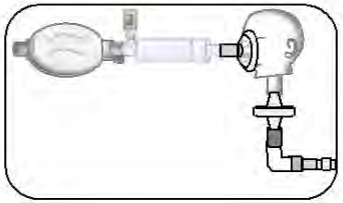


Adapted from Wildhaber. High percentage lung delivery in children from detergent-treated spacers. Pediatr Pulmonol 2000; 29: 389-393.

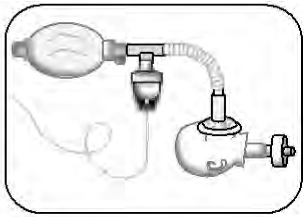
Aerosol to Infants with Ambu Bag: Passive and Active



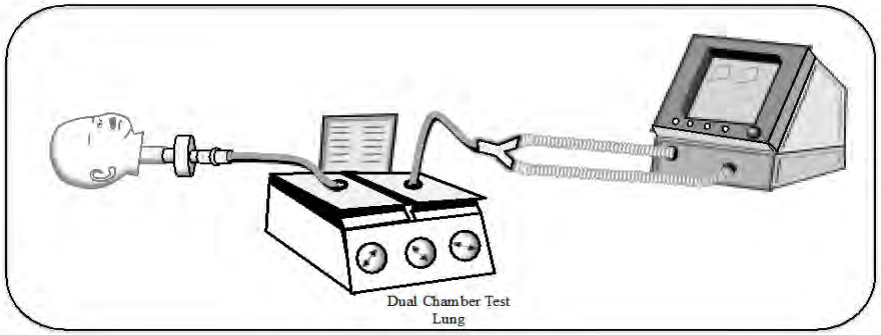
Vibrating Mesh Nebulizer



pMDI/VHC

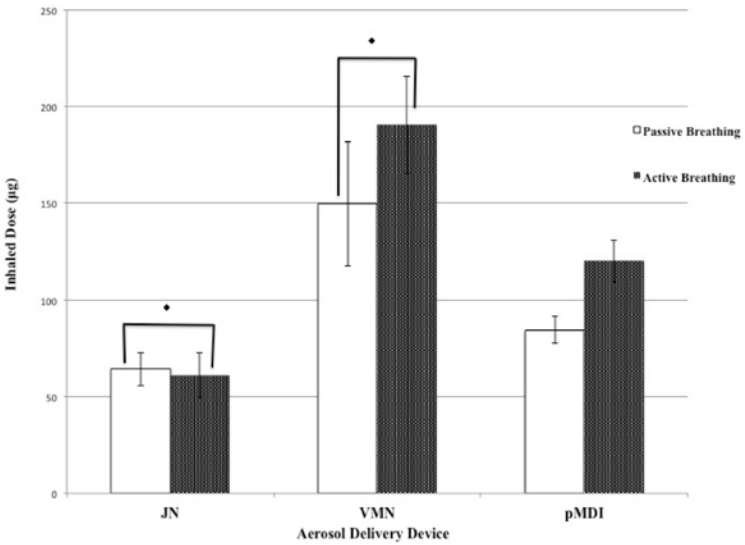


Jet Nebulizer



Vt of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4

Aerosol Device	Passive Breathing	Active Breathing	*p*-values
JN (%)	2.57 ± 0.34	2.45 ± 0.46	0.729
VMN (%)	5.99 ± 1.28	7.62 ± 1.01	0.157
pMDI/VHC (%)	19.55 ± 1.60	27.84 ± 2.52	0.013
p-values	0.0001	0.0001	

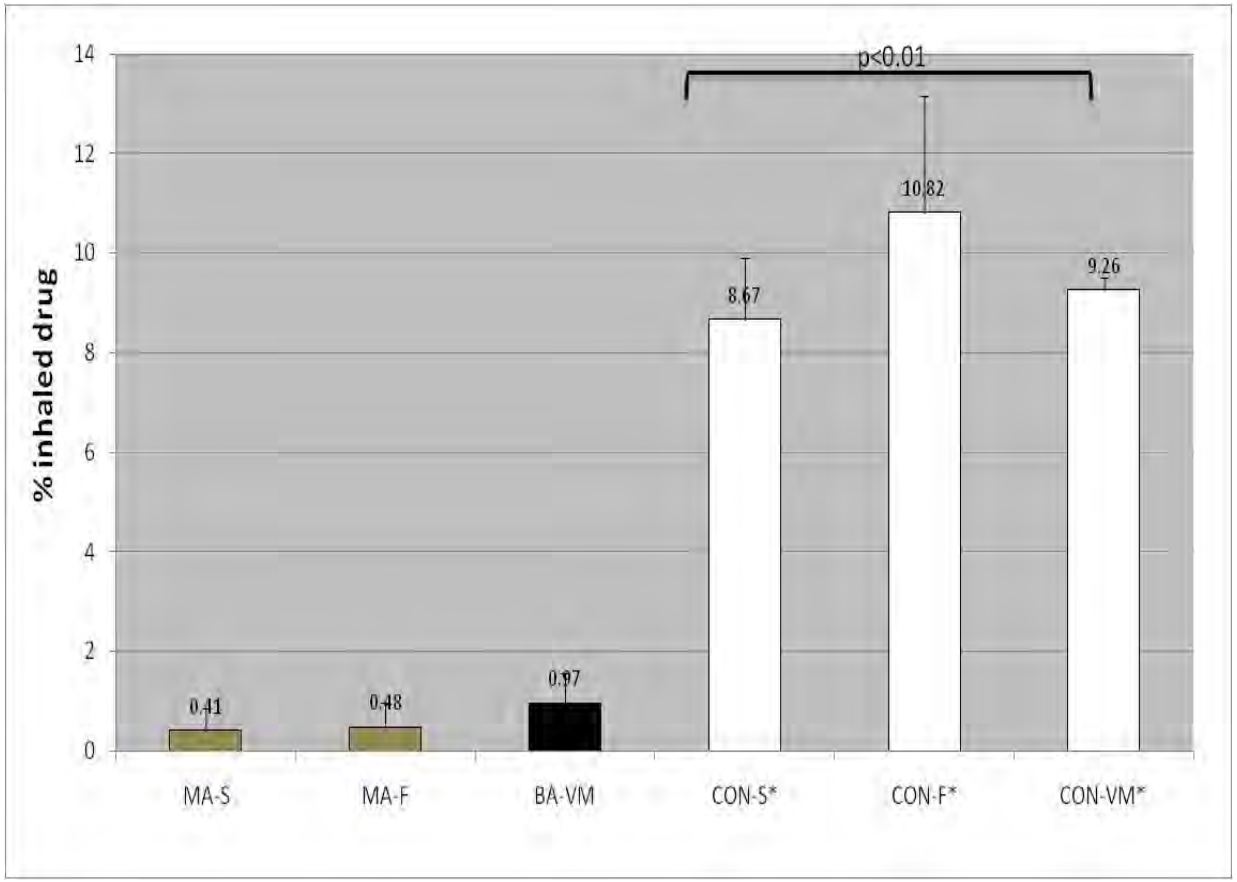


Huriah H. Al Sultan

Breath Actuated Nebulizer vs Continuous Jet Neb with Toddler

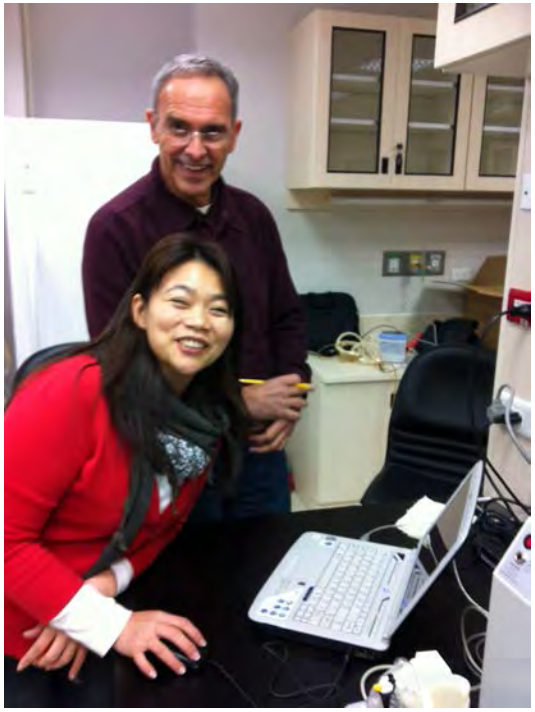
Vt 155 mL

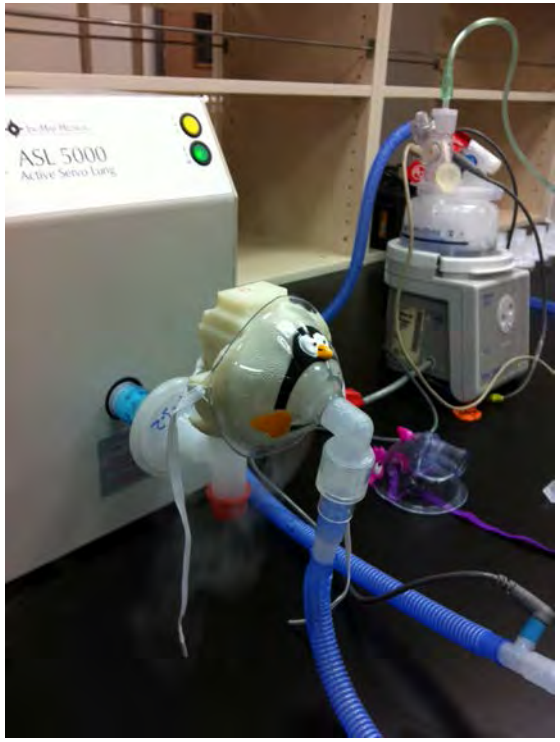
PIF 20 lpm



Lin et al, Respir Care, 2012

Effect of Flow Rate on Aerosol from VM via Mask
Professors Lin and Harwood
Chang Gung University, Tao-Yuan, Taiwan





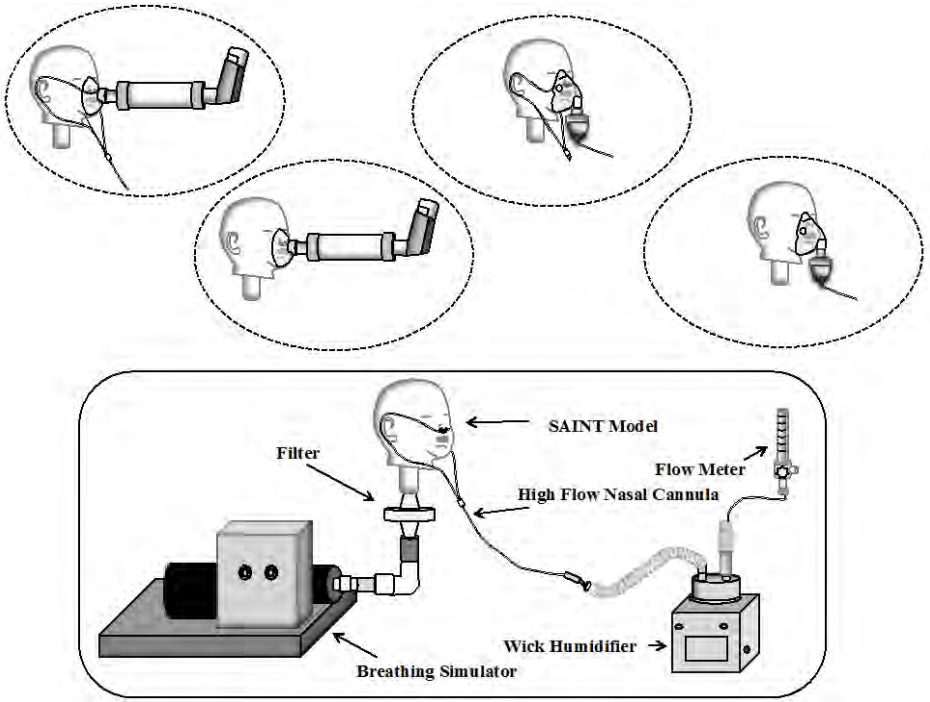
Mask	Dragon Mask		Oxykid Mask	
Flow	Infant	Pediatrics	Infant	Pediatrics
3	4.7±0.82	5.03±1.39	6.44±1.2	7.33±1.09
6	6.24±1.28	8.06±1.12	4.2±0.77	5.81±0.62
12*	3.17±0.44	5.73±0.21	2.75±0.16	3.4±0.36

Aeroneb Solo Off Vent AdaptER

O2 L/min	Mouthpiece	Open Facemask	Valved Facemask
0	71.7 ± 1.1	1.9 ± 0.4	49.6 ± 0.9
2	62.4 ± 1.3	49.5 ± 2.7	64.2 ± 1.9
4	59.3 ± 0.5	45.5 ± 4.4	57.1 ± 1.5
6	55.1 ± 0.9	46.7 ± 1.4	57.3 ± 1.7

Aerogen

Aerosol to infants with and without HFNC



Vt of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4.

Aerosol Device	With HFNC	Without HFNC	*p*-value
Jet Nebulizer	2.91 ± 0.23	6.05 ± 1.53	0.024
pMDI	6.04 ± 0.28	39.54 ± 8.98	0.003
p-value	0.0001	0.003	

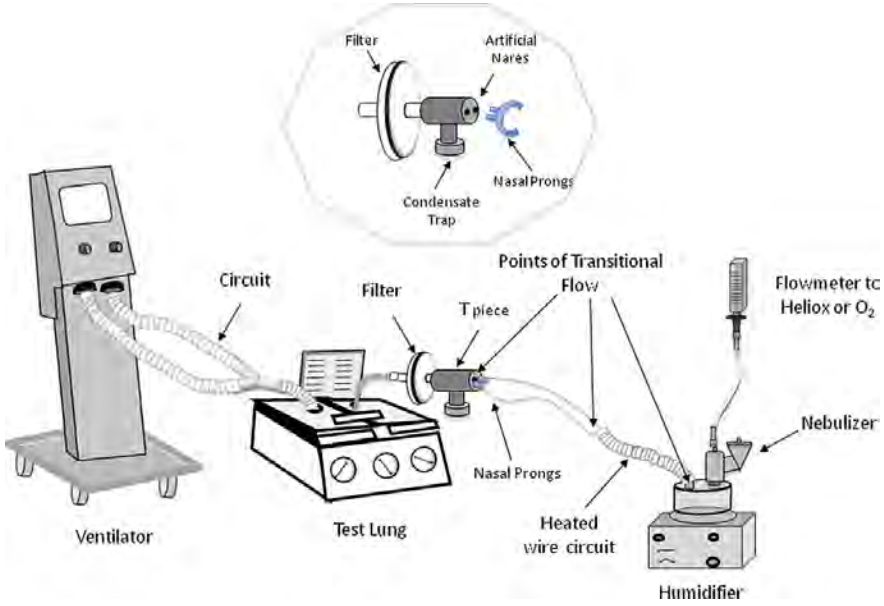
Mahmood Ahmed Alalwan

Aerosol Delivery with High Flow Nasal Cannula
Pediatric Cannula

GAS/FLOW	3 LPM	6 LPM	p-values between Flow Rates
Heliox (80/20%)	11.41 ± 1.54	5.42 ± 0.54	p=0.028
Oxygen (100%)	10.65 ± 0.51	1.95 ± 0.50	p=0.002
p-values between Heliox and Oxygen	p=0.465	p=0.01	

Vt – 100 mL

RR – 30 BPM

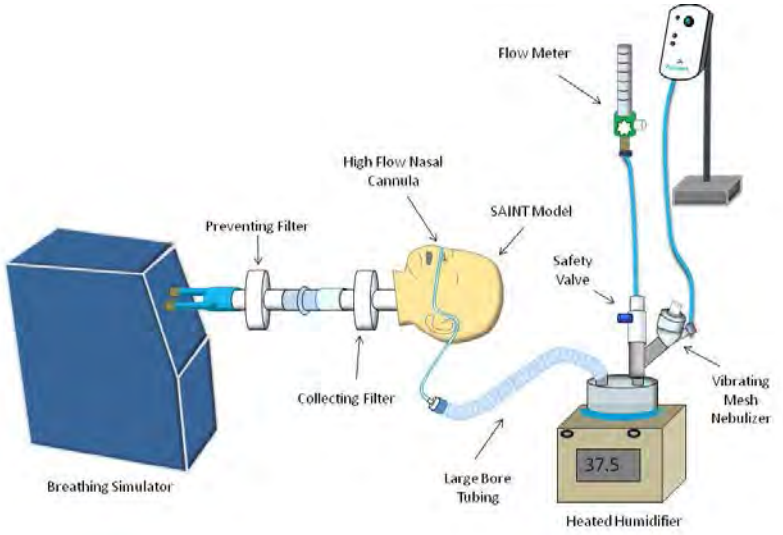


Ari, Dailey, Fink , Peds Pulm, 2011

Aerosol Delivery to Trachea of Neonate Model

Vt – 8 mL
RR – 50 BPM

Cannula size impacts Aerosol Delivery



	INFANT CANNULA		PEDIATRIC CANNULA	
	3 LPM	6 LPM	3 LPM	6 LPM
Fisher Paykel	5.69 ± 0.77	4.78 ± 1.13	13.2 ± 3.29	9.06 ± 2.75
Hudson RCI	4.66 ± 1.10	4.52 ± 0.73	5.75 ± 0.54	4.14 ± 0.38
Vapotherm	4.88 ± 0.42	6.10 ± 1.10	7.17 ± 0.22	7.05 ± 1.10

COMPARISON OF THE RAM CANNULA WITH HIGH FLOW NASAL CANNULA ON AEROSOL DRUG DELIVERY IN A SIMULATED NEONATAL LUNG MODEL

Arzu Ari PhD RRT PT CPFT FAARC[1], Robert Harwood MSA RRT[1], Hui-Ling Lin MS RRT[2], Robert DiBlasi RRT-NPS FAARC[3], William Callas RRT-NPS[4], Meryl Sheard MS RPFT[1], Debbie Gilley RRT-NPS[4], Tracey Roberts RRT-NPS[4], Vickie Arnolde RRT-NPS[4], James B. Fink PhD RRT FAARC, FCCP[1]

1. Georgia State University, Atlanta, GA, USA, 2. Chang Gung University, Taoyuan, Taiwan,
3. Seattle Children's Research Institute, Seattle, WA, USA 4. Lucile Packard Children's Hospital at Stanford, Palo Alto, CA.

Background:

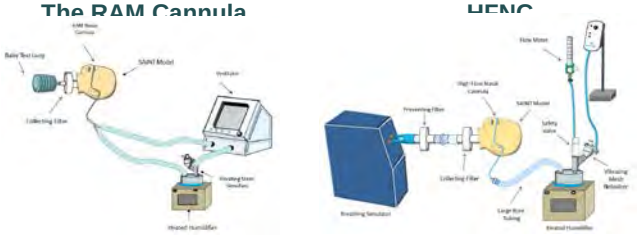
Aerosol delivery through HFNC has been described with in vitro models. The RAM cannula, which is used with noninvasive ventilation (NIV) for support of ventilator-dependent patients, has not been characterized for aerosol delivery.

Purpose: To compare HFNC with RAM cannula on aerosol delivery in a simulated neonatal lung model.

Methods

Lung Model: An in-vitro airway/lung model, using the DiBlasi newborn upper airway model attached to a collecting filter. While the RAM cannula (Premie RAM Cannula, Neotech) was used to ventilate a passive test lung via NIV, an infant HFNC cannula (Fisher& Paykel) was placed in the nares of the model attached to a sinusoidal pump simulating a spontaneously breathing newborn (Figure 1).

Figure 1. Experimental set-up of the study.



Methods

Breathing Parameters Used with HFNC:
Respiratory rate 50 breaths/min, tidal volume 8ml and I:E ratio 1:2 simulating a 1.2 kg infant.

Ventilator Parameters Used with RAM: Based on the RAM manufacturer's recommendations, two ventilator settings were utilized: Minimum & Maximum

	PIP	PEEP	TI	RR
Minimum	15 cmH_2O	5 cmH_2O	0.5 sec	40/min
Maximum	30 cmH_2O	8 cmH_2O	1 sec	48/min

Data Collection: A vibrating mesh nebulizer (Aeroneb Solo, Aerogen) was placed at the inspiratory inlet of a heated humidifier (Fisher&Paykel) in which the temperature was held constant at 37 ° C.

Albuterol sulfate (2.5mg/3mL) was nebulized through the HFNC and the RAM cannula connected to the HFNC and ventilator circuit, respectively.

Data Analysis: Drug deposited on a filter distal to the model's trachea was eluted and analyzed via spectrophotometry.

Independent and paired sample t-test were used for data analysis ($p<0.05$).

Results

Deposition of inhaled dose at the trachea (expressed as mean mass and % of nominal dose ± SD) is shown in the table below.

Comparisons of the RAM cannula with HFNC showed that the RAM cannula delivers significantly less aerosols than HFNC at both 3 lpm ($p=0.002$) and 6 lpm ($p=0.022$).

Using minimum settings with the RAM cannula increases dose efficiency ($p=0.033$) during mechanical ventilation. Decreasing flow rate from 6 to 3 L/min increases aerosol delivery with HFNC ($p=0.119$).

Cannulae Type	RAM		HFNC	
Settings	**Minimum**	**Maximum**	**3 lpm**	**6 lpm**
Inhaled mass (mcg)	16.53 ± 2.9	10.03 ± 2.0	39.96±5.5	28.63 ± 8.6
Inhaled mass Percent (%)	0.66 ± 0.1	0.4 ± 0.08	1.60 ± 0.2	1.14 ± 0.3

Conclusion

For the settings used in this study, aerosol delivery via HFNC is more efficient than the RAM cannula during NIV in this simulated neonatal lung model.

Comparison of HFNC, Bubble CPAP and SiPAP on Aerosol Delivery in Premature Babies: An In-Vitro Study

F Sunbul , JB, R Harwood, A Ari

Georgia State University, Atlanta, GA, USA

Aerosol drug delivery via high flow nasal cannula (HFNC), bubble continuous positive airway pressure (CPAP) and synchronized inspiratory positive airway pressure (SiPAP) has not been quantified in spontaneously breathing premature infants.

A breath simulator set to preterm infant settings (Vt: 9 ml, RR: 50 bpm and Ti:0.5 sec) was connected via collecting filter to the trachea of a preterm infant model(DiBlasi) HFNC (Fisher&Paykel), Bubble CPAP (Fisher&Paykel) and SiPAP (Carefusion) were set to deliver 5 cmH_2O and attached to the model via their proprietary nasal cannula. Albuterol sulfate (2.5 mg/3mL) was aerosolized with a mesh nebulizer (Aeroneb Solo) positioned (1) proximal to the patient and (2) prior to the humidifier (n=5). Drug was eluted from the filter with 0.1 N HCl with analysis via spectrophotometry (276 nm). Descriptive statistics, t-test and ANOVA were applied, with $p<0.05$ significant. Table shows percent of dose (mean ± SD) deposited distal to the trachea. At position 1 the trend to lower deposition across devices was not signficiant, however, in position 2, drug delivery with SiPAP was less compared to both HFNC ($p=0.003$) and bubble CPAP ($p=0.008$) Placement of the nebulizer prior to the humidifier increased deposition with all devices (p,0.05). Device selection and nebulizer position impacted aerosol delivery in this simulated model of a spontaneously breathing preterm infant .

	HFNC	Bubble CPAP	SiPAP
Position 1: Proximal to the patient	0.90 ± 0.26	0.70 ± 0.16	0.59 ± 0.19
Position 2: Prior to the humidifier	1.30 ± 0.17	1.24 ± 0.24	0.79 ± 0.11

QUANTIFYING AEROSOL DELIVERY IN NEWBORNS, INFANTS AND TODDLER USING DIFFERENT DRUG DOSAGES WITH HIGH FLOW NASAL CANNULA

Arzu Ari, PhD, RRT, PT, CPFT, FAARC, Robert Harwood, MSA, RRT, Meryl Sheard, MS, RPFT,
James B. Fink, PhD, RRT, FAARC, FCCP
Georgia State University, Division of Respiratory Therapy, Atlanta, GA, United States.

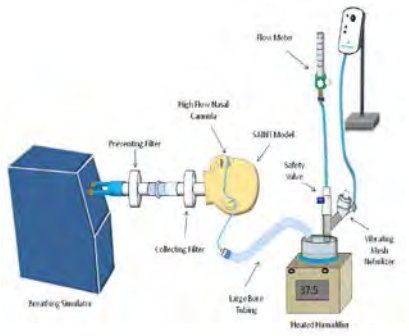
Background

There is little information in the literature quantifying aerosol drug delivery to children via high flow nasal cannula.

The objective of this study was to quantify aerosol delivery with breathing patterns of term newborns, infants and toddlers at two different drug dose volumes using a vibrating mesh nebulizer with a pediatric high flow nasal cannula (HFNC).

Methods

Lung Model: An in-vitro lung model consisting of a SAINT infant upper airway with collecting filter at the trachea was attached to a breathing simulator using breathing parameters.



Methods

Breathing Parameters: Vt 25 ml, RR 40/min for term newborns, Vt 50 ml, RR 33 /min for infants, and Vt 100 ml, RR 24/min for toddlers. The I:E ratio was set at 1:2 in all runs.

Data Collection & Analysis: A vibrating mesh nebulizer (Aeroneb Solo, Aerogen) was placed at the inspiratory inlet of a heated humidifier (Fisher& Paykel) in which the temperature was held constant at 37 ˚ C while oxygen was administered via heated wire circuit to a pediatric nasal cannula at 6 lpm. Albuterol sulfate (2.5 mg) was nebulized in two dose volumes (0.5 mL and 3 mL). Drug deposited on an absolute filter distal to the model's trachea was eluted and analyzed via spectrophotometry (276 nm). One-way ANOVA and paired samples t-test were used for data analysis ($p<0.05$).

	Term Newborn	Infant	Toddler	
2.5mg/0.5 mL	17.66±2.83	25.91±3.62	13.80±3.42	p=0.011
2.5 mg/3 mL	13.77±0.98	17.43±0.84	17.20±0.15	p=0.002
p values	p=0.068	p=0.062	p=0.236	

Results

The percent (%) of nominal dose delivered to the trachea (mean ± SD) and p values are presented in the table below. Delivered doses of albuterol ranges between 13.8% and 17.7% with both dose volumes for the neborn and toddler breathing parameters.

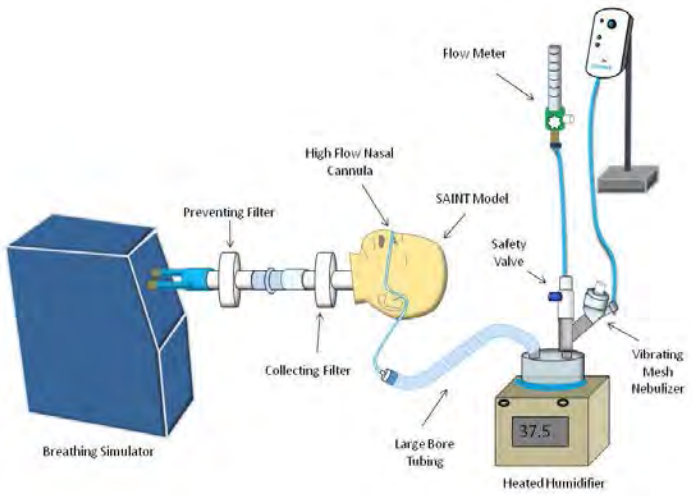
Greater deposition was observed witthe 0.5 mL dose under infant parameters than with term newborn or toddler parameters ($p<0.05$). Increasing tidal volumes with decreasing respiratory rates did not correlate with increased delivered doses.

Conclusions

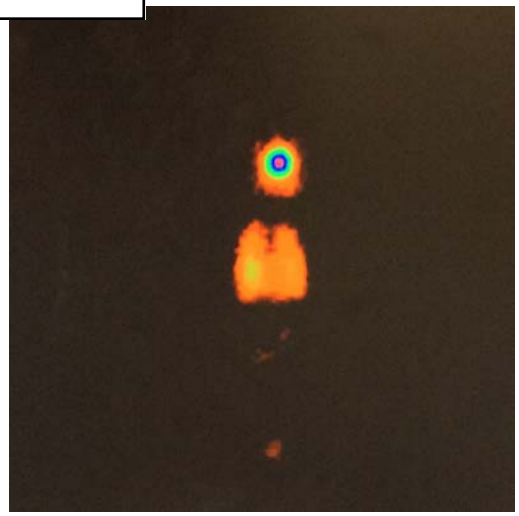
In this simulated model of aerosol delivery via HFNC to newborns through toddlers, deposition to the level of the trachea was similar across the breathing patterns tested, and similar or greater with the smaller dose volumes used with the vibrating mesh nebulizer.

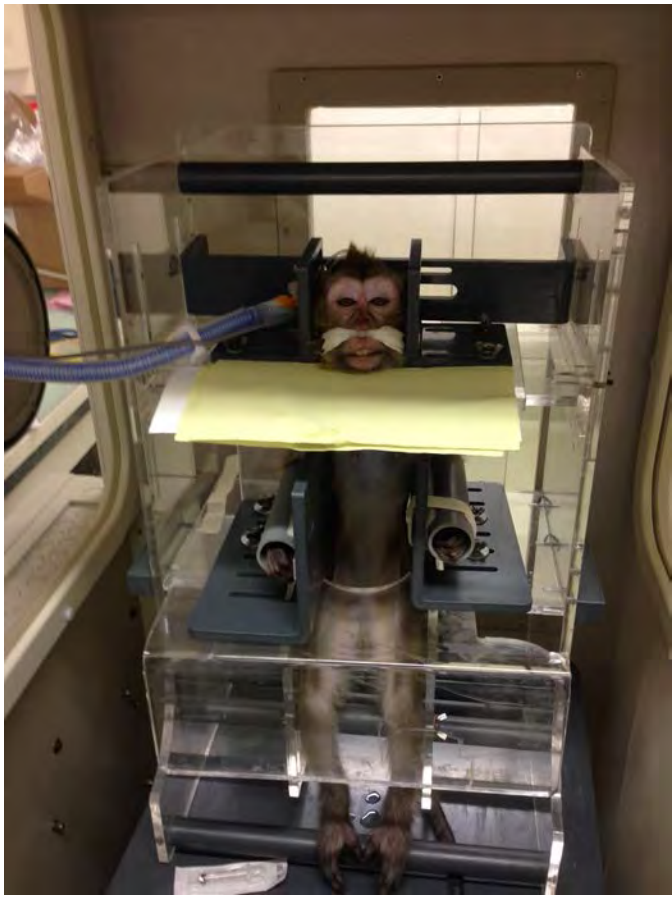
Aerosol Delivery via HFNC with Oxygen and Heliox

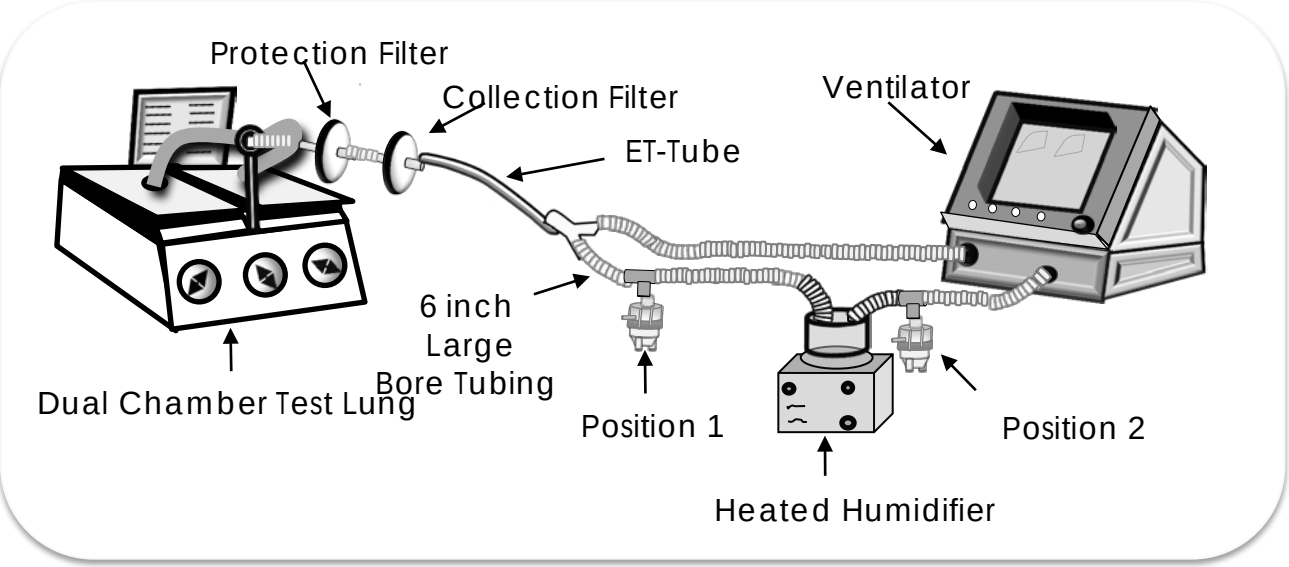
HFNC	FLOW RATE	HELIOX	OXYGEN
ADULT HFNC	30 LPM	14.2 ± 0.8	11.5 ± 1.1
	50 LPM	5.8 ± 1.7	3.5 ± 0.1
PEDIATRIC HFNC	3 LPM	11.4 ± 1.5	10.6 ± 0.5
	6 LPM	5.4 ± 0.5	1.9 ± 0.5
INFANT HFNC	3 LPM	4.5 ± 0.6%	5.7 ± 0.7%
	6 LPM	6.9 ± 0.5%	4.7 ± 1.1%



High Flow Nasal Cannula - Macaque



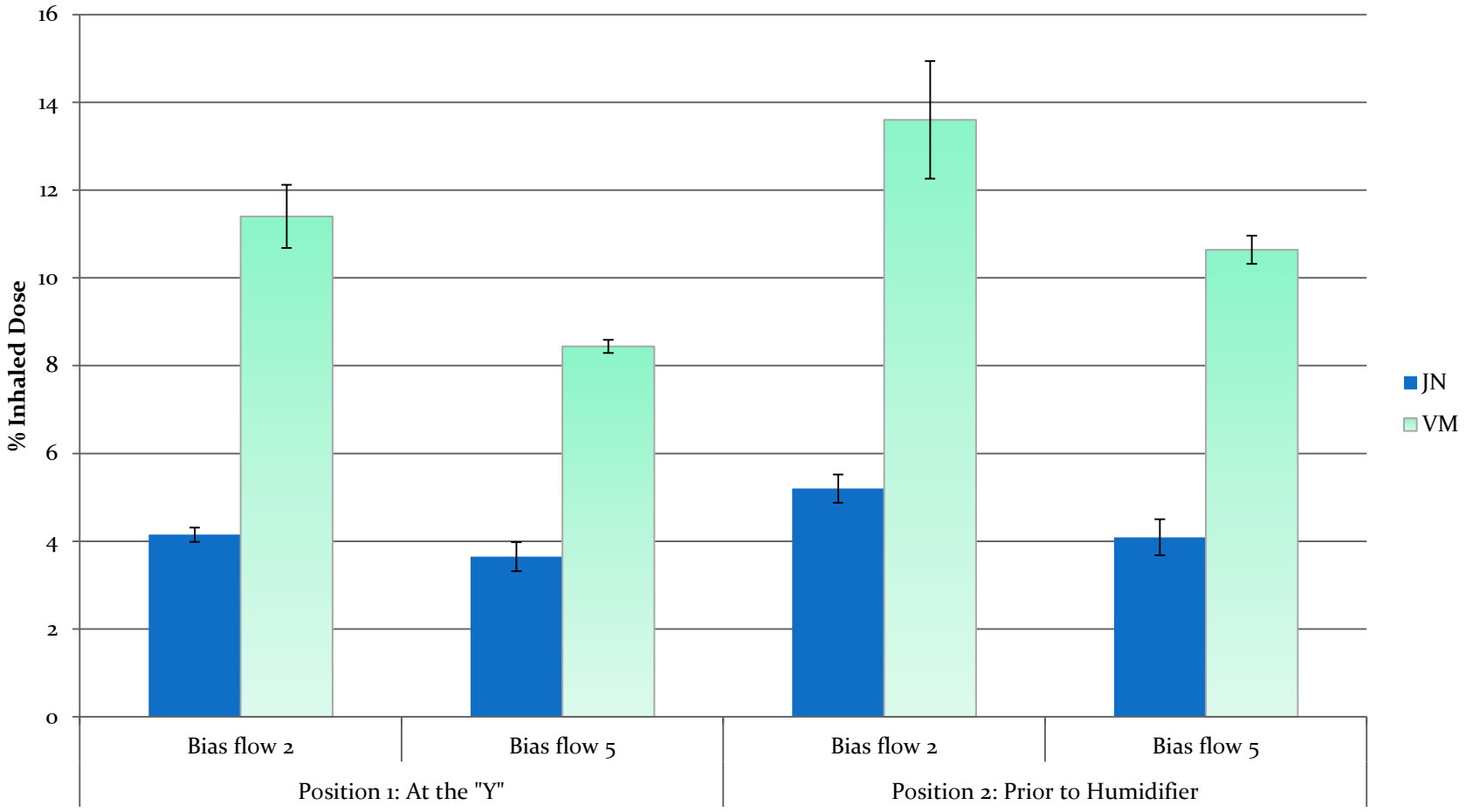




	ADULT STUDY	PEDIATRIC STUDY
Mode	Volume Control	Volume Control
Tidal Volume	500 ml	100 ml
Respiratory Rate	20/min	20/min
PEEP	5 cmH_2O	5 cmH_20
Waveform	Descending	Descending
Bias Flow	2 and 5 lpm	2 and 5 lpm

Ari et al. Respiratory Care 2010; 55 (7): 845-851.

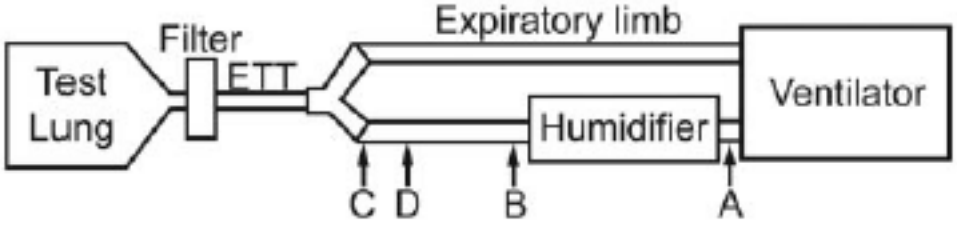
Pediatric



Ari et al. Respiratory Care 2010; 55 (7): 845-851.

4 Nebulizers in 4 Positions of Pediatric Vent

Fig. 1. Nebulizers tested. From right to left: Aerogen Solo, Maquet Ultrasonic model N06302595E400E, Salter 8900, and Hudson Updraft II Opti-Neb.

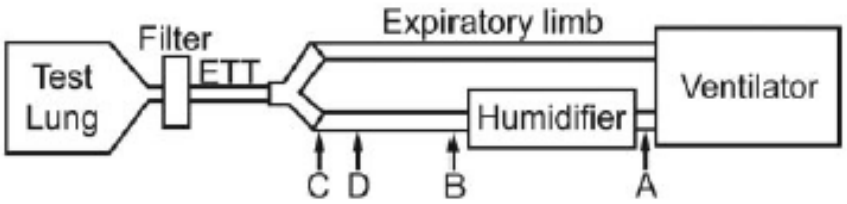


Pressure Regulated Volume Control. Vt 200 mL, Rate 20 bpm, PEEP 5, T_{insp} 0.75 s, bias flow 2L/min, 37 degree C

Berlinski A and Willis JR. 2013 Respir Care

Bench study: Nebulizer position determines nebulizer performance

Albuterol Loading volume	Nebulizer	Nebulizer position			
		At Ventilator	At Humidifier	At Y-piece	30cm Before Y-piece
2.5mg/ 3ml	Hudson Updraft II Opti-Neb	5.4 ± 0.6	4.7 ± 0.8	2.0 ± 0.1	4.3 ± 0.8
	Salter 8900	3.1 ± 0.9	4.6 ± 0.9	2.8 ± 0.4	2.9 ± 0.7
	Maquet Ultrasonic	12.8 ±1.5	17.1 ± 1.5	8.7 ± 0.7	10.5 ± 2
	Aeroneb Solo	28.5 ± 8.6	33.3 ± 3.6	8.7 ± 2.5	10.3 ± 3.3



- **Bias Flow 2L/min**

The Aeroneb Solo performance was 5-6 times superior to small volume nebulizers ad outperformed all others at all locations.

Berlinski & Willis, 2013.

Bench Study: Pediatric aerosol delivery during non-invasive ventilation

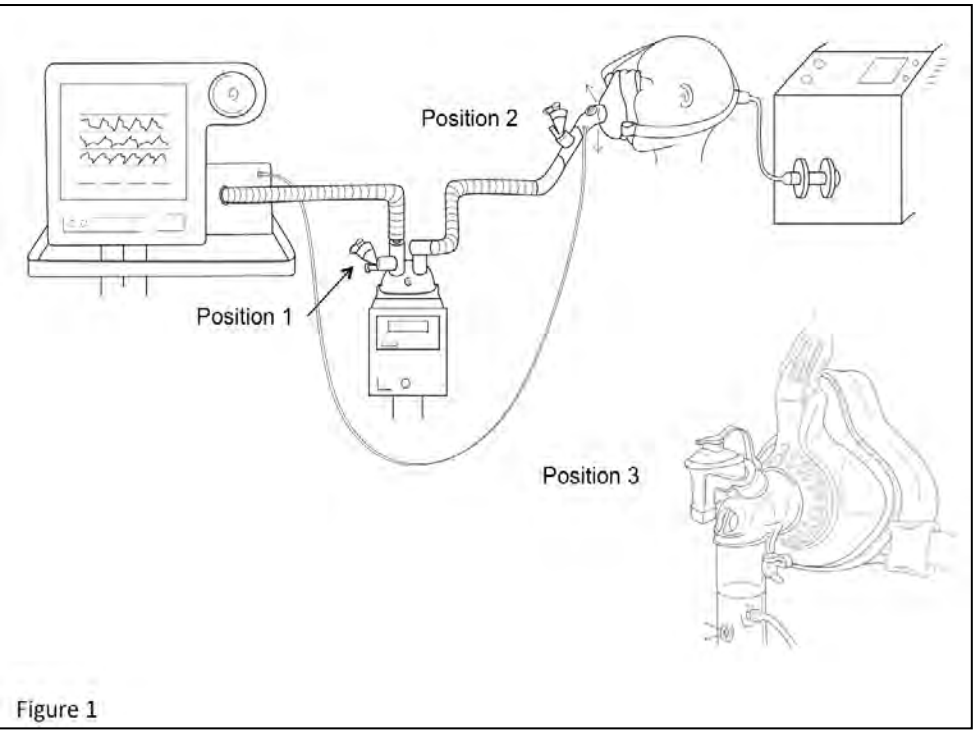


Figure 1

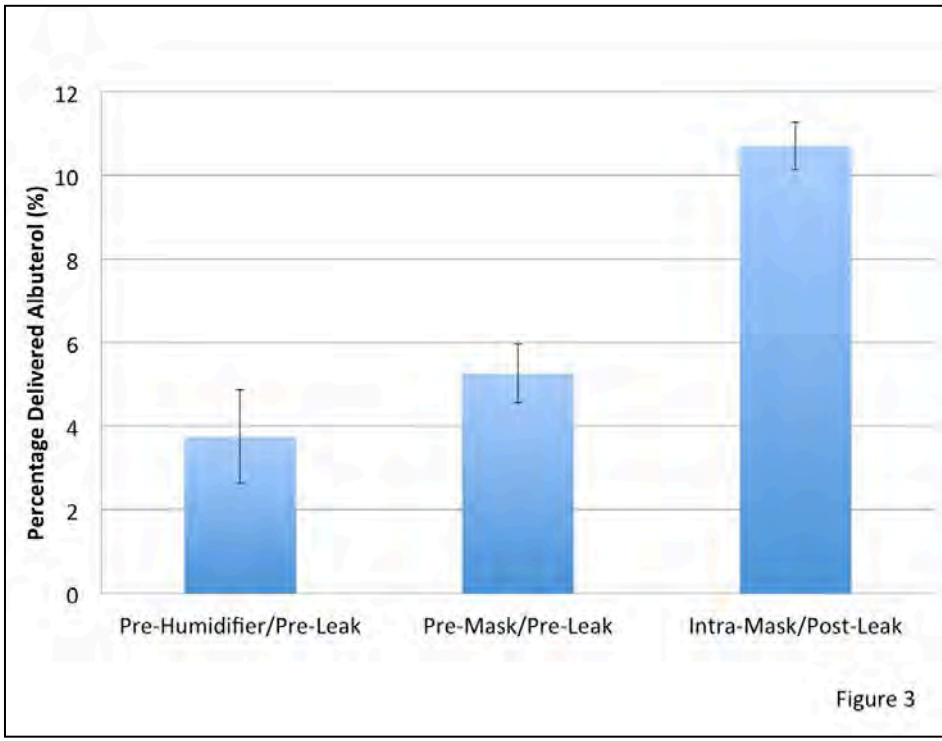


Figure 3

Comparison of aerosol delivery with the NIVO and the Aeroneb Solo during non-invasive ventilation

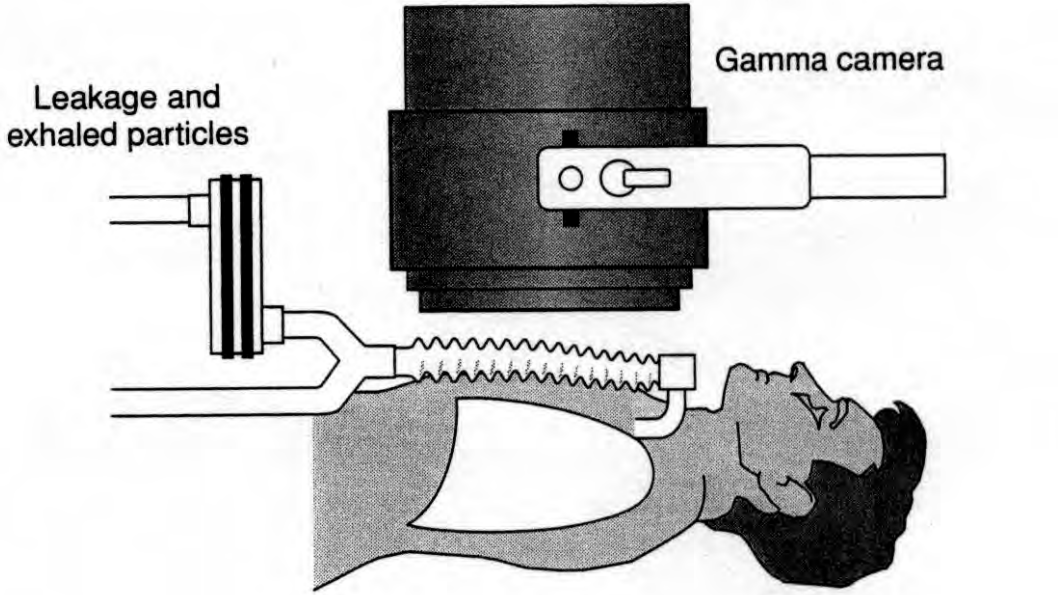
White CC, 2013. Bronchodilator delivery during simulated pediatric noninvasive ventilation. Respiratory Care. Published ahead of print February 5, 2013, doi:10.4187/respcare.02171

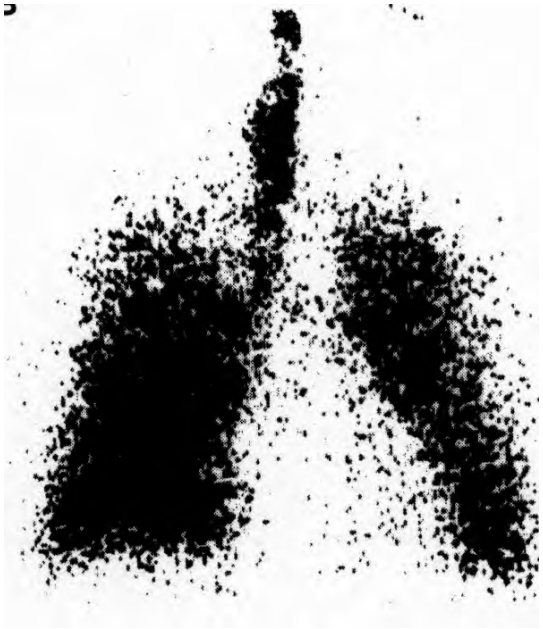
Aerogen

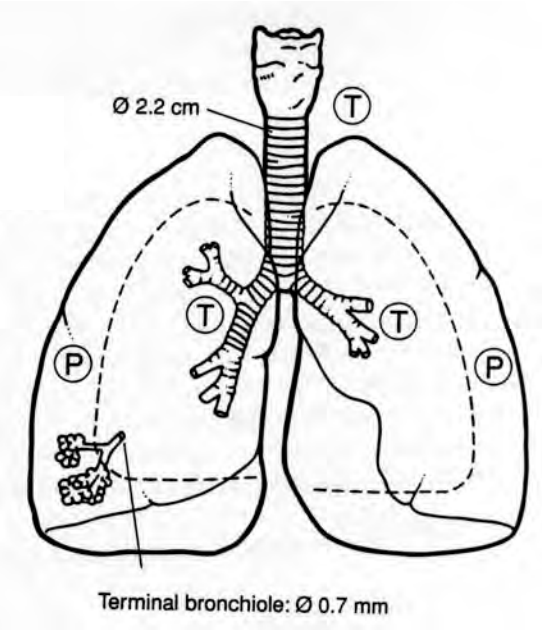
Aerosol Deposition During Neonatal Mechanical Ventilation

- 10 ventilated infants/ 13 nonintubated
- MDI/spacer 200 ug – Neb 100 ug over 5 min
- Ventilated infants – 0.98%
  - MDI 0.98 ± 0.19%
  - NEB 0.22 ± 0.08%
- Nonventilated infants – 0.67%
  - MDI 0.67 ± 0.17%
  - NEB 0.28 ± 0.014%

1996 – Fok et al. Ped Pulmonol 1996 21:301-9


Gamma camera
Leakage and
exhaled particles

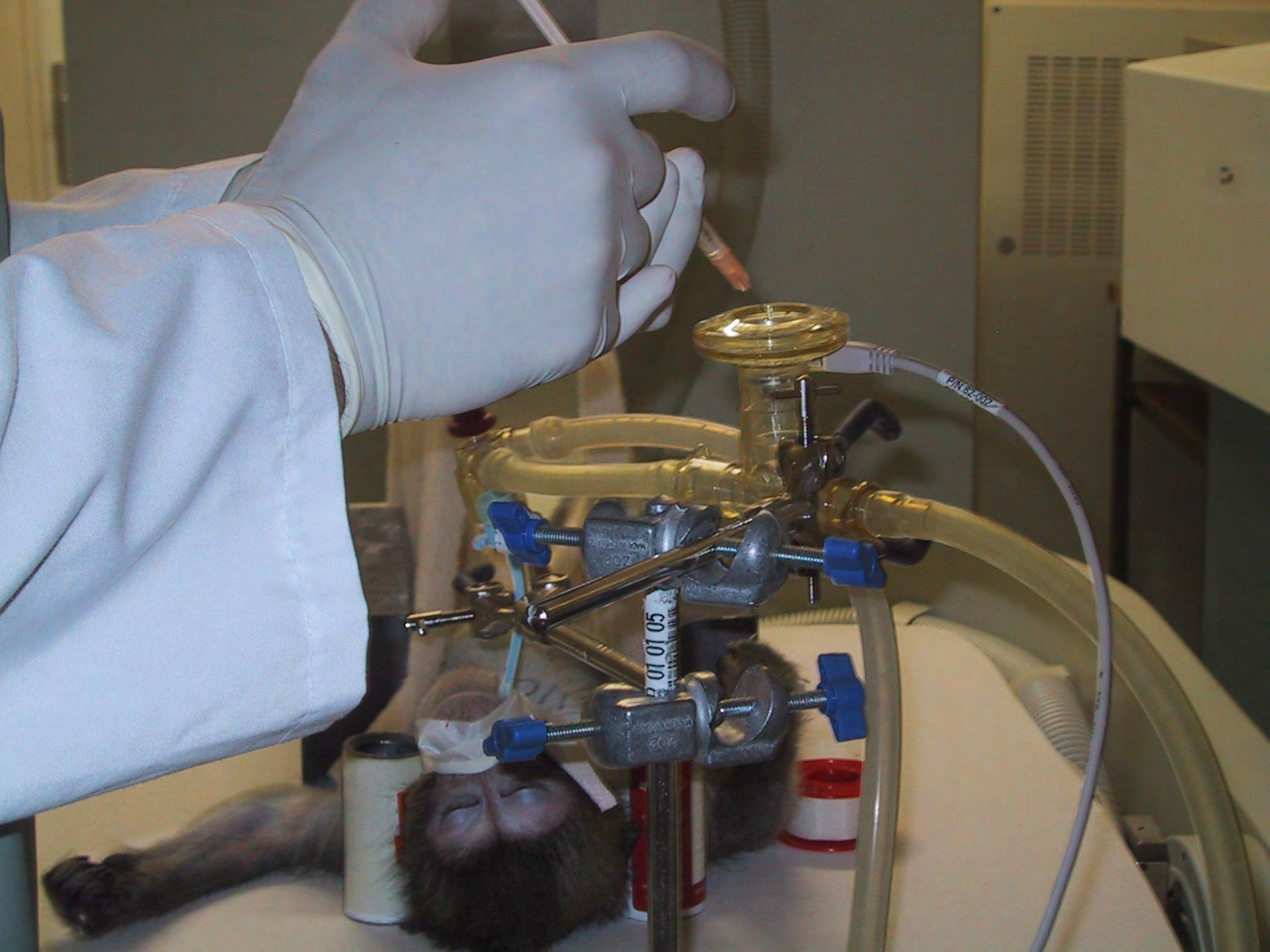


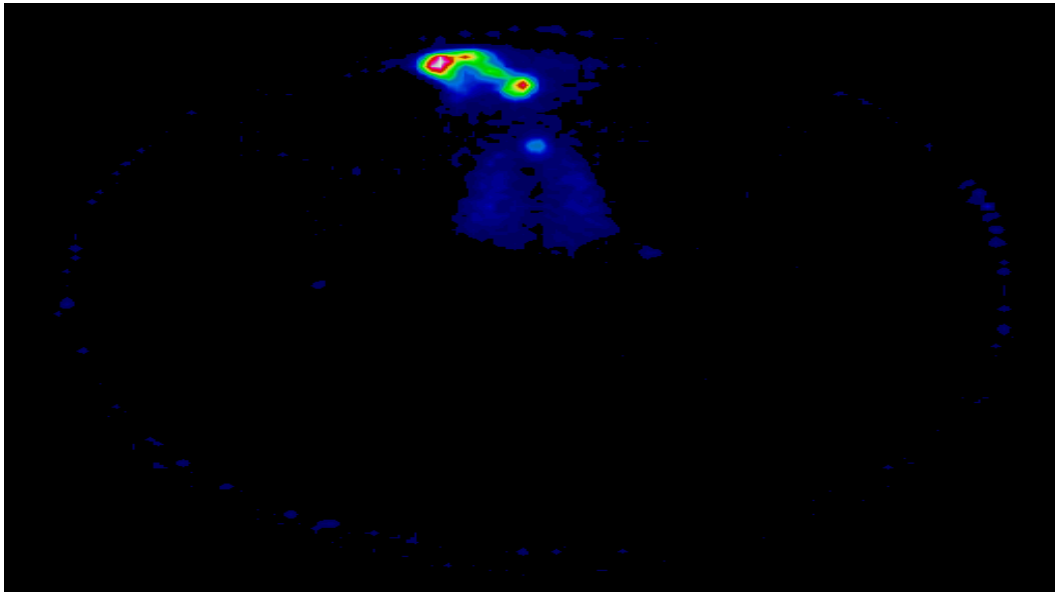

Ø 2.2 cm
T
T
T
P
P
Terminal bronchiole: Ø 0.7 mm

Pulmonary Deposition Macaque Model of Infant Ventilation

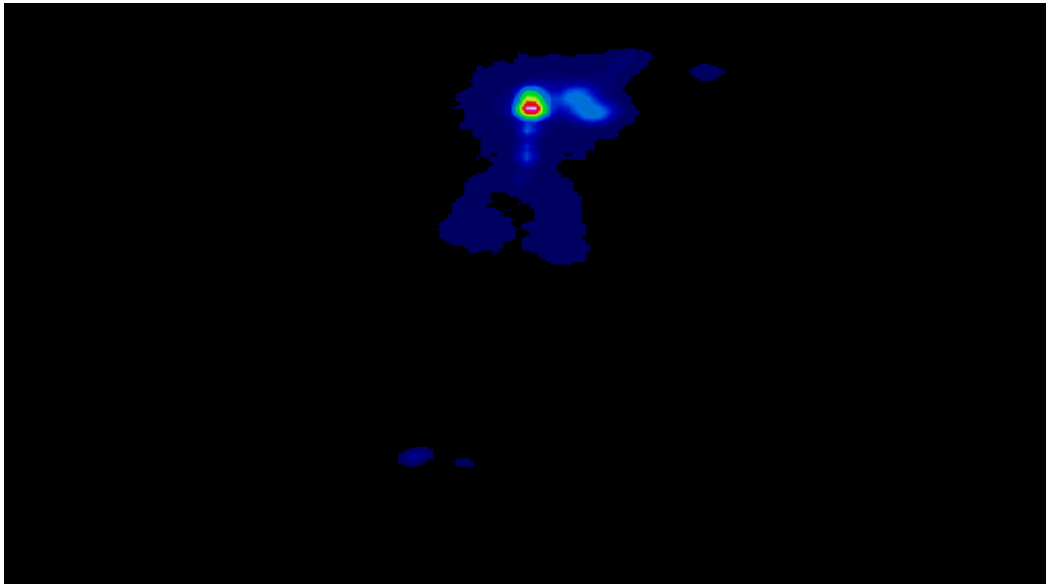
	Deposition Lung	Range
Aeroneb Cont 4.8 µm continuous 0.5 ml with 30 millicurie	13.9 ± 5.1 %	9.6 - 20.6%
Misty Neb 3.0 ml with 30 millicurie	0.7 ± 0.4 %	0.2 – 0.8%

Dubus et al, Pediatric Research 2005





2 drops with Aeroneb Pro



3 ml with Misty Neb

Pulmonary Deposition with 2 Drops Optimized Phasic

Aerosol Generator Size	Deposition Lung	Range
2.8 µm	20.8 ± 19.1 %	6.0 – 48.5 %
4.8 µm	12.13 ± 4.1 %	6.0 – 15.0 %

Deposition expressed as percent of 2mC (30 µl) 99 Tc DPTA

ILOPROST DRUG DELIVERY DURING INFANT MECHANICAL VENTILATION: INFLUENCE OF NEBULIZER POSITION DURING CONVENTIONAL AND HIGH FREQUENCY VENTILATION

Robert M DiBlasi RRT-NPS FAARC,[1,2] Shuijie Shen PhD,[1] David N Crotwell RRT-NPS FAARC,[2] John Salyer RRT-NPS FAARC,[2] Delphine Yung MD[1,3]

[1] Center for Developmental Therapeutics, Seattle Children's Research Institute, Seattle WA, United States

[2] Respiratory Therapy Department, Seattle Children's Research Institute, Seattle WA, United States

[3] University of Washington School of Medicine, Seattle WA, United States

* This study was funded through a grant provided by CDT at SCRI and drug was provided by Actelion

ORIGINAL ABSTRACT

rewire with chronic lung disease (CLD) commonly require prolonged invasive ventilation extending beyond the CLD. **INTRODUCTION:** Ventavis (Iloprost, inhalation Solution) is a selective pulmonary vasodilator that is commonly used in critically ill neonates with hypoxic lung disease and pulmonary hypertension. The Pediastaff AAD® System is the only FDA approved delivery device to Ventavis but this exclusivity cannot be used in any during conventional ventilation. There are currently no recommendations for selecting aerosol delivery devices or how these devices should be configured to efficiently deliver Iloprost during mechanical ventilation. Many clinicians are hesitant to deliver aerosolized drugs during high frequency oscillatory ventilation (HFOV) because it is believed that medication delivery is negligible due to the small volumes, short inspiratory times and high gas flows used with this form of ventilation. We designed studies in vitro to test the hypothesis that there were no differences in drug delivery between conventional and HFOV, testing two different nebulizer locations with each ventilator. We compared studies in vitro to test the hypothesis that there were no differences in drug delivery between two different nebulizer locations during conventional and HFOV. **METHODS:** A mechanical lung model (ASL 5000, Ingmar Medical) was configured with C: 1.0 mL/cmH$_2$O and R: 50 cmH$_2$O/L/s. The lung model was ventilated with a conventional ventilator and HFOV with standard settings and heated humidification (38°C). Iloprost (30 mcg) was nebulized using the Aerosol Pro (Aerogen, n=3) placed between the patient wye and the ET tube (Proximal) and the ventilator and humidifier (Distal). Measurements were obtained in triplicate using three different nebulizers in each of the circuit locations. Iloprost drug was recovered by eluting the filter with ethanol and quantified using high pressure liquid chromatography. Differences between mean drug mass were compared at each condition using ANOVA with Tukey post-hoc test. Significance was determined as p<0.05. **RESULTS:** Under no during conditions, greater drug delivery was observed with the nebulizer placed in the Proximal position than the Distal position during conventional and HFOV (p<0.05). There was nearly a 3-fold greater increase in drug delivery during HFOV than conventional ventilation (Figure). **DISCUSSION/CONCLUSIONS:** Iloprost drug delivery is best achieved when the nebulizer is placed between the ET tube and patient wye during mechanical ventilation. Future investigations will be needed to better understand why drug delivery appears to be more efficient during HFOV than conventional ventilation.

BACKGROUND

- Ventavis (Iloprost) Inhalation Solution is a selective pulmonary vasodilator that has been used in critically ill neonates with hypoxic lung disease and pulmonary hypertension
- There are currently no recommendations for selecting aerosol delivery devices or how those devices should be configured to efficiently deliver Iloprost during mechanical ventilation
- Many clinicians are hesitant to deliver aerosolized drugs during high frequency oscillatory ventilation (HFOV) because it is believed that medication delivery is negligible due to the small volumes, short inspiratory times and high gas flows used with this form of ventilation

HYPOTHESIS

We designed studies in vitro to test the hypothesis that there were no differences in drug delivery between conventional and HFOV, testing two different nebulizer locations with each ventilator.

FIGURES

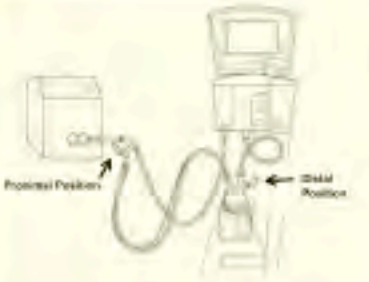


FIGURE 1. Schematic of experimental set-up during conventional ventilation

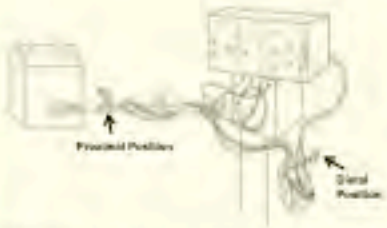
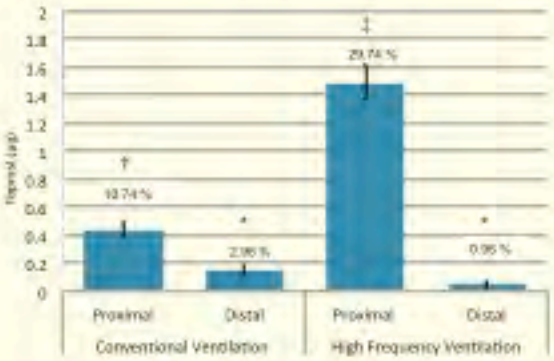


FIGURE 2. Schematic of Experimental Set-up during High-frequency oscillatory ventilation

FIGURE 3. Inhaled Drug Mass



Values represented as Mean±SD; Values not sharing similar symbols are different *p<0.05; Values also expressed as % nominal dose

METHODS

- An ASL 5000 (Ingmar Medical) configured with compliance: 1.0 mL/cmH$_2$O and resistance: 50 cmH$_2$O/L/s was ventilated with a conventional ventilator and HFOV with standard settings and heated humidification (38°C) connected to a 3.5 ID ET- tube (FIG. 1 and 2)
- The Aerosol Pro® (Aerogen, Galeway, Ireland) was tested in two different locations: 1) between the humidifier probe and patient wye (Proximal) and 2) between the ventilator and humidifier (Distal)
- Iloprost (30 mcg) was nebulized in three trials with new nebulizers (n=3) in each of the circuit locations. Iloprost was recovered from a filter by eluting the filter with ethanol and quantified using high pressure liquid chromatography
- Differences between mean drug mass were compared at each condition using ANOVA with Tukey post-hoc tests. Significance was determined as p<0.05

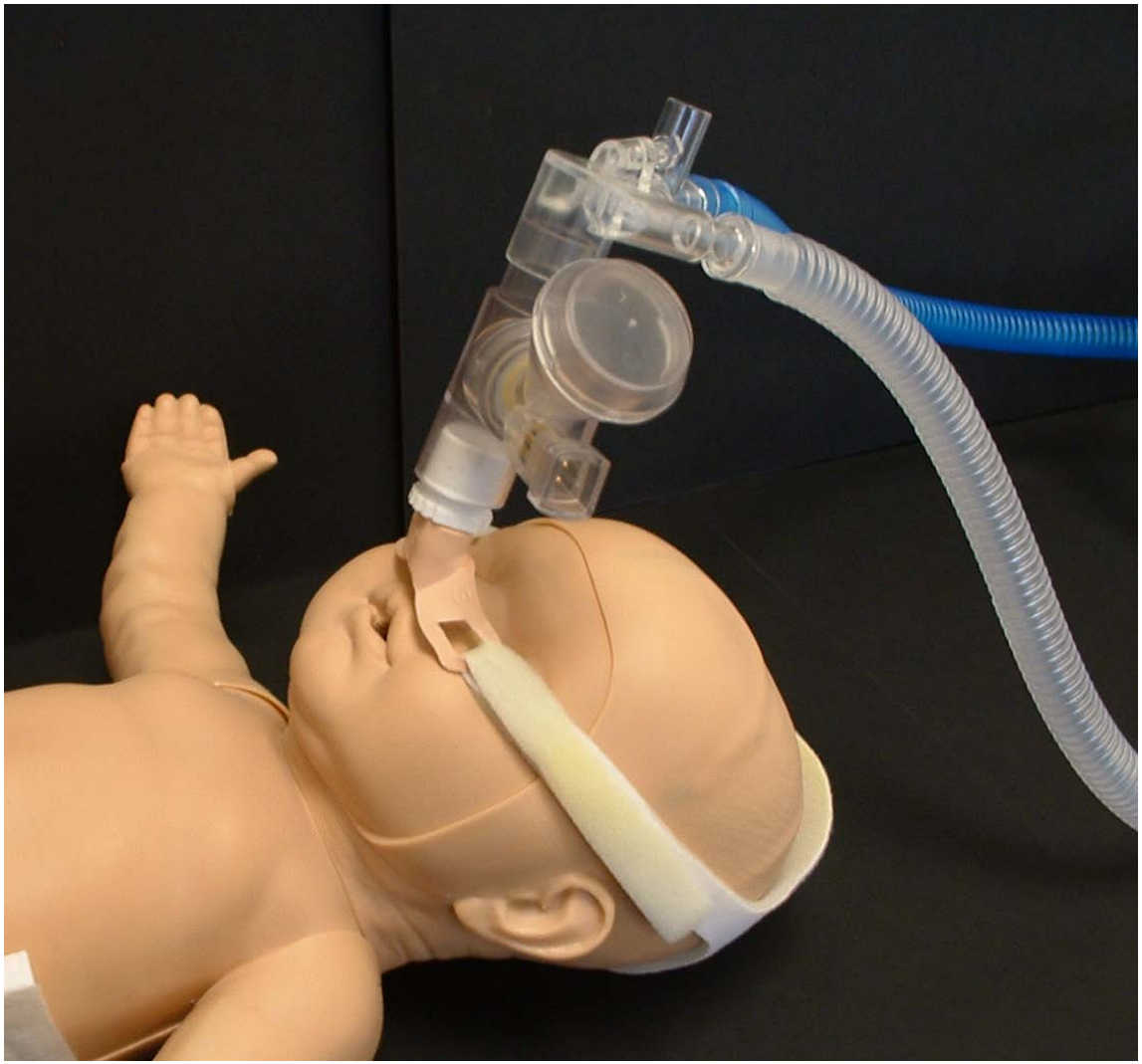
RESULTS

- During conventional and HFOV, drug delivery was greater with the nebulizer placed in the proximal position compared to the distal position (p<0.05)
- There was nearly a 3-fold greater increase in drug delivery during HFOV than conventional ventilation in the Proximal position (FIG. 3, p<0.05)

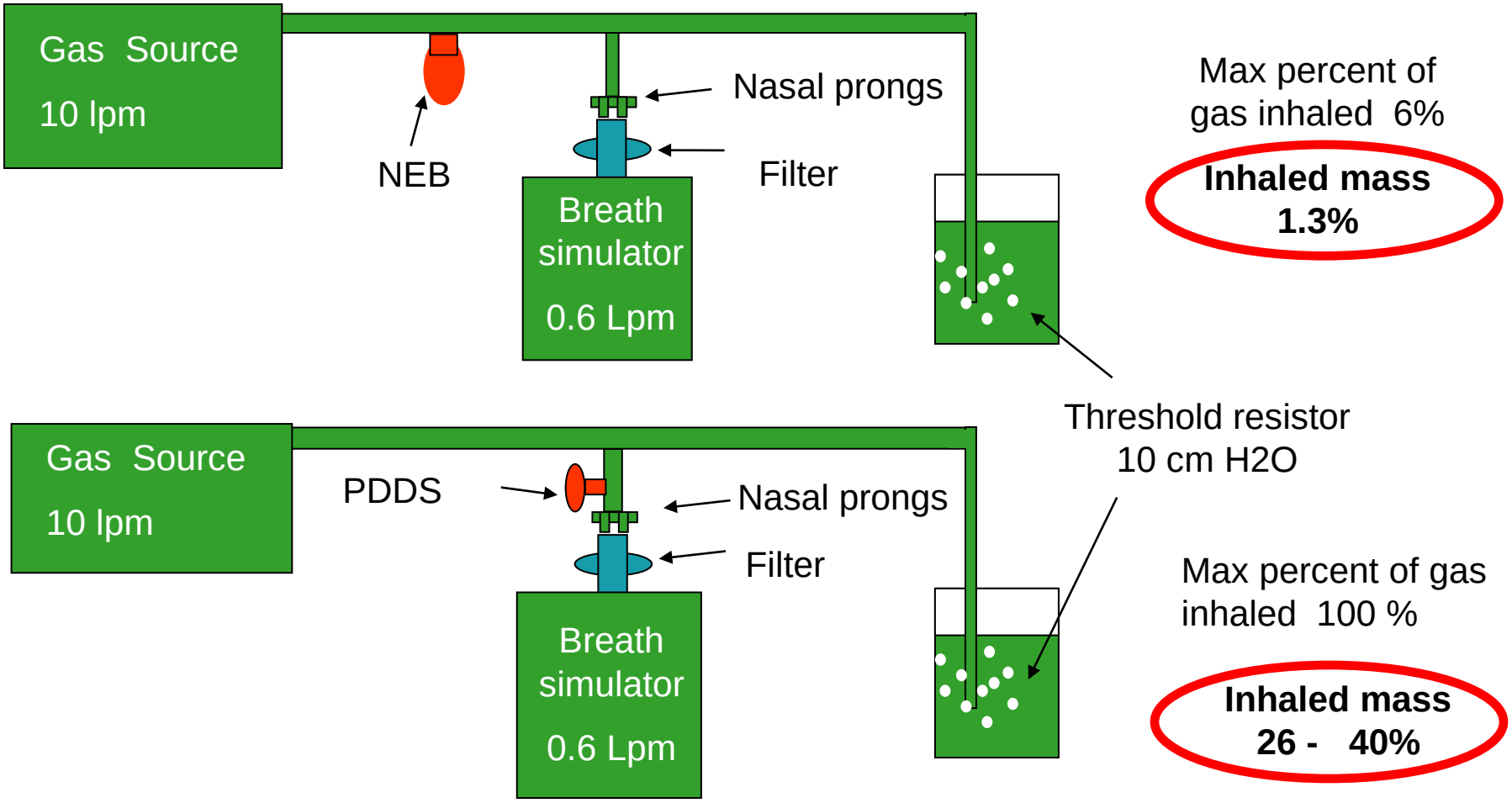
DISCUSSION/CONCLUSION

- Iloprost drug delivery is best achieved when the nebulizer is placed proximal to the patient-wye during neonatal mechanical ventilation
- Future investigations will be needed to better understand why drug delivery appears to be more efficient during HFOV than conventional ventilation.

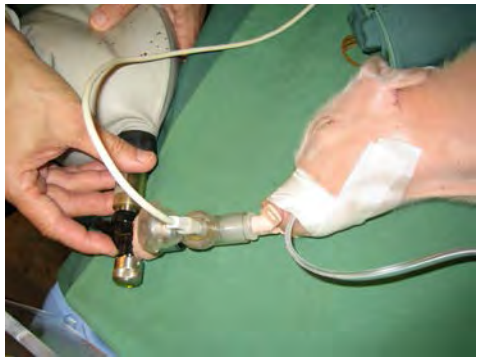
Pilot Study: Continuous Aerosol Generated Between Patient Airway and nCPAP Circuit using Argyle Prongs



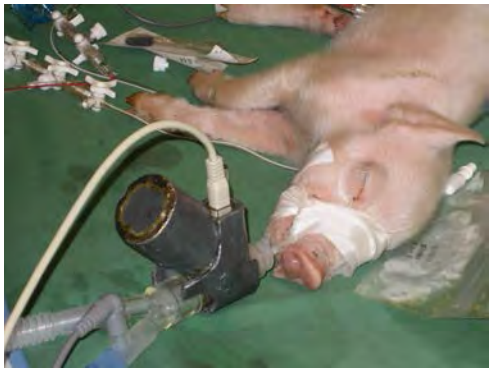
In Vitro Model Inhaled %
Position of Nebulizer



Piglet Study



nCPAP, nebulization



Intubated, nebulization

Group	Percent of dose deposited in the lungs mean (range) median		
	Both lungs	Dependent lung	Upper lung
nCPAP, nebulization	5.59 (0.6 – 10.1) 6.6	5.3(0.2 – 8.9) 7.06	0.9 (0.2 – 1.8) 0.89
Intubation, nebulization	15.90 (7 – 37) 16.04	11.43 (4-31) 6.7	4.47 (3 – 8) 4.1
Intubation, instillation	98.76 (89-110) 98.97	83.47 (63 – 104) 85.7	15.86 (4 - 30) 14.8

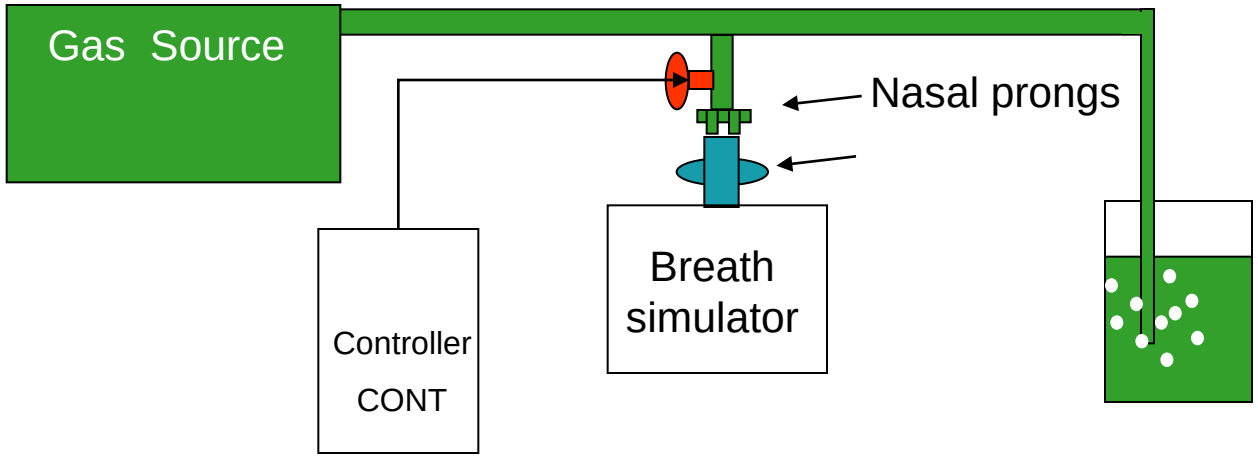
Piglet Study

% of Aerosol Dose Delivered to Respiratory System

Continuous Nebulization Measured by Scintigraphy

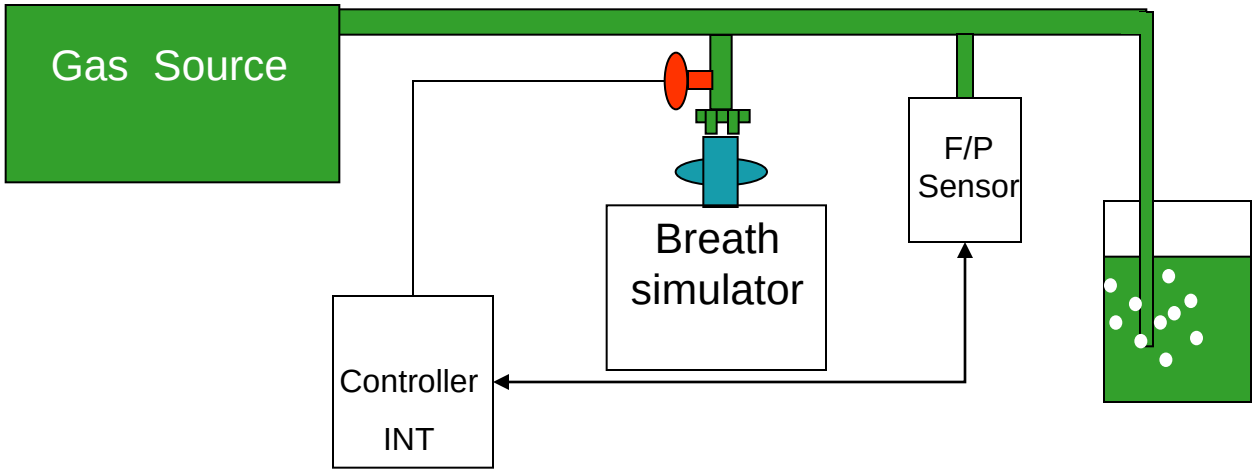
	Lungs	Upper Airway	Trachea	Stomach	Inhaled %
NP1	5.65	13.72	2.68	1.40	23.44
NP2	8.90	8.46	2.32	0.11	19.79
NP3	7.55	14.73	12.26	2.13	36.66
NP4	0.58	8.10	0.89	0.08	9.65
NP5	0.75	5.28	0.94	0.00	6.97
NP6	10.12	11.44	8.73	3.97	34.26
Mean	5.59	10.29	4.64	1.28	21.79
SD	4.09	3.63	4.73	1.58	12.25

In Vitro Model Inhaled %
Continuous vs Intermittent Nebulization



Continuous neb

Inhaled 20 – 26%



Intermittent neb

Monitoring downstream changes in pressure or flow

Inhaled mass 38 – 45%

Summary

- Effective Aerosol Delivery to Neonates, Children and Adults is possible
- Application of new and emerging technologies have improved lung delivery of aerosols
- New technology presents opportunities for new applications
- A working knowledge of aerosol devices and techniques can benefit even the smallest patients in the Intensive Care and Emergency Departments

Fink.jim@gmail.com