New Frontiers: Medical Aerosols in Critical Care

Jim Fink, RRT, PhD, FAARC, FCCP
Independent Consultant
Adjunct Professor, GA State University and Rush Medical School, Chicago
Fink.jim@gmail.com

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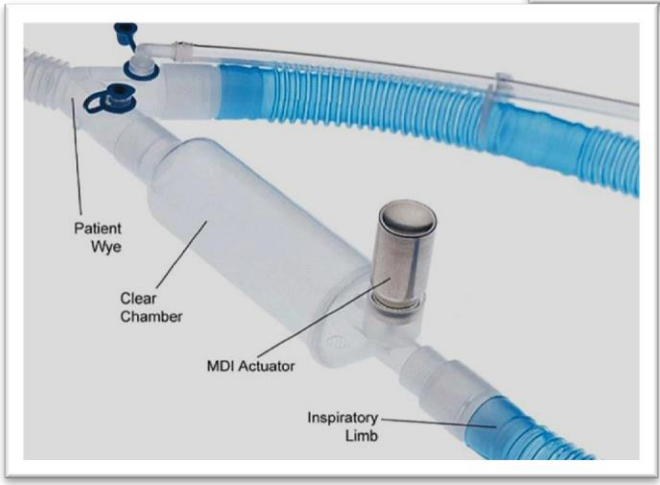
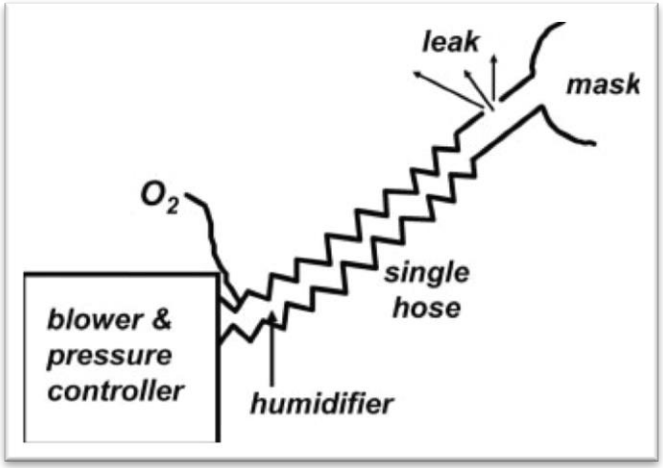
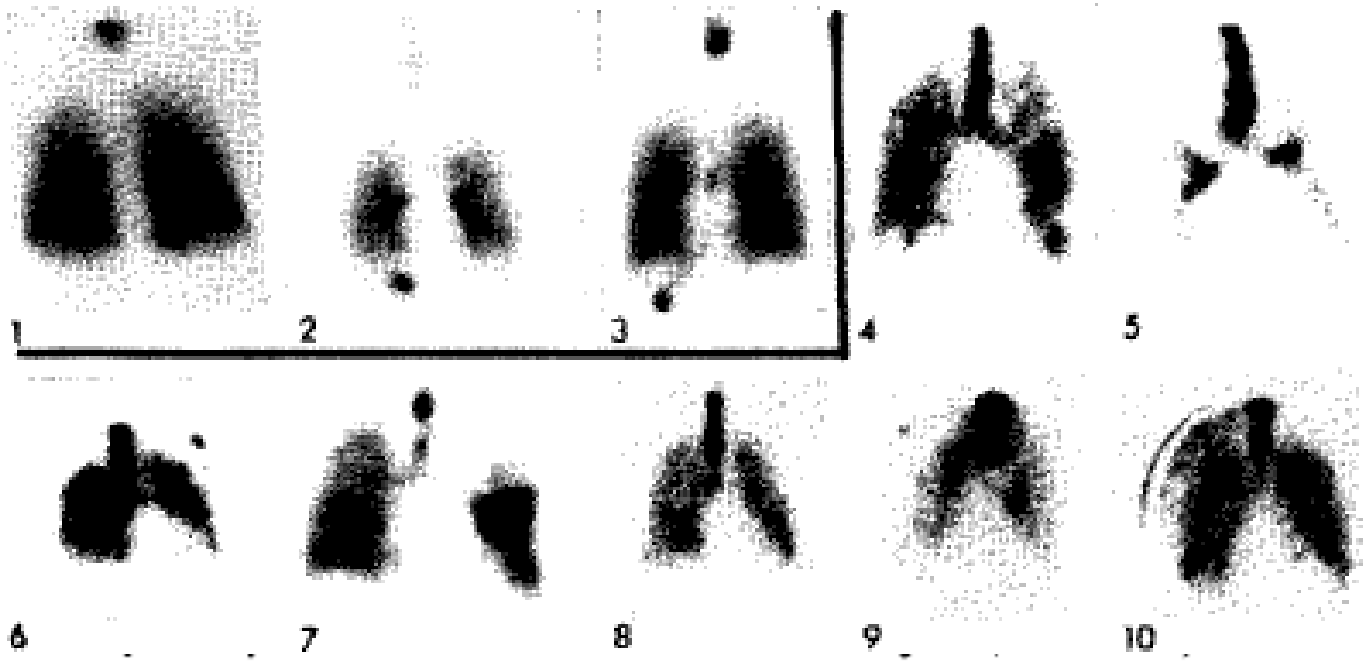
Disclosures

- **Scientific advisory board , Chief Clinical Officer**
  - Aerogen, ireland
- **Consultant**
  - Aerogen
  - Ansun
  - Aridis
  - Bayer
  - Boerhinger Ingleheim
  - Dance Biopharm
  - Parion
  - Quark
  - WHO
- **The opinions expressed during this presentation are those of the speaker, and not necessarily those of the organizing committee, association or sponsor.**

Types of Ventilators : Invasive and Noninvasive

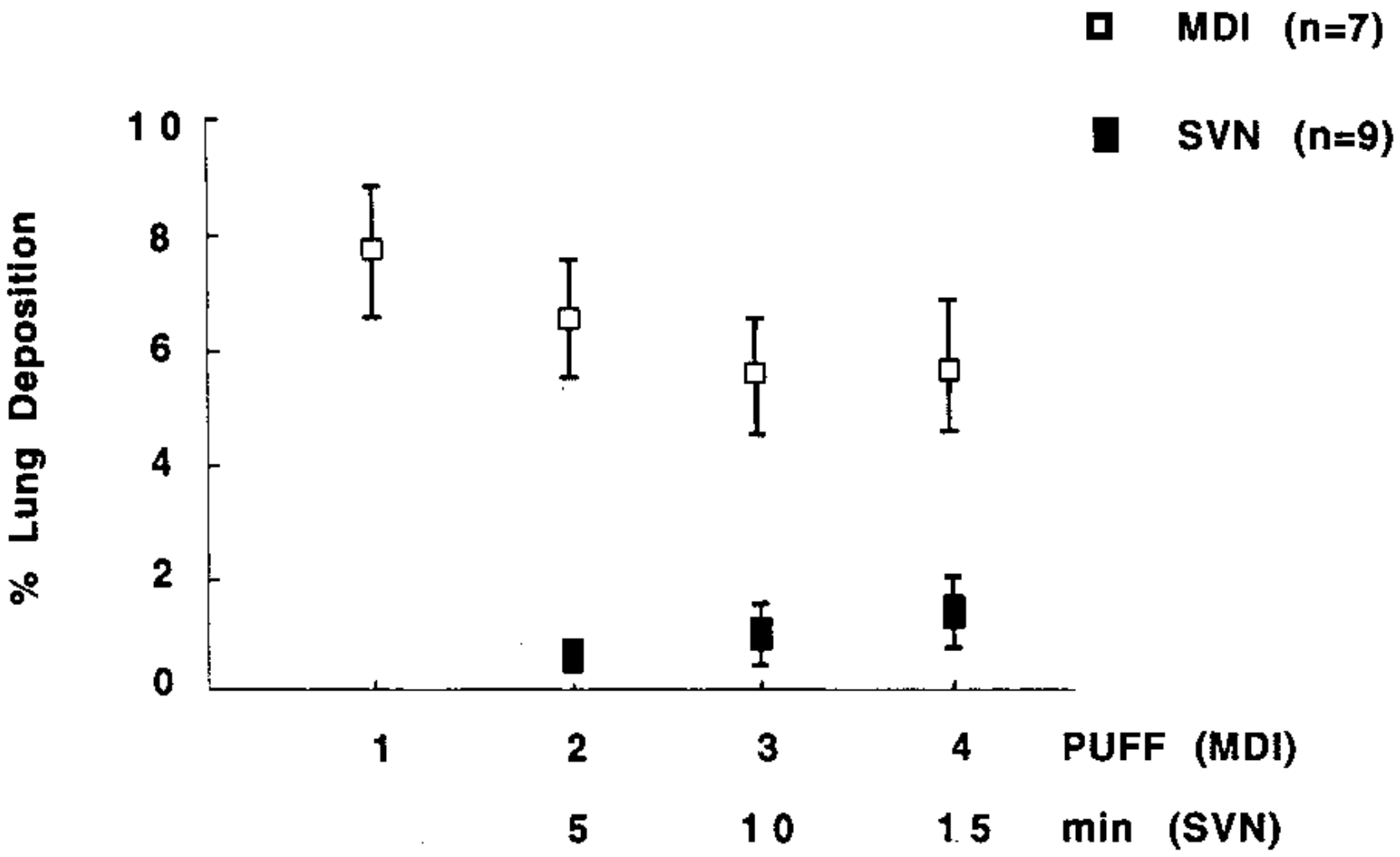






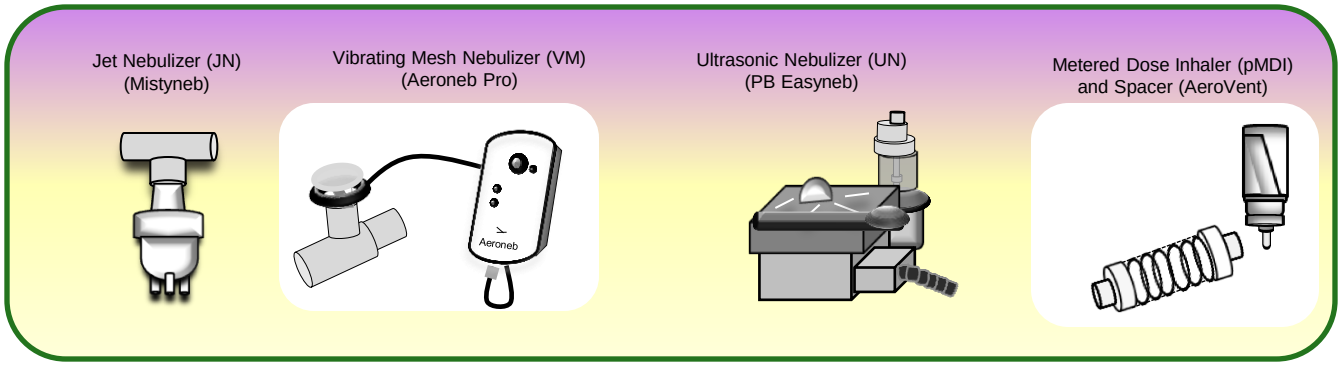
	Intubated Subjects	Nonintubated Subjects
Administered radioactivity	5.75 ± 1.3 mCi	6.53 ± 0.4 mCi
Percent of administered radioactivity in:		
Trachea (includes portion of endotracheal tube in intubated patients)	1.6 ± 1.1%[a]	0.3 ± 0.1%[a]
Lung parenchyma	2.9 ± 0.7%[b]	11.9 ± 2.2%[b]
Stomach	—	7.3 ± 2.05%
Oral cavity	—	15.0 ± 13%
Nebulizer circuitry	—	65.5 ± 16%

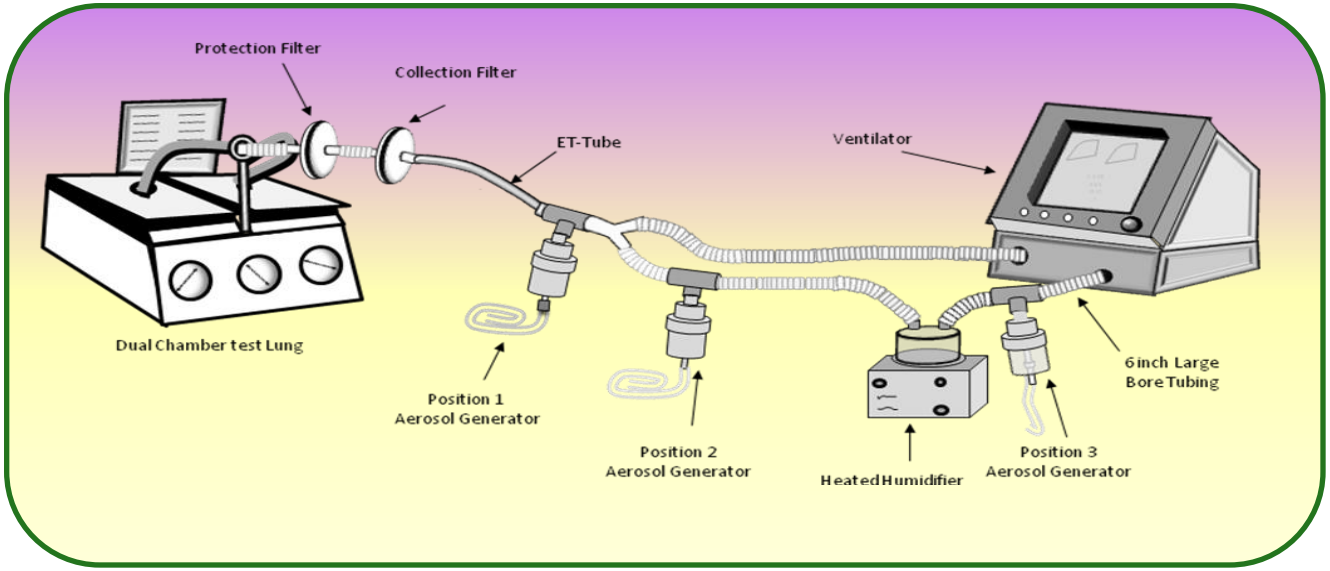
Macintyre Crit Cre Med 1985



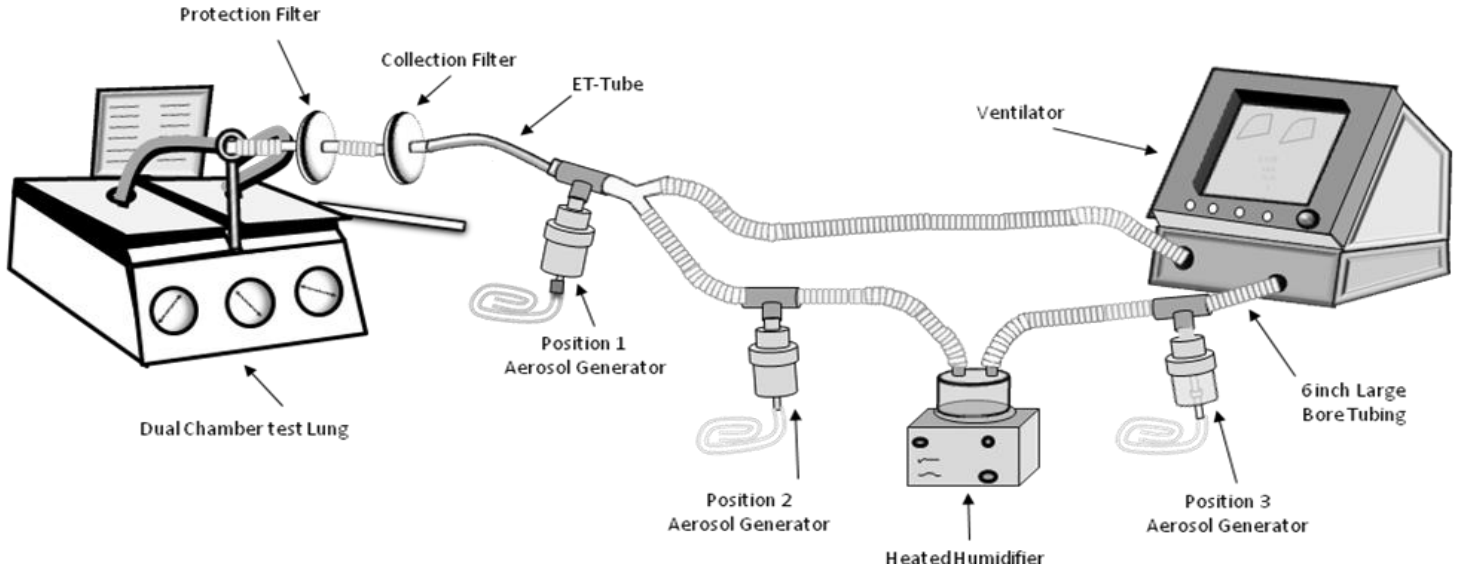
Fuller et al. 1990. ARRD 141:440-444.

Four types of aerosol generators in 3 positions during CMV with no bias flow



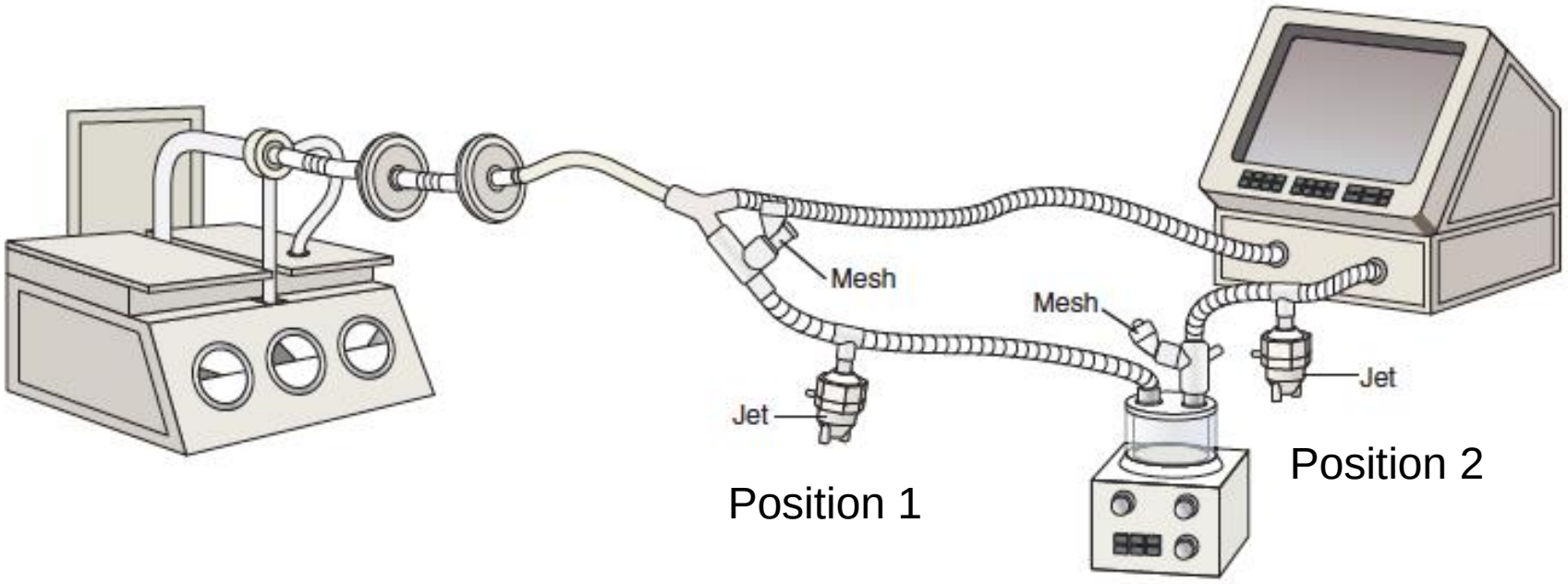


Ari et al. Respiratory Care 2010; 55 (7): 837-844.



Neb Position	Pos 1 - Between ETT & Y		Pos 2 - 6 in from Y		Pos 3 - 6 in from Vent	
Ventilator Circuit	Heated	Unheated	Heated	Unheated	Heated	Unheated
JN	**4.66 (0.5)**	**7.62 (0.9)**	**3.61 (0.2)**	**9.66 (1.5)**	**5.98 (0.1)**	**14.66 (1.5)**
VM	**12.82 (0.5)**	**14.54 (1.0)**	**16.79 (2.6)**	**30.24 (1.0)**	**8.39 (2.1)**	**24.20 (1.2)**
UN	**10.07 (3.9)**	**10.70 (1.5)**	**16.53 (4.3)**	**24.68 (4.4)**	**4.59 (2.0)**	**10.51 (0.3)**
pMDI	**7.6 (1.3)**	**22.1 (1.5)**	**17 (1.0)**	**27.8 (3.3)**	**2.5 (0.8)**	**7.9 (1.5)**

Ari et al, Respir Care 2010



	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.

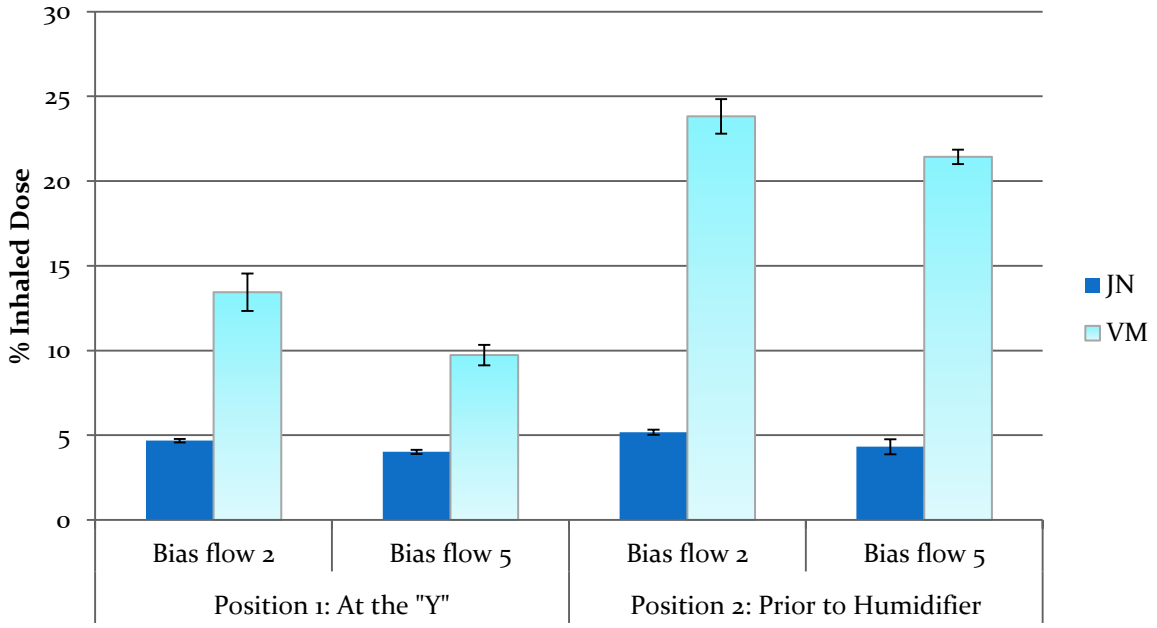
With Bias Flow

VM and JN more Efficient Placed Prior to Humidifier

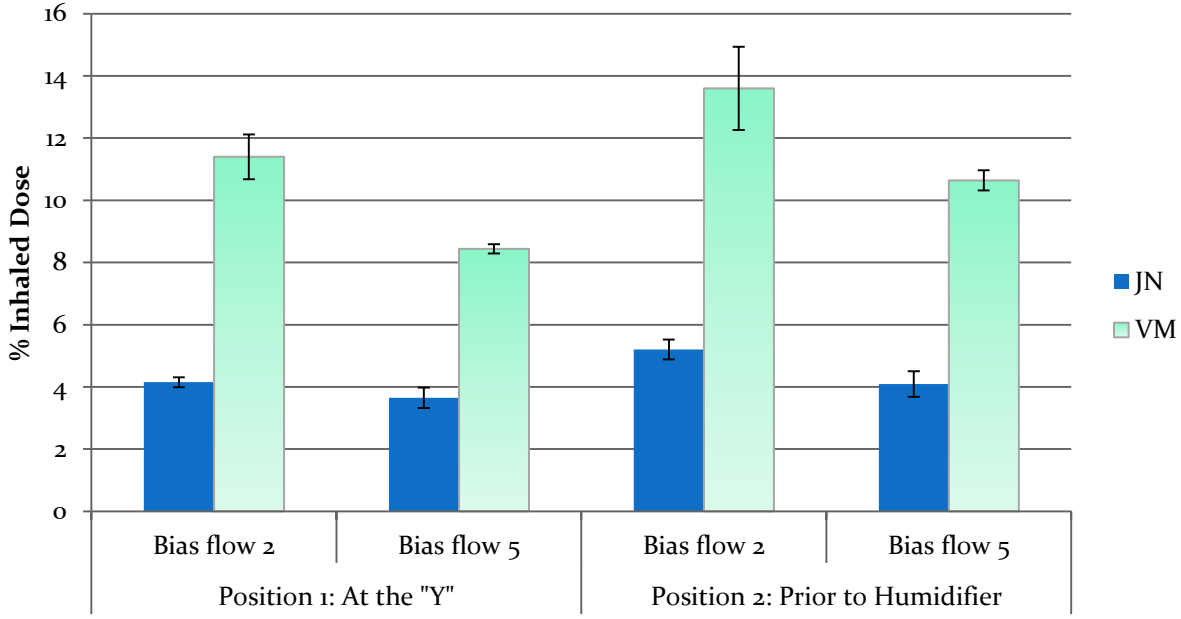
As Bias flow Increases deposition decreases

VM > JN

Adult



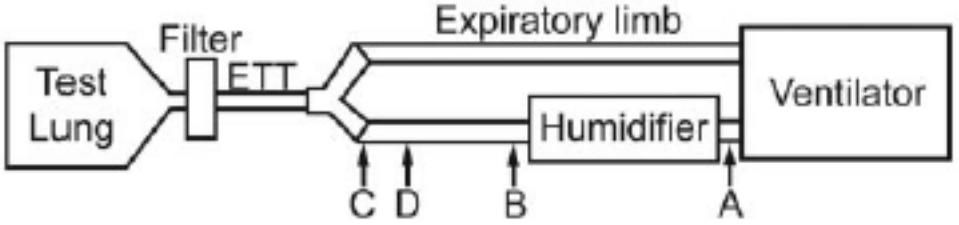
Peds



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.

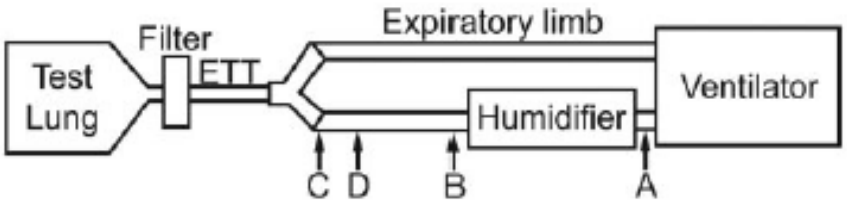


Pressure Regulated Volume Control. Vt 200 mL, Rate 20 bpm, PEEP 5, T_{insp} 0.75 s, bias flow 2L/min, 37 degree C

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

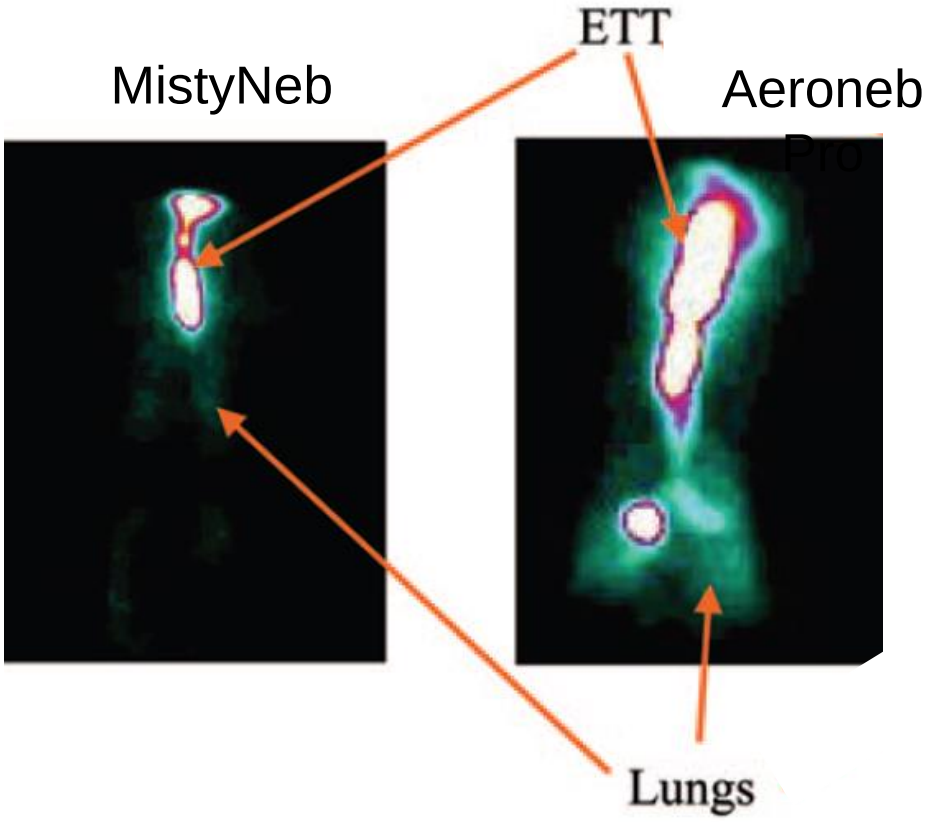


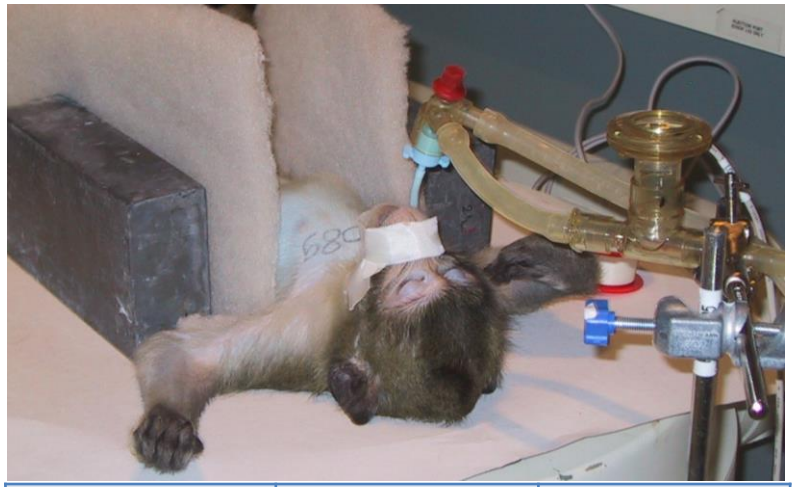
- **Bias Flow 2L/min**

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

Berlinski & Willis, 2013.

Vibrating Mesh - Drug Deposition in animal model of infant ventilation





	Aeroneb Pro	MistyNeb
Deposition in the lung	12.6%	0.5% (p=0.006)

~25-fold greater lung deposition with Aeroneb Pro compared to a Jet nebulizer during infant ventilation

Dubus et al. 2005 Aerosol deposition in neonatal ventilation

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

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

ORIGINAL ABSTRACT

Infants with chronic lung disease (CLD) commonly require prolonged invasive ventilation extending beyond the ICU. **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 Prodose®-AAD® System is the only FDA approved delivery device for iloprost but this nebulizer cannot be used in line during mechanical 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. Moreover, many clinicians are hesitant to deliver iloprost during high frequency oscillatory ventilation (HFOV) because it is believed that medication delivery is negligible due to turbulence, small tidal volumes, and high bias flow with this form of ventilation. We designed 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 neonatal test 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 (39°C). Iloprost (30 mcg) was nebulized using the Aeroneb 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 tests. Significance was determined as p<0.05. **RESULTS:** Under all testing 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

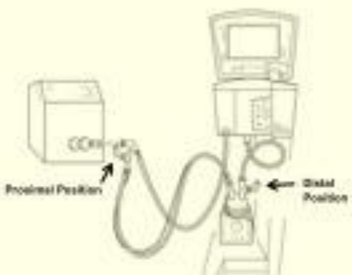
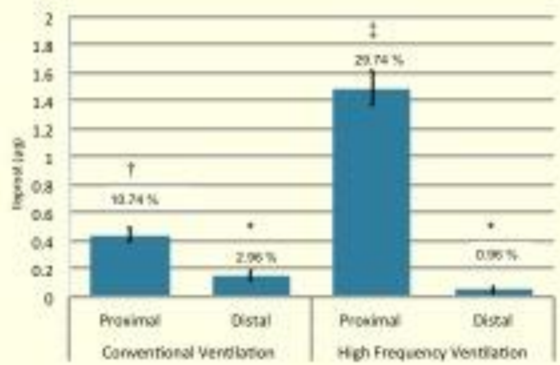


FIGURE 1. Schematic of experimental set-up during conventional ventilation

FIGURE 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

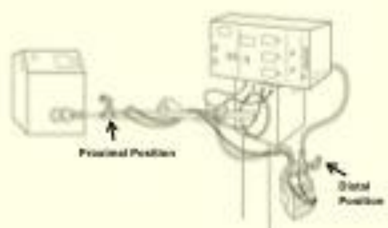


FIGURE 2. Schematic of Experimental Set-up during high-frequency oscillatory ventilation

METHODS

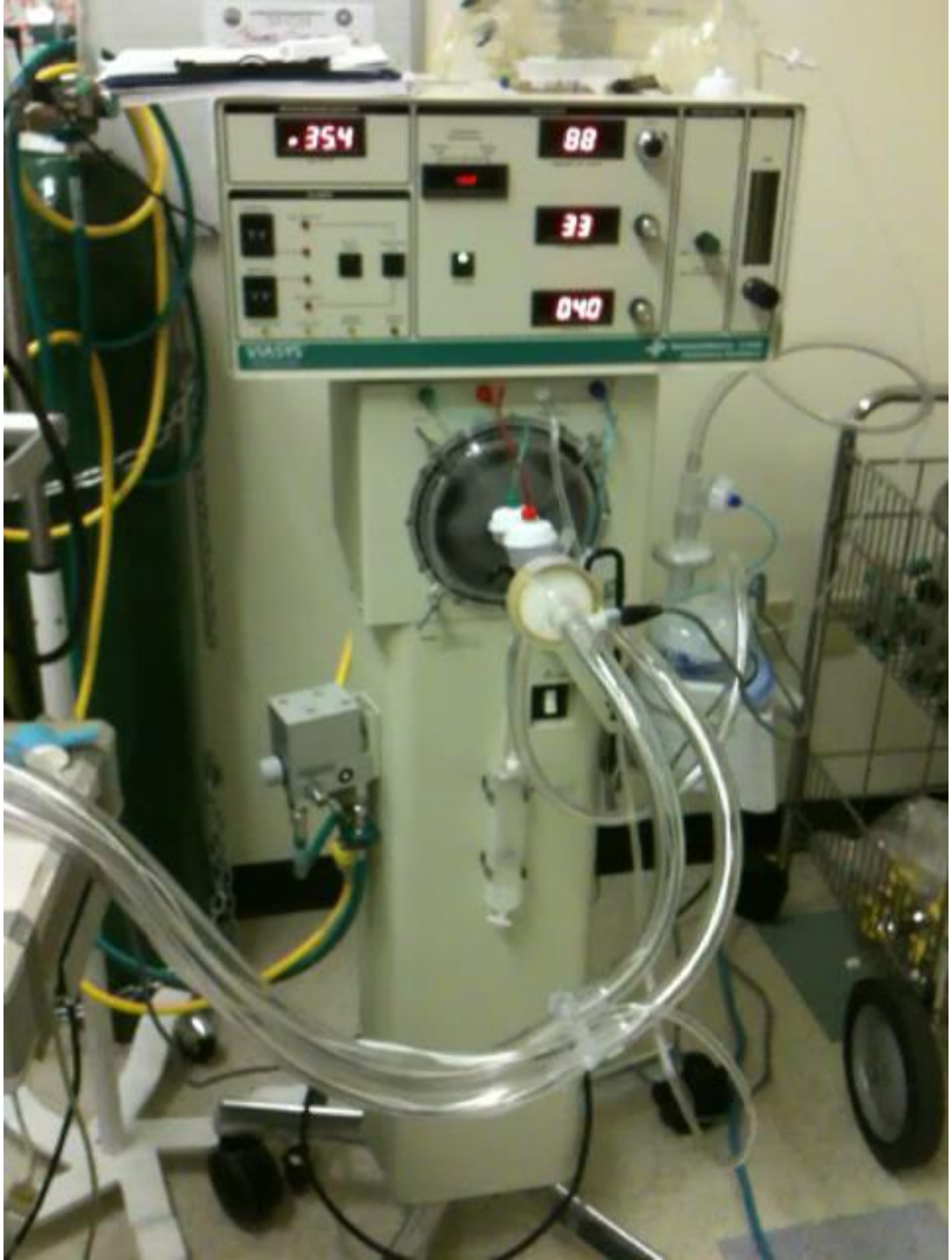
- An ASL 5000 (Ingmar Medical) configured with compliance: 1.0 mL/cmH$_2$O and resistance: 50 cmH$_2$O/L/s was ventilated with a conventional ventilator and HFOV with standard settings and heated-humidification (39°C) connected to a 3.5 ID ET- tube (FIG. 1 and 2)
- The Aeroneb Pro® (Aerogen, Galeway, 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.


.354
88
33
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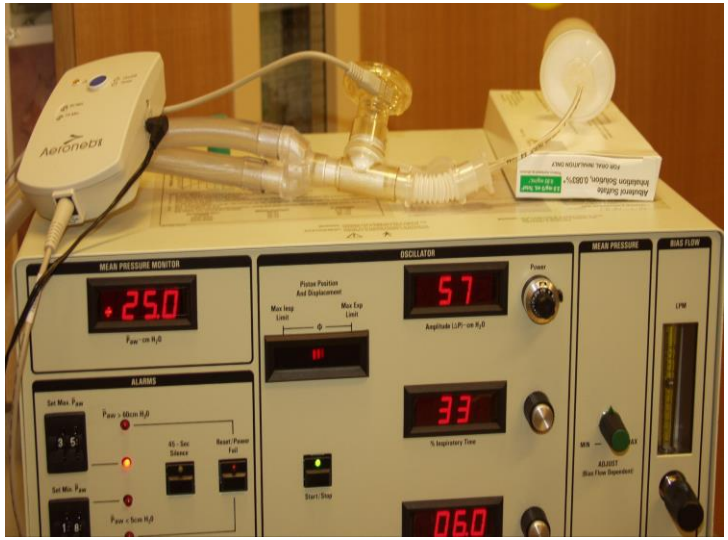
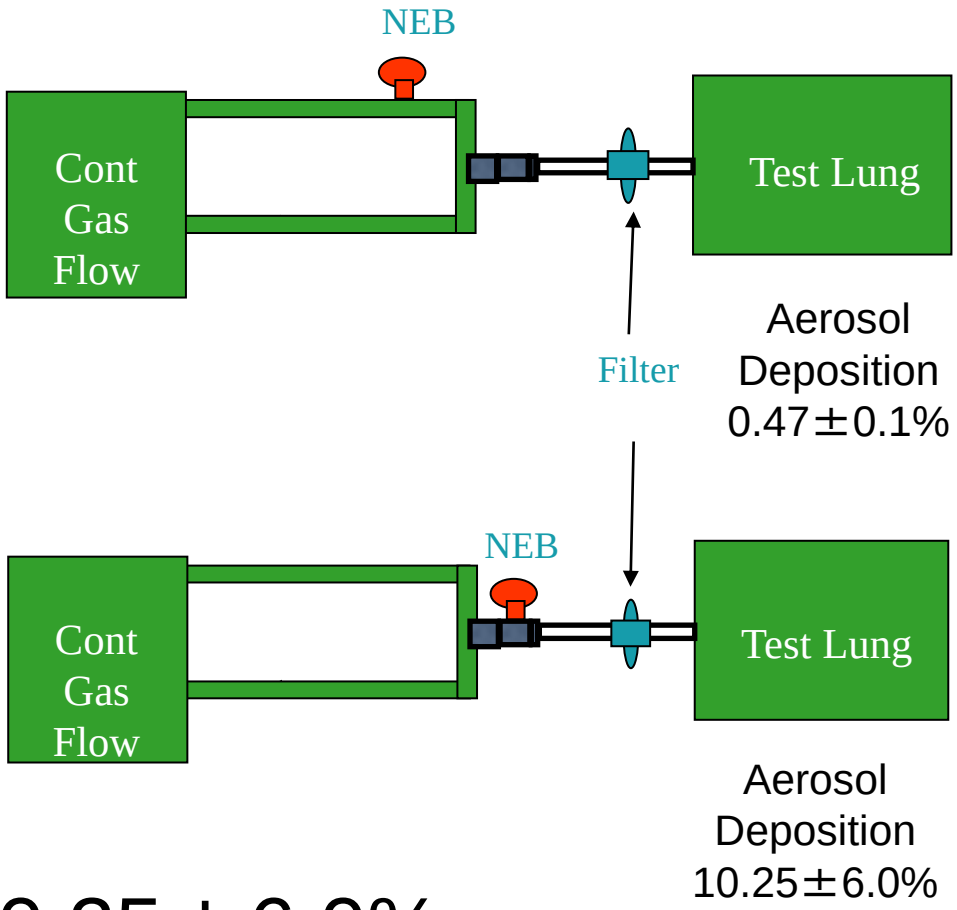
For HFOV:
Place Neb between circuit and ETT

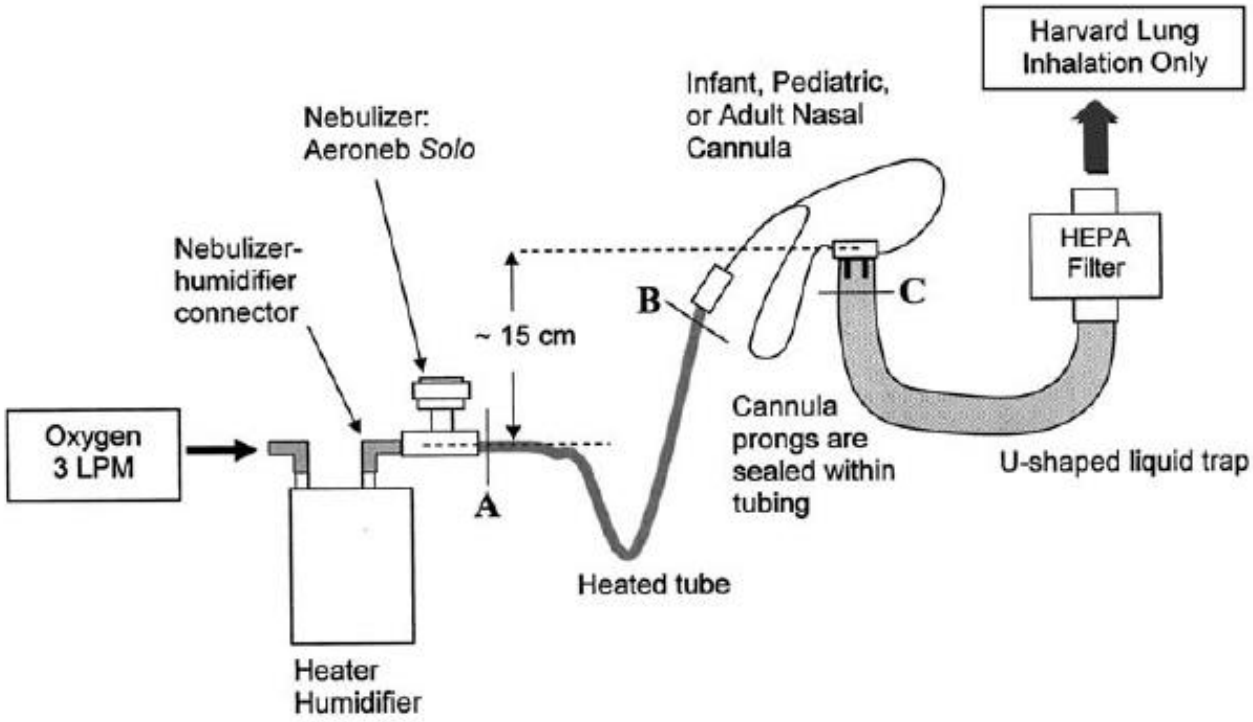




Aerosol Deposition 10.25±6.0%

Demers et al. ATS San Diego, 2005

Aerosol Delivery via Nasal Cannula



	Infant cannula		*Pediatric cannula*		*Adult cannula*	
	No Harvard lung	*Harvard lung*	*No Harvard lung*	*Harvard lung*	*No Harvard lung*	*Harvard lung*
Aerosol output dose (%)	8.4 ± 2.3	18.6 ± 4.0	18.1 ± 4.2	25.4 ± 1.7	25.1 ± 5.0	26.9 ± 4.9
delivery time (min)	13.1 ± 2.5	10.8 ± 0.7	13.0 ± 0.0	10.9 ± 1.4	12.5 ± 0.4	12.1 ± 0.8

Bhashyam et al. JAM 2008

Aerosol Delivery via Nasal Cannula

TABLE 2. SUMMARY OF COMPONENT LOSSES FOR THE NASAL CANNULA AEROSOL DELIVERY SYSTEM SHOWN IN FIGURE 1

	Infant cannula		*Pediatric cannula*		*Adult cannula*	
	No Harvard lung	*Harvard lung*	*No Harvard lung*	*Harvard lung*	*No Harvard lung*	*Harvard lung*
Losses in cannulas	3.5 ± 2.0	7.5 ± 1.1	7.8 ± 5.2	6.6 ± 3.1	12.3 ± 5.0	10.8 ± 2.9
Losses in nebulizer	2.2 ± 0.3	3.4 ± 0.6	3.5 ± 1.1	2.7 ± 0.8	2.8 ± 1.4	2.4 ± 0.6
Losses in nebulizer–humidifier connectors	25.6 ± 5.9	20.4 ± 17.7	27.8 ± 12.7	17.3 ± 11.9	26.0 ± 16.2	20.7 ± 8.2
Losses in heated tube	30.7 ± 4.3	32.1 ± 7.8	37.3 ± 2.5	35.0 ± 11.6	27.1 ± 1.7	28.5 ± 2.5
Losses in U-shaped liquid trap	3.0 ± 3.8	1.0 ± 1.0	3.8 ± 3.0	1.8 ± 0.5	1.1 ± 0.4	2.1 ± 1.5
Losses in heater/humidifier (assumed)	26.7 ± 3.7	17.1 ± 8.8	1.7 ± 1.1	11.1 ± 5.4	5.6 ± 11.8	8.7 ± 5.8

TABLE 3. AEROSOL SIZE MEASUREMENTS AT DIFFERENT POINTS IN THE NASAL CANNULA AEROSOL DELIVERY SYSTEM

Meas. point		*VMD μm*	*Dv90 μm*
A	Exit of nebulizer	5.0 ± 0.2*,**	8.9 ± 0.8
B	Exit of heater tubing	4.2 ± 0.7*,**	6.8 ± 1.5
C	Adult cannula	2.2 ± 0.2*,,***	4.2 ± 0.4
C	Pediatric cannula	1.9 ± 0.3**,***	3.8 ± 0.5
C	Infant cannula	NM	NM

Bhashyam et al. JAM 2008

Aerosol Delivery with High Flow Nasal Cannula with Adult Cannula

	10 lpm	30 lpm	50 lpm
O2	27.1%	12.03%	3.6%
80%Heliox	27.9%	14.4%	5.6%

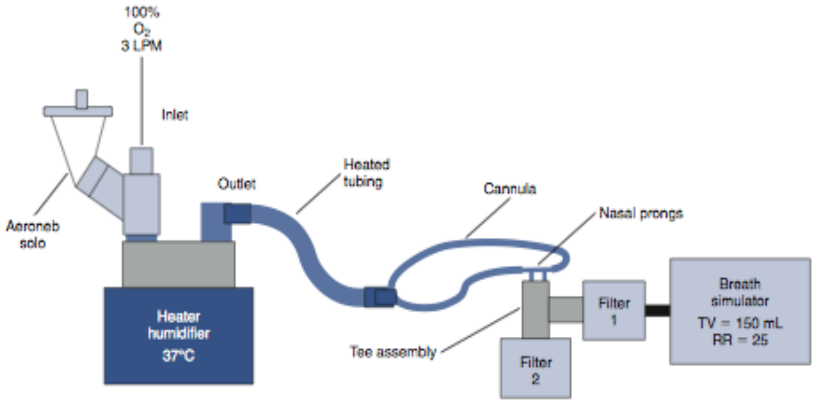
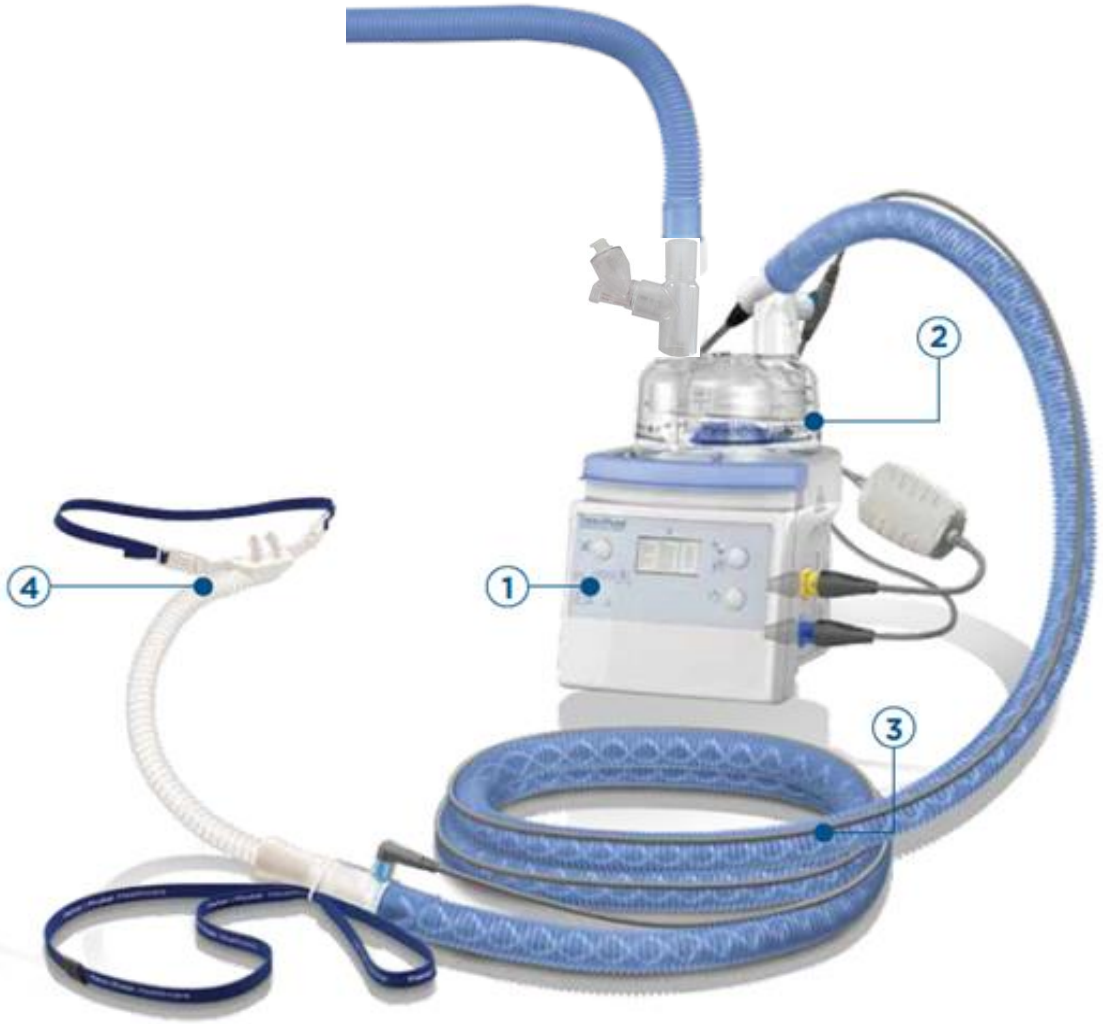


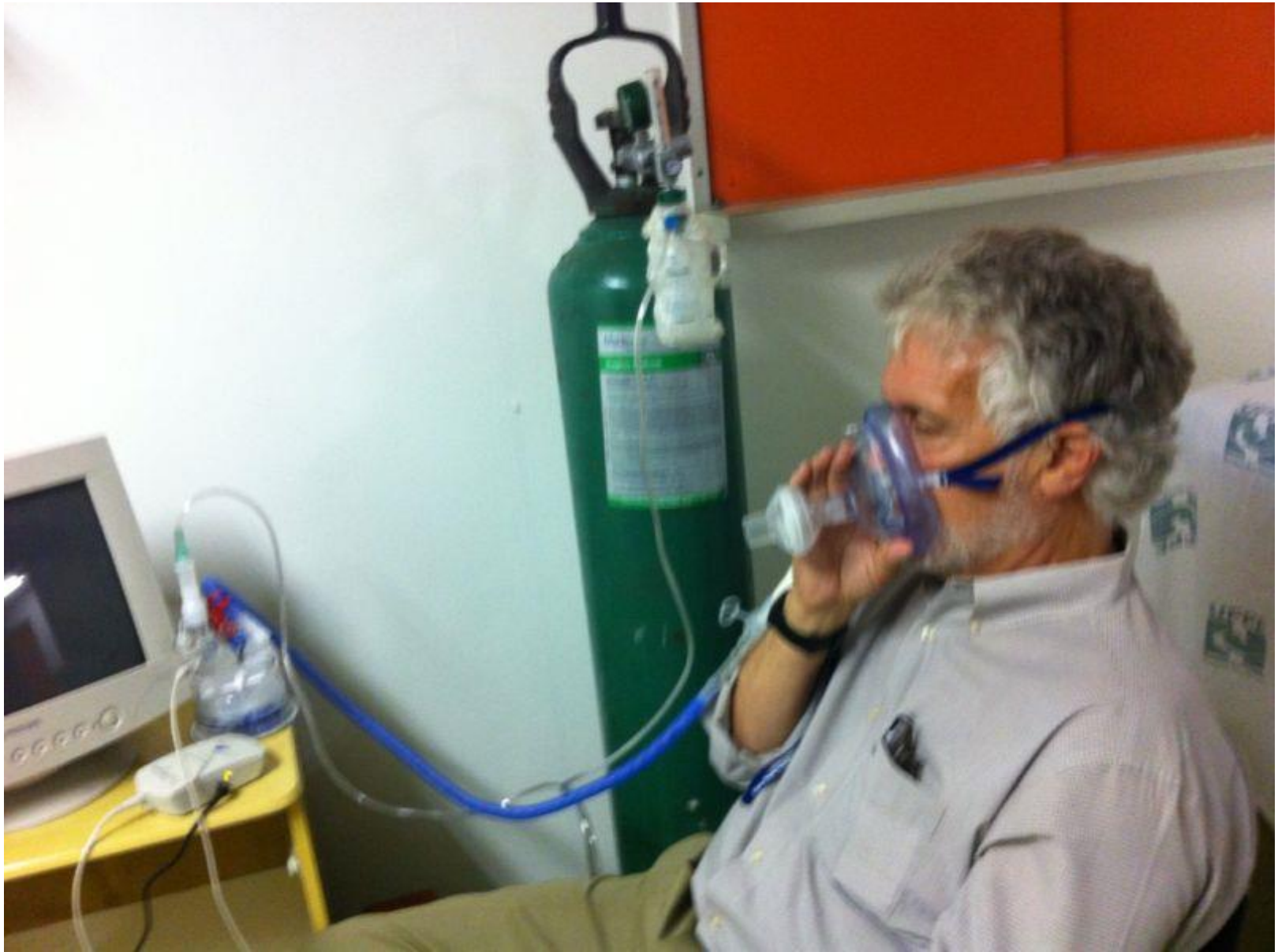
FIGURE 4-44 In vitro setup for testing aerosol delivery with a heated humidifier through a nasal cannula. The nebulizer is placed at the inlet of the humidifier, and the cannula is attached to a T-piece that allows aerosol to collect on filter 1 and condensate to collect on filter 2. This device can be used in infants, children, and adults.

Ari, Dailey, Fink 2009

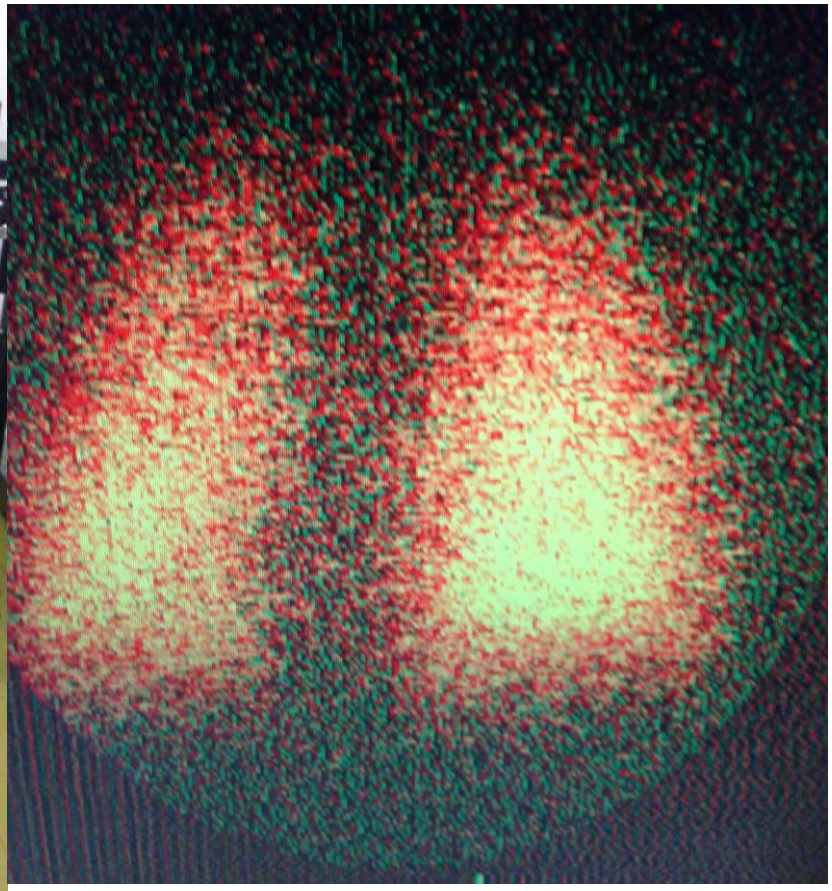
High Flow Nasal Cannula



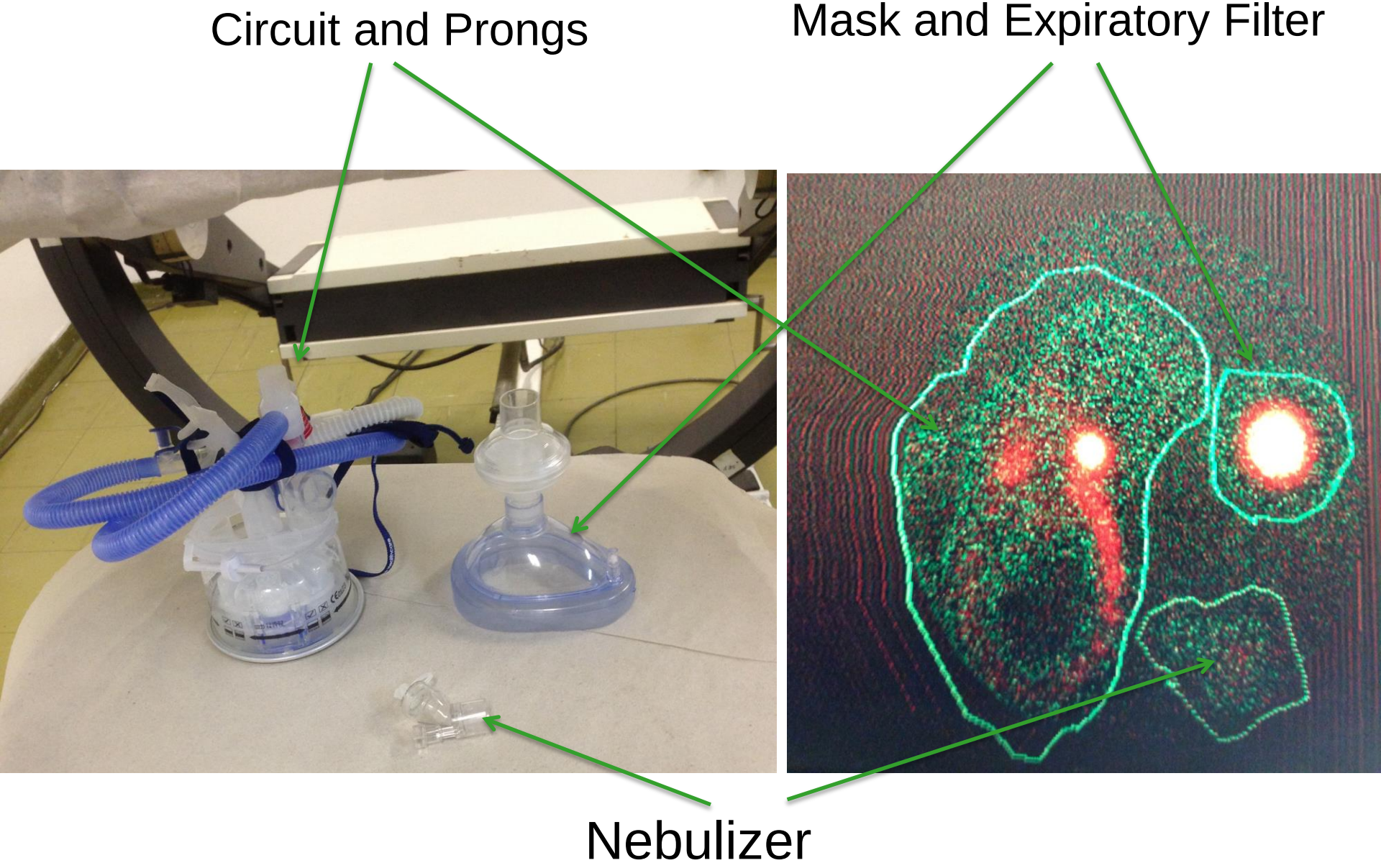
Mask with filter placed over the nasal cannula to collect aerosol that is not inhaled and aerosol that is exhaled.



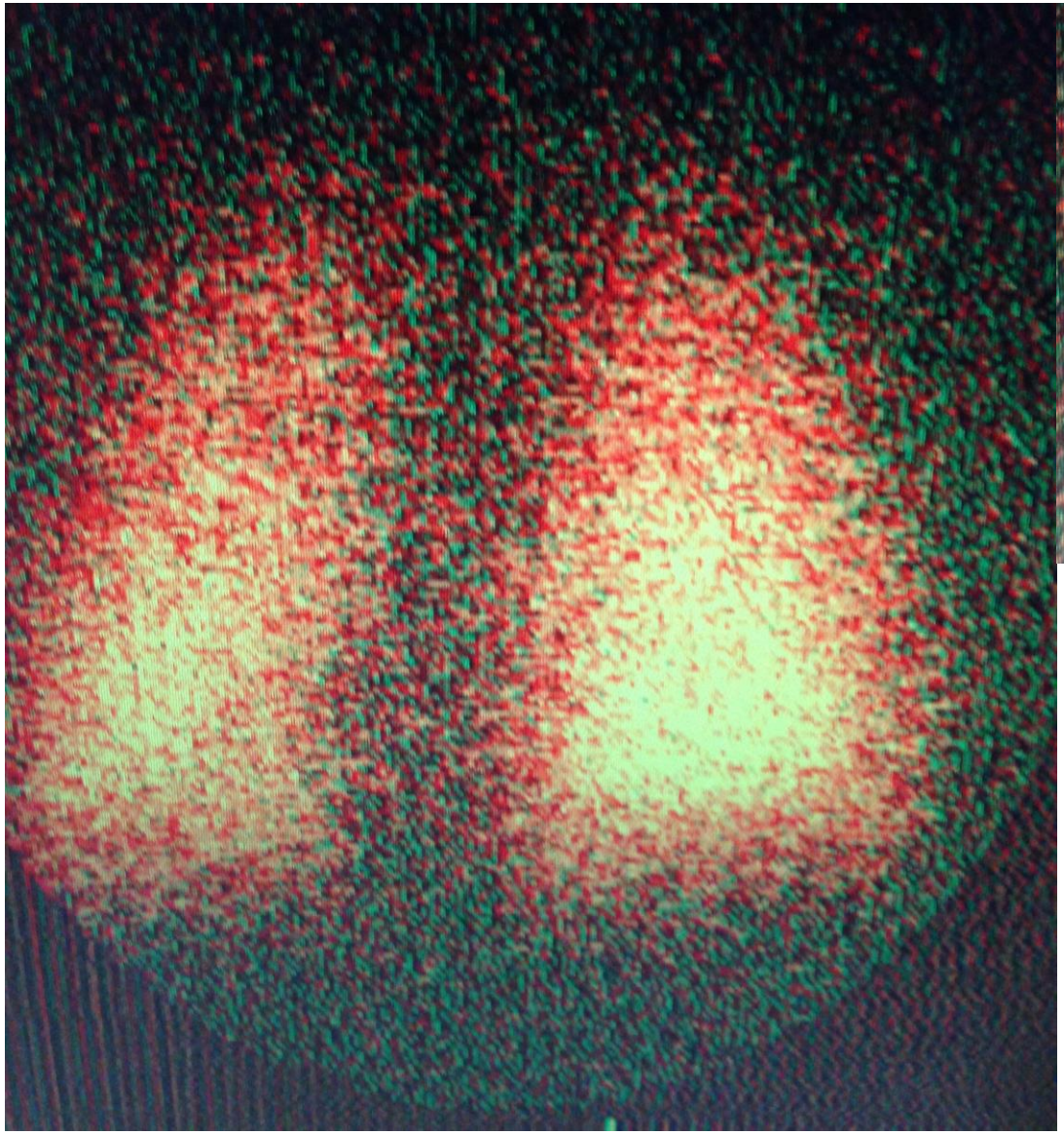
After administration, anterior scan of thorax for 300 secs with a 256x256 matrix.

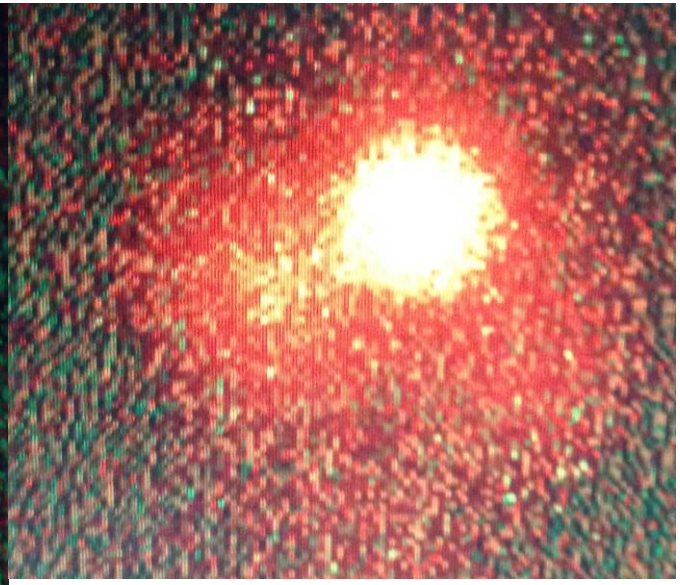


Circuit and nasal prongs, Mask with filter, nebulizer scanned.



HFNC 10 L/min 1 mCi in 1 mL





Study of Deposition with HFNC in an adult using two radiation doses
1 mL total dose with Vibrating Mesh nebulizer with 10 L/min Oxygen

HFNC 10 lpm

			1 mCi				1/2 mCi
Left Lung	73136			Left Lung	36962		
Right lung	87462			Right lung	46972		
Lung total	160598		15.4%	Lung total	83934		15.6%
stomach	2371		0.2%	stomach	1351		0.3%
Head	82133		7.9%	Head	47761		8.9%
Inhaled		245102	23.4%	Inhaled		133046	24.8%
Neb	15496		1.5%	Neb	9600		1.9%
circuit	277622		26.5%	circuit	163141		32.3%
Filter	347085		33.2%	Filter	115468		22.9%
		706840	61.2%			279569	57.0%
Total Count	1045903			Total Count	505189		

Observations Conclusion

- **N=2 feasibility study in an adult subject**
- **Consistent results with both 1 and 0.5 mCi**
  - Future studies should be with the lower inhaled dose, and determine lower limits
- **23 – 24% inhaled dose**
  - Consistent with previous in vitro models
- **15% lung dose**
- **Very low stomach deposition**
- **Homogenous distribution through lungs**

Ergonomic and High Efficiency Trans-Nasal Aerosol Delivery Platform Targeting Pulmonary Deposition with Minimal Deposition in the Nose

T Navratil[1], KL Zeman[2], F Fuller[2], D Taylor[3], W Thelin[1], P Boucher[1], B Button[2], J Fink[4], AJ Hickey[5], RC Boucher[2], MR Johnson[1], S Donaldson[2], WD Bennett[2]

1. *Parion* Sciences, Inc., Durham, NC, *United States;* 2. *University of North Carolina,* Chapel Hill, NC, *United States;* 3. *Cambridge Consultants,* Cambridge, *United Kingdom;* 4. *Georgia State University,* Atlanta, GA, *United States;* 5. *RTI International,* Research Triangle Park, NC, *United States.*

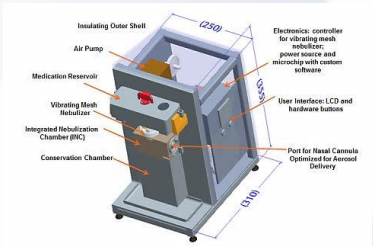
Background

- Trans-nasal delivery of aerosols to the lungs may offer benefits over the oral route for a range of patient populations and healthcare settings
- In supplemental oxygen studies, patients favor ergonomic nasal cannulas over face masks
- However, aerosols from conventional nebulizers are not suitable for delivery via narrow-bore nasal cannulas (large particles > 4 µm impact or sediment during the travel through the nasal cannula)
- The reported pulmonary deposition efficiencies of trans-nasal aerosols in human subjects have been low (approximately 1-5% of the emitted dose)
- Parion's Trans-nasal Pulmonary Aerosol Delivery (tPAD) platform aims to enable delivery of aerosols via an ergonomic, optimized supplemental oxygen-like nasal cannula over extended periods of time with deposition efficiencies equaling that of oral aerosol delivery

Objectives

- To design and develop a Trans-Nasal Pulmonary Aerosol Delivery device (tPAD device) for use with hyperosmotic agents, antibiotics, mucolytics and other agents for extended administration towards (1) accommodating patient preferences; (2) improving efficacy and tolerability of these agents; and (3) reducing daytime treatment burden in CF and other respiratory diseases
- To determine safety, tolerability and deposition efficiency of the tPAD device in a Phase 1 clinical study in healthy human subjects

tPAD-1 Clinical Device
(Designed for Phase 1 and 2 Clinical Studies)



Patient Preferences for the tPAD Device

- A Human Factors Study was conducted to determine patient preferences for a concept trans-nasal aerosol delivery device were determined in interviews with 31 CF patients
- The conceptual tPAD platform was presented as an overnight aerosol delivery device to replace daytime inhaled CF medications

Table 1. Select Demographic and Inhaled Pharmacotherapy Data for CF Patients in Human Factor Study (Median of 2.5 h of Pharmacotherapy/Day)

Key Traits	Age			Concomitant Medications			
	5-12	13-17	18+	DNase	HS	Tobramycin	Cayston
% (n)	26% (8)	26% (8)	48% (15)	97% (30)	77% (24)	45% (14)	42% (13)

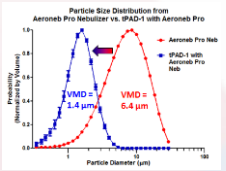
STUDY RESULTS:

- 90% of CF patients spontaneously indicated they would use tPAD platform
- Most suggested to deliver all inhaled therapy in tPAD
- Supplemental oxygen cannula was preferred to CPAP or other face-piece device

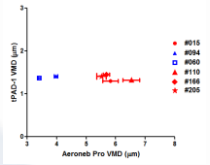
Studies Funded by Parion Sciences and NIH Grant 1 PO1 HL 108801-01A1

tPAD Device Performance

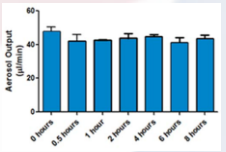
tPAD-1 Device Produces Optimized Aerosol for Nasal Delivery



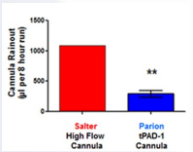
tPAD-1 Uniform Particle Size Output Regardless of Aerosol Input



tPAD-1 Consistent Aerosol Output from the Nasal Cannula over 8h



Significantly Less Rainout with tPAD-1 than High Flow Oxygen Cannulas

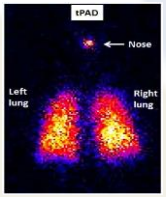


tPAD-1 Deposition Study in Healthy Volunteers

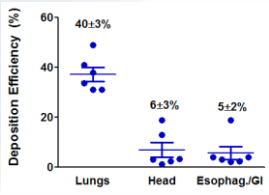
- Parion conducted a Phase 1 Safety, Tolerability and Deposition Efficiency Study of Radio-Labeled 7% Hypertonic Saline (^{99m}Tc-DPTA) Administered by the tPAD-1 Device to Healthy Human Subjects in collaboration with the University of North Carolina at Chapel Hill

STUDY RESULTS:

- In 6 healthy human subjects (3 males, 3 females; age >18 years), there were no adverse events, intolerability events, or measurable decreases in FEV_1 as detected in safety spirometry
- The tPAD-1 Device demonstrated substantially higher pulmonary deposition (and lower nasal deposition) compared to traditional nasal aerosol delivery techniques)



Representative gamma-camera scan following 15-min administration of ^{99m}Tc-labeled 7% hypertonic saline by the tPAD-1

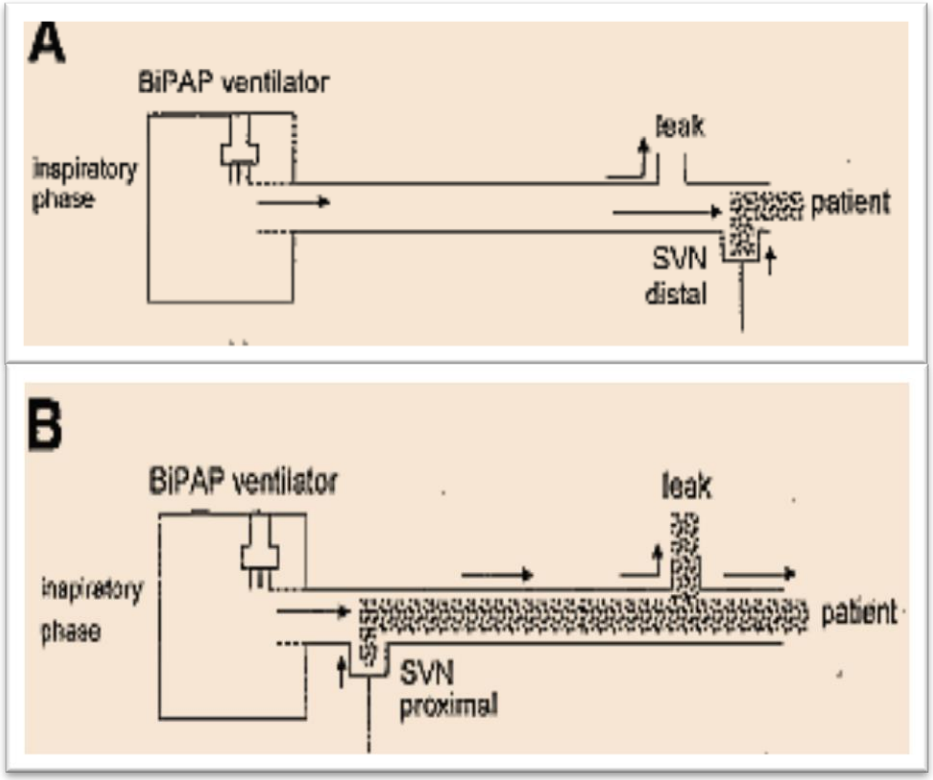


Regional deposition efficiencies for 7% hypertonic saline administered by the tPAD-1 Device (Mean±SEM)

Conclusions

- High level of patients' willingness (28/31) to adopt the tPAD platform was identified in a human factor study preceding the tPAD device development
- tPAD-1 Devices produces consistent aerosol output, controlled aerosol particle size ~1.4 µm VMD, and very limited "sputter" from the prongs of nasal cannula were achieved
- Excellent safety, tolerability and high pulmonary deposition efficiency (38% based on emitted dose) were demonstrated with the tPAD-1 device in healthy human subjects in Phase 1 clinical study
- Parion Sciences is developing the tPAD platform in combination with hydrating agents to improve the efficacy and tolerability of these agents and to reduce the daytime treatment burden in CF and other respiratory diseases

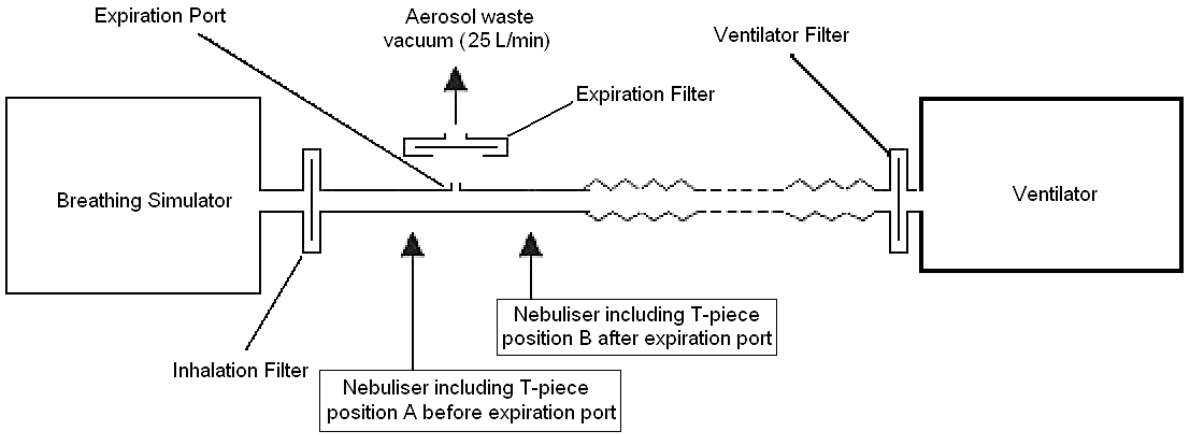
Aerosol Delivery and NIV – place neb between leak and patient



- Drug delivery influenced by:
  - Nebulizer position
  - Breathing frequency
  - IPAP/EPAP settings

Chatmongkolchart S et al *Crit Care Med* 2002;30:2515-2519.

Position Neb Between Leak and Mask for best delivery



Nebulizer	Position closer to filter (A)		Position farther from filter (B)	
	Inhalation Filter (µg)	Nebulizer (µg)	Inhalation Filter (µg)	Nebulizer (µg)
Aeroneb	2573 ± 151	891 ±163	936 ± 273	1001 ± 263
Sidestream	1207 ± 161	2261 ± 795	341 ± 70	2420 ± 154

Abdelrahim ME et al *J Pharmac Pharmacol* 2010; 62;966-72.

Bench Study: Pediatric aerosol delivery during non-invasive ventilation

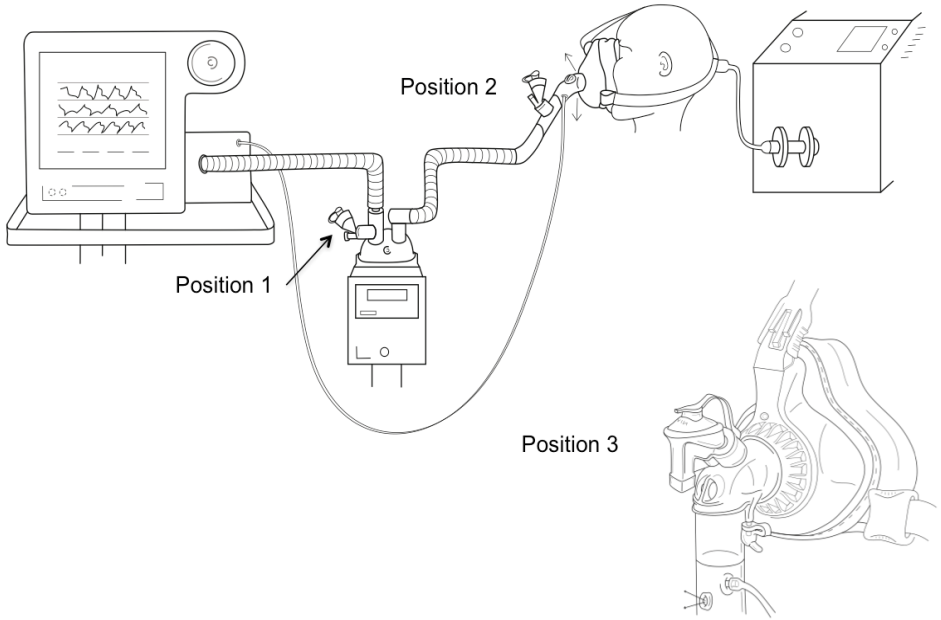


Figure 1

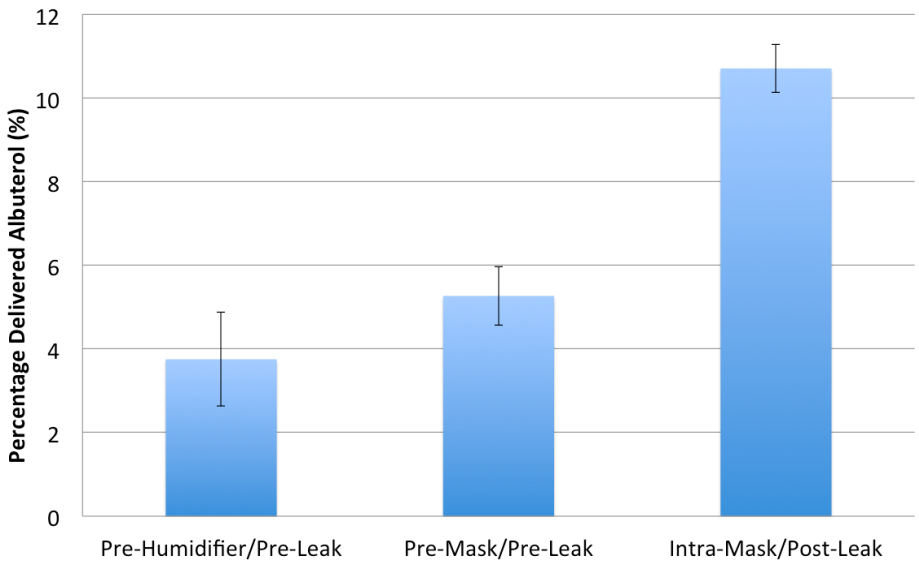


Figure 3

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

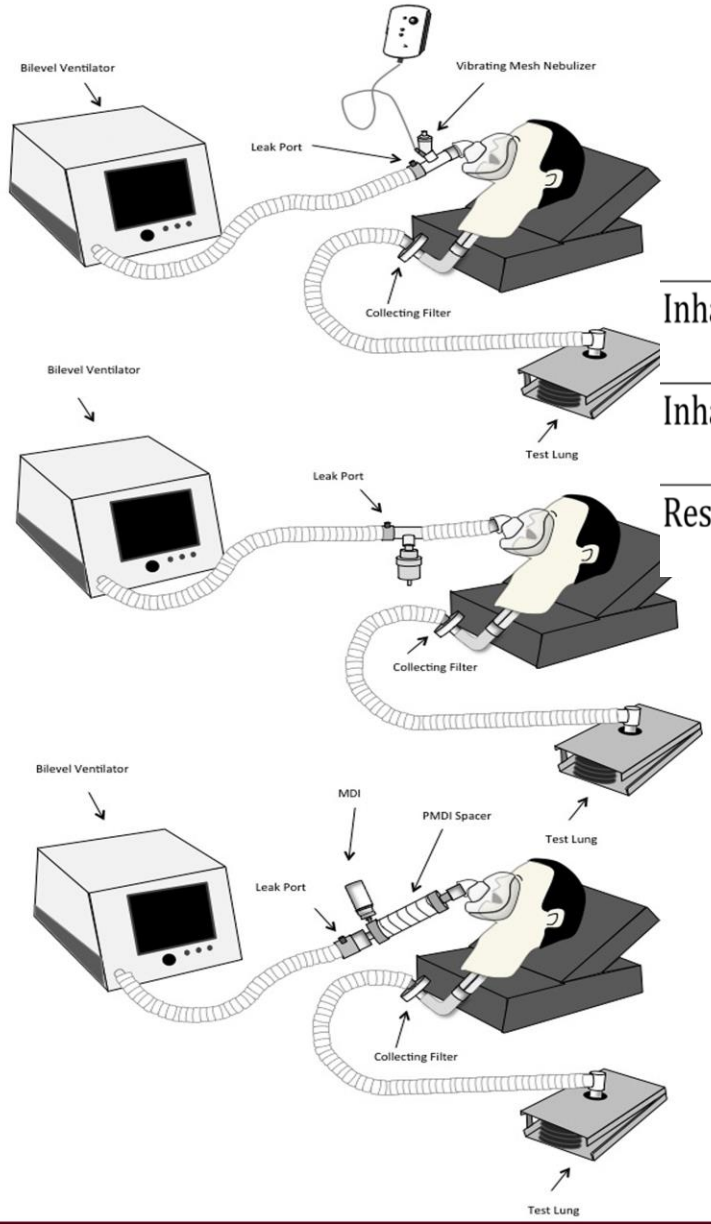
White CC, 2013. Bronchodilator delivery during simulated pediatric noninvasive ventilation. Respiratory Care. Published ahead of print February 5, 2013, doi:10.4187/respcare.02171

Aerogen®

EFFICIENCY OF AEROSOL DEVICES DURING NONINVASIVE POSITIVE PRESSURE VENTILATION IN A SIMULATED ADULT LUNG MODEL

Maher M. AlQuaimi BsRc RRT, James Fink PhD, RRT, FAARC, FCCP, Robert Harwood,MSA,RRT,Meryl M Sheard MSc RPFT, Arzu Ari, PhD, RRT, PT, CPFT,FAARC
Georgia State University, Atlanta, GA

Experimental setup used with VMN, JN, and pMDI

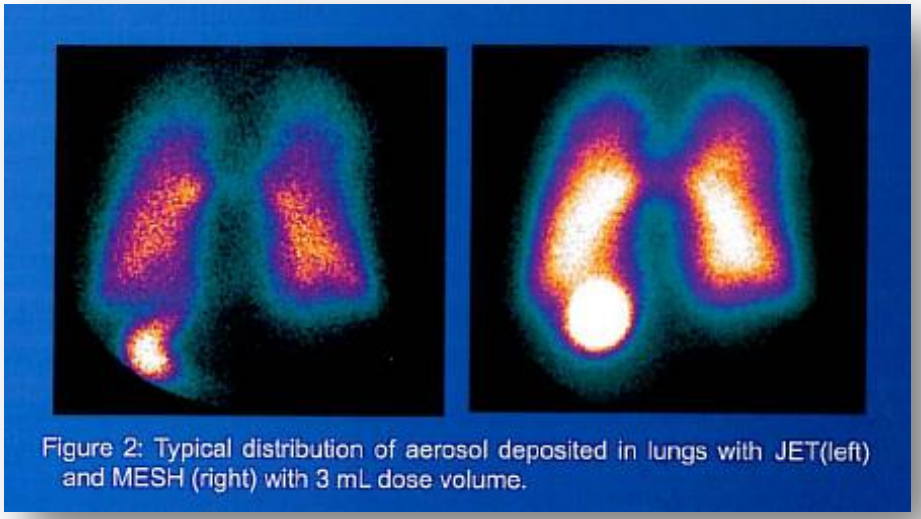


	JN	VMN	pMDI-N	pMDI-R
Inhaled Mass (mg)	0.33 ± 0.02	0.72 ± 0.05	0.10 ± 0.01	0.09 ± 0.01
Inhaled Mass Percent (%)	13.12 ± 0.72	28.83 ± 1.93	23.53 ± 2.03	21.38 ± 0.32
Residual volume (ml)	1.65 ± 0.14	0.10 ± 0.07		

Vibrating Mesh (VMN) > 2 fold more than Jet

VMN and pMDI similar dose efficiency

Lung Dose JN vs Mesh



Lung deposition (corrected for absorption) with the Mesh was > 3 fold greater than JN, independent of dose volume used with the MESH.

Neb/Dose	JET NEB 3 mL	MESH 3 mL
Total Lungs	1.97 ± 0.8%	8.26 ± 1.1 %*
Inhaled Dose	7.31 ± 4.3%	27.3 ± 10.1 %*

*p<0.0001 (MESH 3 mL vs JN 3 mL) and
**p<0.007 (MESH 1 mL vs JN 3 mL).

Medications via Aerosol to Intubated Patients

- Bronchodilators
- Anti-infectives
- Prostanoids
- Anticoagulants - Heparin
- Diuretics
- Insulin
- Perfluorocarbons (PFCs)

Limitations to Delivery of Prostacyclincs in the ICU/OR

- **Iloprost and Treprostinil are only drugs approved for treatment pulmonary hypertension for inhalation in adults, but not readily available for use in the ICU**

- **Flolan is not approved for inhalation**
  - Has short half life – 2 – 3 minutes, requiring continuous aerosol delivery

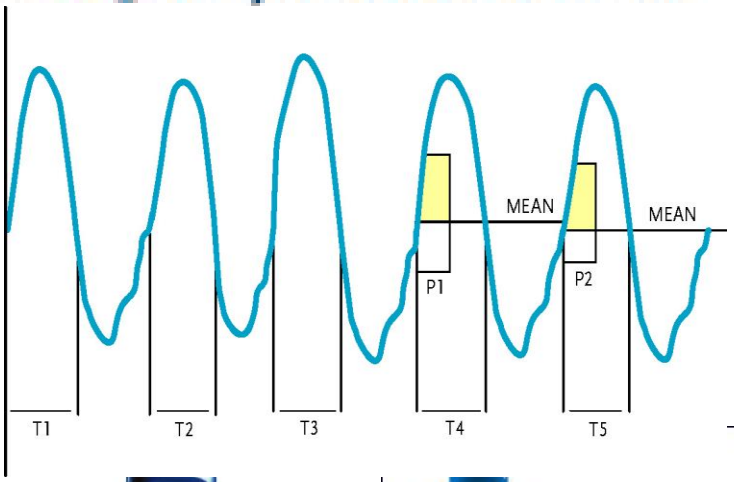
- **In general it is better to use drugs approved for inhalation when they are available.**

- **Difficult to translate between devices to determine comparable dosing.**

INHALED

Ventavis®

(iloprost) INHALATION SOLUTION



Aerosolized Iloprost is a Viable Alternative to Inhaled Nitric Oxide in Post Cardiothoracic Surgery Patients

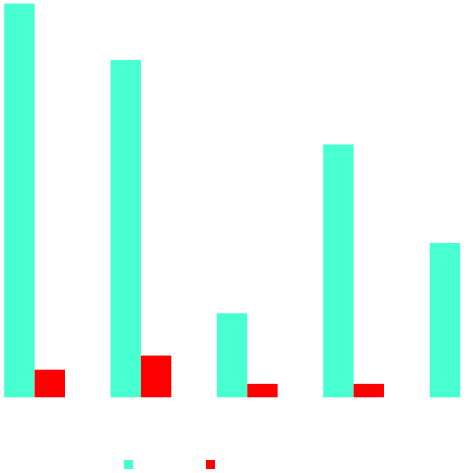
John D. Davies MA RRT FAARC, Michael A. Gentile RRT FAARC, Janice J. Thalman MHS RRT FAARC, Neil R. MacIntyre MD FAARC
Duke University Medical Center
Durham, NC

Background

Results

NO_x Reactive, propensity for toxic cellular reactions

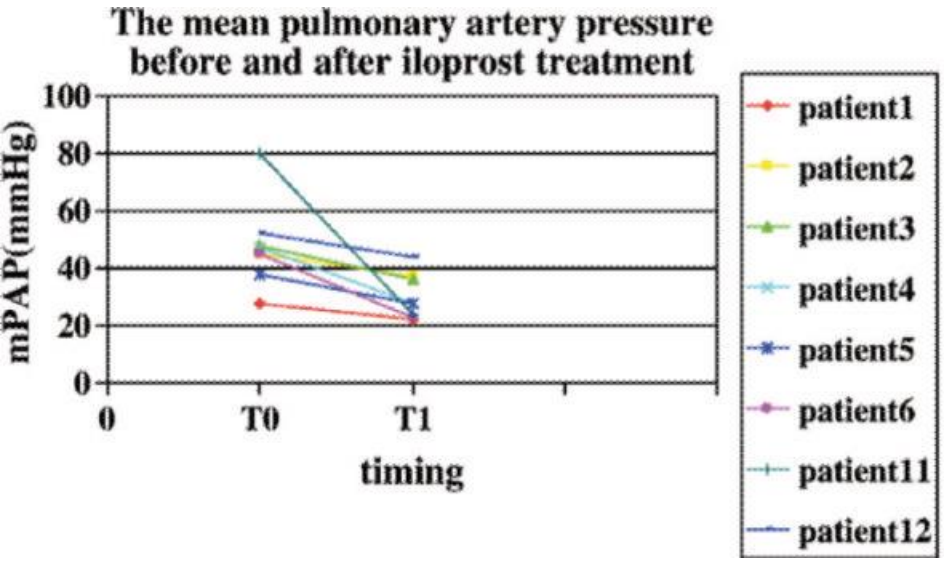
↑ cGMP

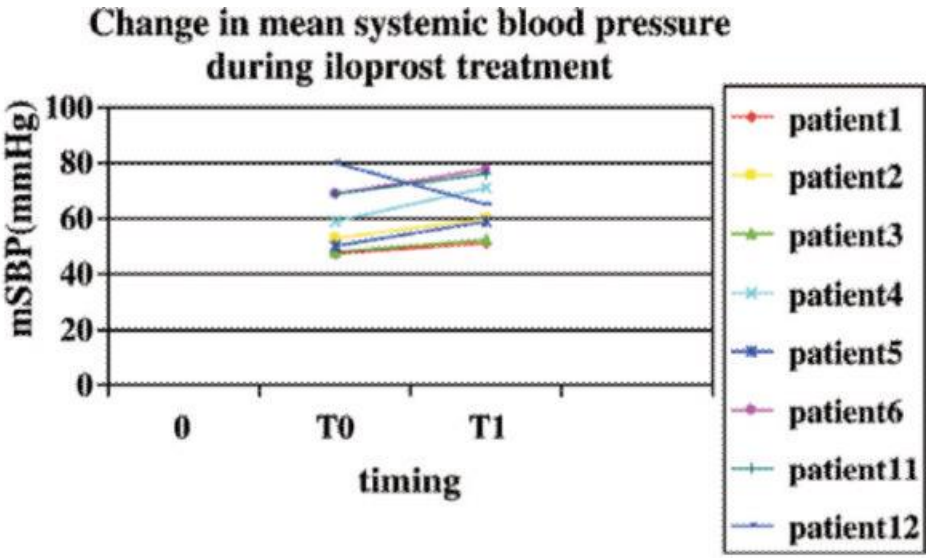


Methods

Results

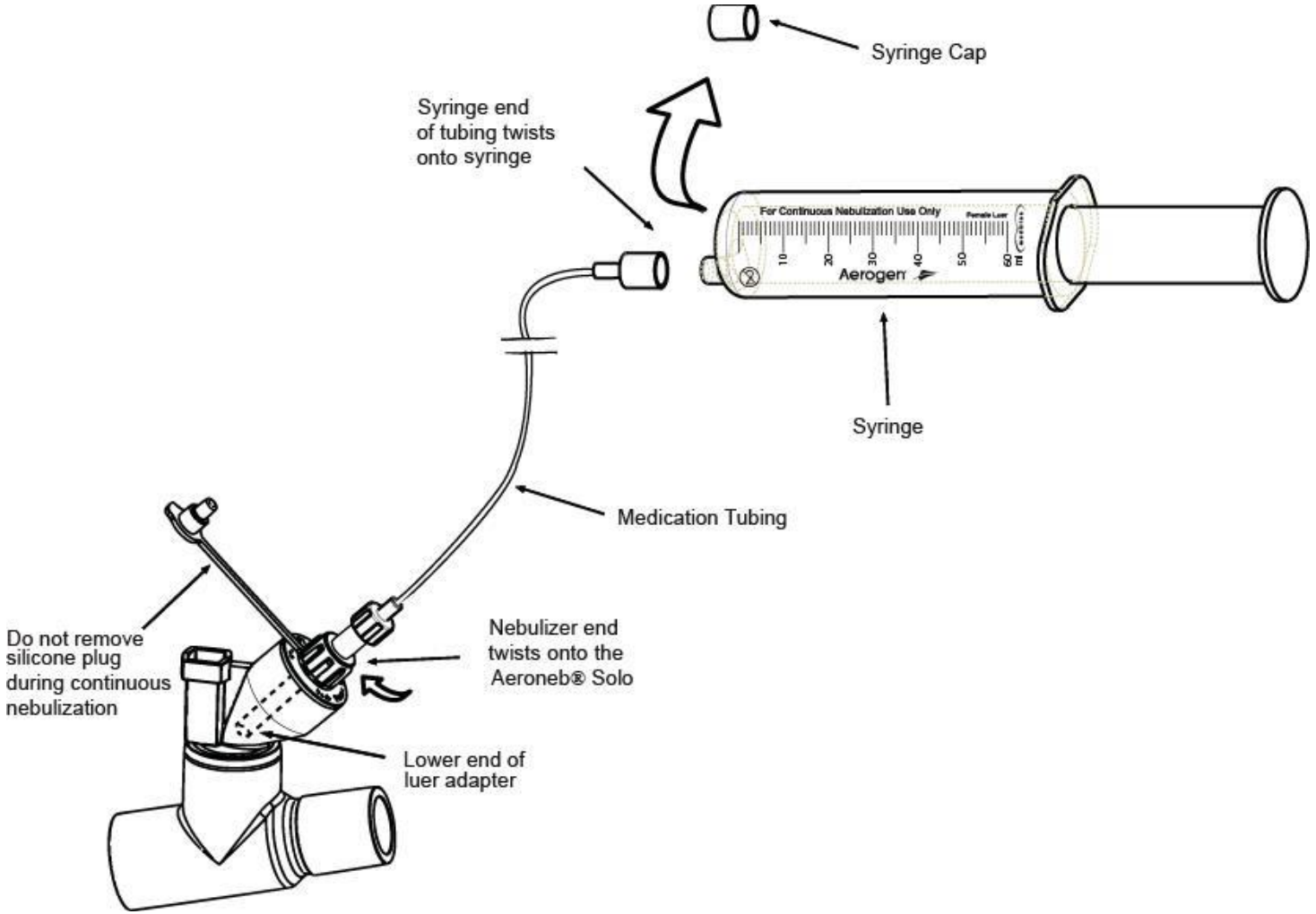
Conclusion





Effect of inhaled iloprost in 12 children with postoperative congenital heart disease. Iloprost lowered mean pulmonary artery pressure (mPAP) without lowering mean systemic blood pressure (mSBP). Limsuwan et al

Continuous Feed Set



Aerogen®

The Pulmonary Infusion Pump

- A precise variable aerosol delivery system
- Medication is nebulized “ drop by drop “ as it reaches the aerosol generator
- Aerosol is not generated between drops
- For continuous aerosol therapy Mesh is on continuously, and aerosol is generated intermittently
- Pump rate is directly linear with aerosol output rate.
- No buildup of aoerosl in reservoir.

Conversion from inhaled nitric oxide to inhaled epoprostenol reduces costs of inhaled pulmonary vasodilator therapy in critically ill patients

Susan LaGambina RRT[1], Paul Nuccio MS RRT FAARC[1], Heather Torbic PharmD BCPS[2], Kevin E. Anger PharmD BCPS[2], Paul M. Szumita PharmD BCPS[2], Gerald Weinhouse MD[3]

Department of Respiratory Care Services[1]; Department of Pharmacy[2]; Pulmonary Division [3], Brigham and Women's Hospital, Boston, MA

HARVARD MEDICAL SCHOOL *TEACHING AFFILIATE*

Background

- Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO) are potent pulmonary vasodilators that have been given off label as rescue therapy for severely hypoxic, critically ill patients
- Limited data exists evaluating the efficacy of these agents in a diverse cohort of critically ill patients

Purpose

- To describe process and associated costs for inhaled epoprostenol use

Methods

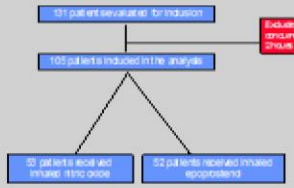
- Retrospective, single-center analysis of adult mechanically ventilated (MV) patients receiving iNO or iEPO for pulmonary vasodilation
- Patients were enrolled between January 1, 2009 and October 31, 2010
- This study was approved by our institutional IRB
- Inclusion criteria
  - ≥ 18 years old
  - Admitted to an intensive care unit at Brigham and Women's Hospital
  - Received either iNO or iEPO
- Exclusion criteria
  - Received > 2 hours of concomitant iNO and iEPO

Methods

- Data assessed
  - Patient demographics
  - Therapy duration
  - Cost
- Outcomes
  - Cost
    - Total cost of iNO
      - Duration of therapy (hours) x low/mean/high University HealthSystem Consortium contract pricing
    - Patient Cost of iNO
      - Duration of therapy (hours) per patient x low/mean/high University HealthSystem Consortium contract pricing
    - Total Cost of iEPO
      - Quantity of therapy used (bags) x AWP non-contract generic epoprostenol pricing
    - Patient Cost of iEPO
      - Quantity of therapy used (bags) per patient x AWP non-contract generic epoprostenol pricing
- Statistical analysis
  - Categorical and continuous variables were compared by using the Student *t* test, χ^2, and the Mann-Whitney U test where appropriate
  - All *p* values were two tailed and statistically significant at an alpha of ≤ 0.05

Results

Patient Enrollment



Patient Characteristics

	Inhaled Nitric Oxide (N=53)	Inhaled Epoprostenol (N=52)	p value
Age, years*	51.8 ± 17.9	56.4 ± 15.3	0.21
Gender – Male**	22 (41.5%)	21 (40.4%)	0.91
Weight, kg*	84.2 ± 28.7	102.9 ± 47.3	0.04
Ethnicity			
White**	44 (83.0%)	47 (90.3%)	0.74
African American**	4 (7.5%)	2 (3.8%)	0.66
Hispanic**	3 (5.7%)	2 (3.8%)	0.98
Asian**	2 (3.8%)	1 (1.9%)	0.57
APACHE II‡	18 (15.5-21)	18 (15-22)	0.69
Comorbidities			
Hypertension**	20 (37.7%)	21 (40.4%)	0.94
Coronary Artery Disease**	26 (49.1%)	16 (30.8%)	0.09
PAH**	8 (15.1%)	12 (23.1%)	0.43
CHF**	13 (24.5%)	7 (13.5%)	0.23
COPD**	11 (20.8%)	7 (13.5%)	0.46
Asthma**	6 (11.3%)	6 (11.5%)	0.97
Active Malignancy**	6 (11.3%)	4 (7.7%)	0.76
SOT**	8 (15.1%)	1 (1.9%)	0.04
Indication			
Pulmonary Resection**	6 (11.3%)	3 (5.8%)	0.50
ARDS**	15 (28.4%)	29 (55.8%)	0.008
Heart/Lung Transplant**	5 (9.4%)	1 (1.9%)	0.22
Acute RV Failure**	27 (50.9%)	19 (36.5%)	0.20

‡ Median (IQR)
* Mean±SD
** n (%)

Therapy Duration

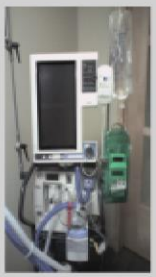
	Inhaled Nitric Oxide (N=53)	Inhaled Epoprostenol (N=52)	p value
Duration of Study Therapy, days	3.5 ± 2.7*	3.2 ± 2.6*	0.66
	2.3 (0.6-4.8)†	2.0 (0.9-4.3)†	0.63
Amount of Study Therapy Used, hrs	83.3 ± 90.0*	72.7 ± 85.4*	0.54
	54.4 (15-115.5)†	47.9 (20.9-102.6)†	0.63

† Median (IQR)
‡ Mean±SD

Cost

	iNO (N=53)	iEPO (N=52)	p value
Total Cost, USD*			
Low iNO Contract Price	206,345		<0.0001
Mean iNO Contract Price	486,775	43,995	<0.0001
High iNO Contract Price	749,190		<0.0001
Cost of Therapy Per Patient, USD*			
Low iNO Contract Price	3,930 ± 4,210		<0.0001
Mean iNO Contract Price	9,250 ± 9,910	838 ± 997	<0.0001
High iNO Contract Price	14,240 ± 15,255		<0.0001

USD = U.S. Dollar
*Based off University HealthSystem Consortium (UHC) survey of nitric oxide contract pricing range



Limitations

- Single center study, retrospective study
- Small population size
- Change in practice

Conclusion

- Our inhaled epoprostenol requires a multidisciplinary effort from order entry to administration
- Inhaled nitric oxide is 4.5-17 times more expensive per patient than inhaled epoprostenol

Disclosures

- The authors of this presentation have no disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

References

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2. Khan TA, Schmickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg.* 2003;126(6):1417-1424.
3. Fiser SM, Cope JT, Kron IL, et al. Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantion. *J Thorac Cardiovasc Surg.* 2001;121:981-982.

Dixon et al. Critical Care 2010, 14:R180
http://ccforum.com/content/14/5/R180

CRITICAL CARE

RESEARCH Open Access

Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: a randomized controlled trial

Barry Dixon[1*], Marcus J Schultz[2], Roger Smith[1], James B Fink[3], John D Santamaria[1], Duncan J Campbell[4,5]

Abstract

Introduction: Prolonged mechanical ventilation has the potential to aggravate or initiate pulmonary inflammation and cause lung damage through fibrin deposition. Heparin may reduce pulmonary inflammation and fibrin deposition. We therefore assessed whether nebulized heparin improved lung function in patients expected to require prolonged mechanical ventilation.

Methods: Fifty patients expected to require mechanical ventilation for more than 48 hours were enrolled in a double-blind randomized placebo-controlled trial of nebulized heparin (25,000 U) or placebo (normal saline) 4 or 6 hourly, depending on patient height. The study drug was continued while the patient remained ventilated to a maximum of 14 days from randomization.

Results: Nebulized heparin was not associated with a significant improvement in the primary end-point, the average daily partial pressure of oxygen to inspired fraction of oxygen ratio while mechanically ventilated, but was associated with improvement in the secondary end-point, ventilator-free days amongst survivors at day 28 (22.6 ± 4.0 versus 18.0 ± 7.1, treatment difference 4.6 days, 95% CI 0.9 to 8.3, $P = 0.02$). Heparin administration was not associated with any increase in adverse events.

Conclusions: Nebulized heparin was associated with fewer days of mechanical ventilation in critically ill patients expected to require prolonged mechanical ventilation. Further trials are required to confirm these findings.

Trial registration: The Australian Clinical Trials Registry (ACTR-12608000121369).

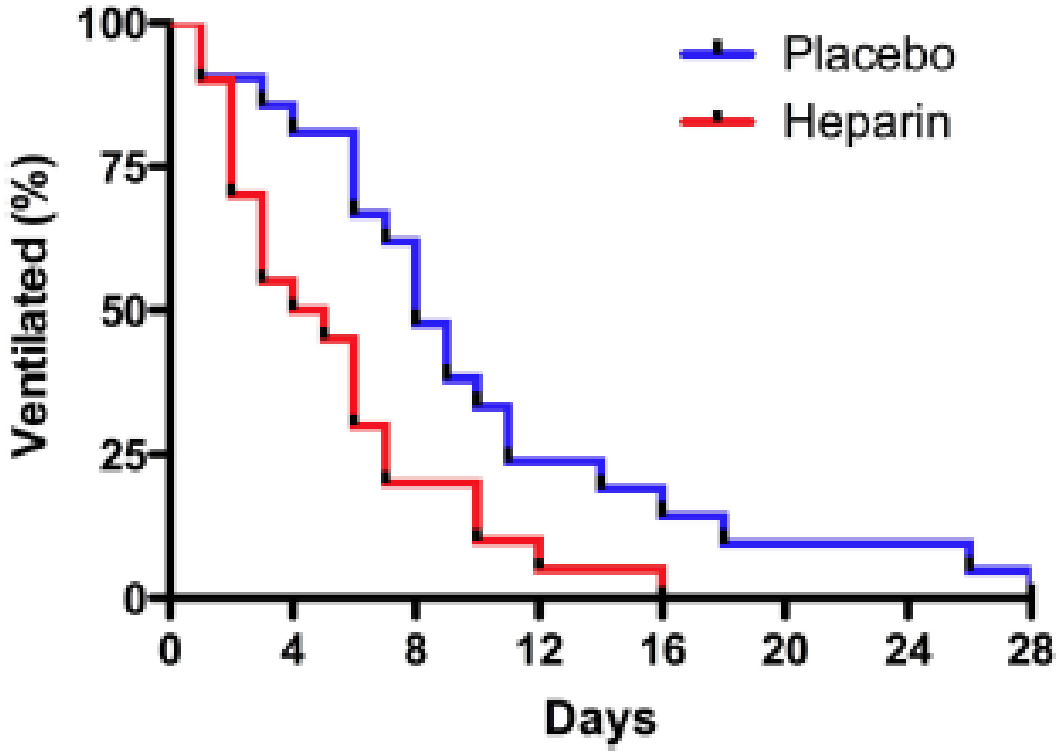
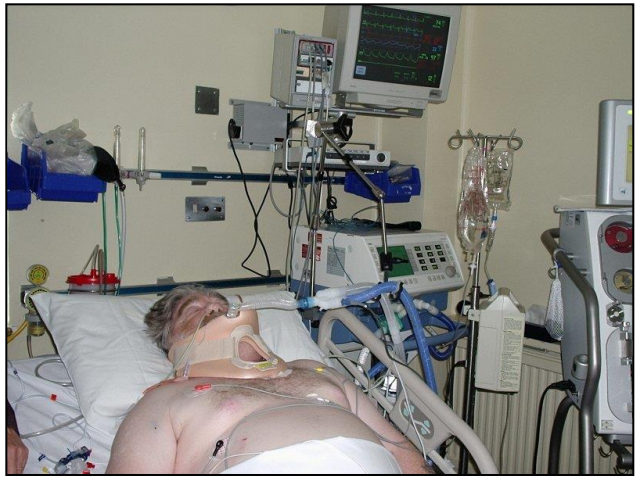


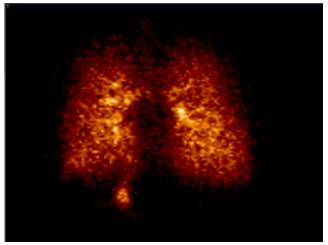
Figure 3 Rate of freedom from mechanical ventilation. Over the first 28 days among surviving patients, the rate of freedom from mechanical ventilation was higher in patients administered heparin. Median times of ventilation were 5 days in the heparin group ($n = 20$) and 8 days in the placebo group ($n = 21$) ($P = 0.01$) (log-rank test).

Ventilator and Hospital Acquired Pneumonias (VAP/HAP)

(MRSA)

Prevalence of pneumonia high in ventilated patients





ICU Patients

***Multiple conditions require ventilation**

5% - 10% on Mechanical Ventilation (MV)

8-28% of MV patients develop VAP[1]

Patients with MV VAP in 2007[2]

US: 250K patients

EU: 300K patients

Mortality from VAP ranges from 33-50%[3]

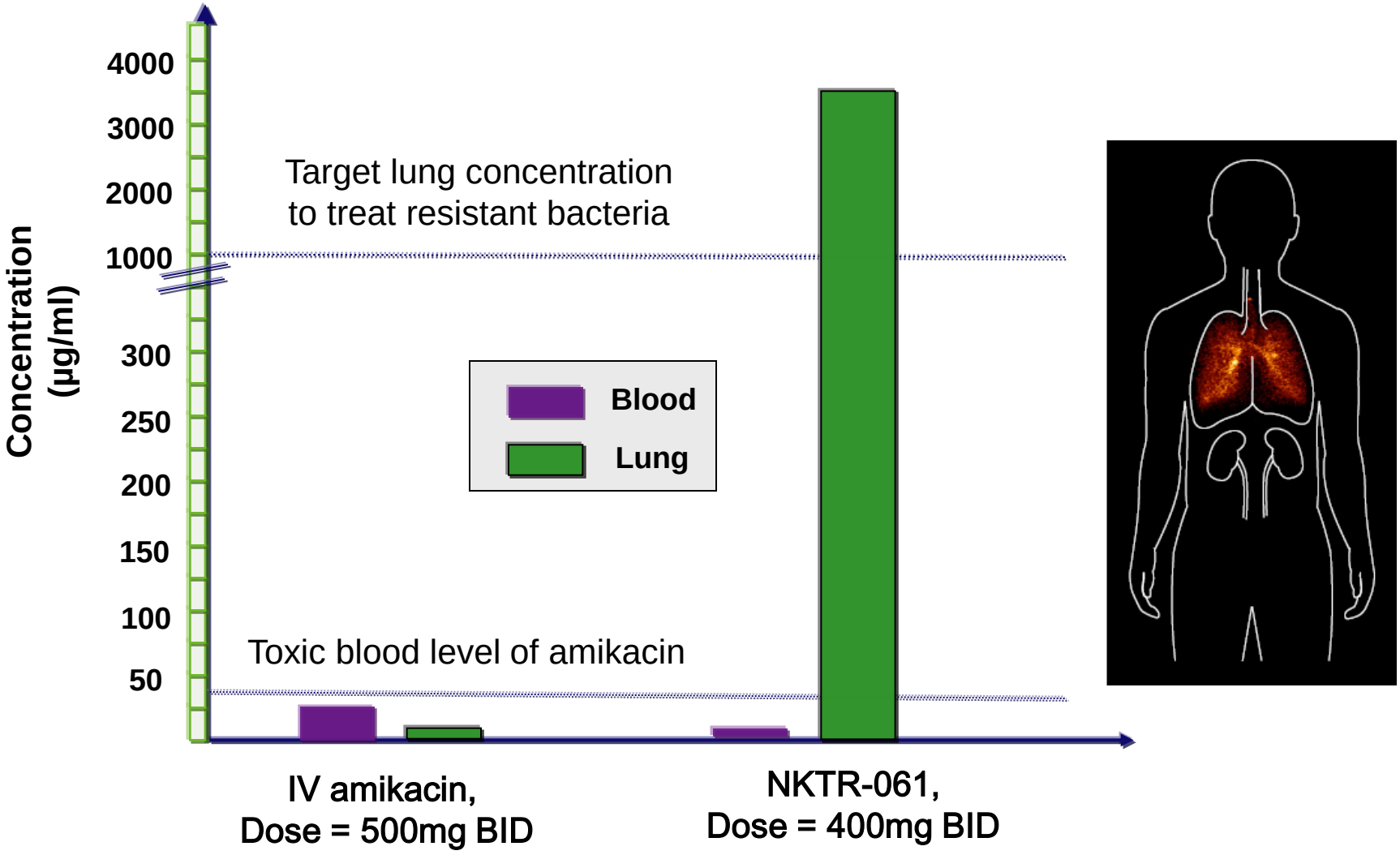
Up to 250K Deaths per year

New treatment options needed

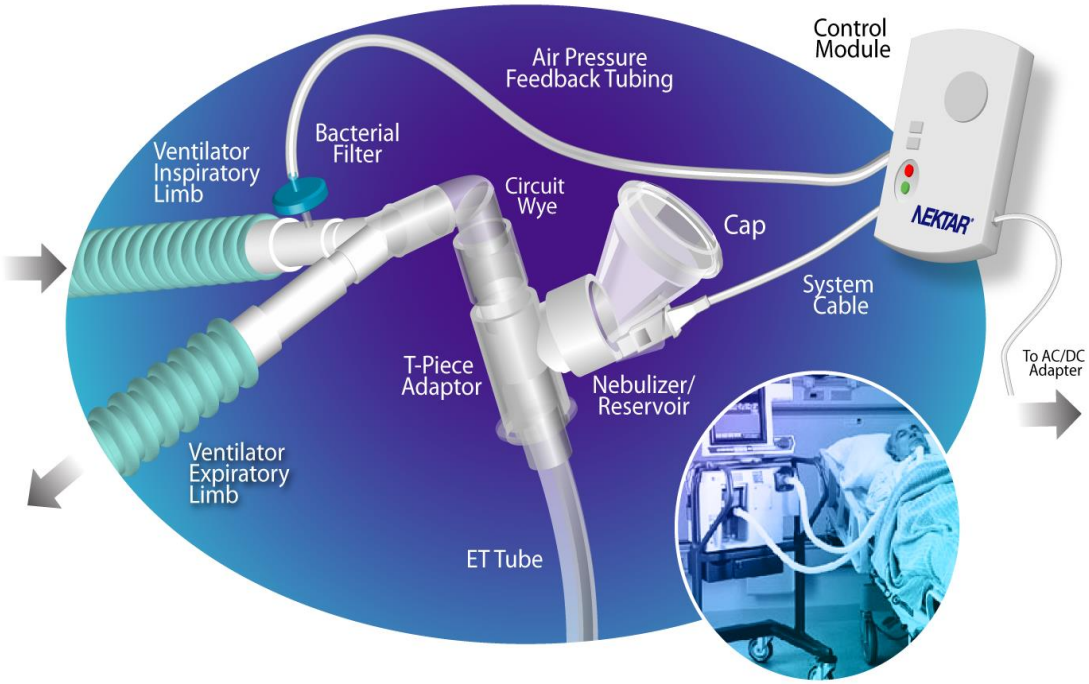
Note: *Acute Lung Injury, Acute Respiratory, Acidosis, Apnea, Chronic Obstructive Pulmonary Disease, Hypotension, Hypoxemia, Tachypnea

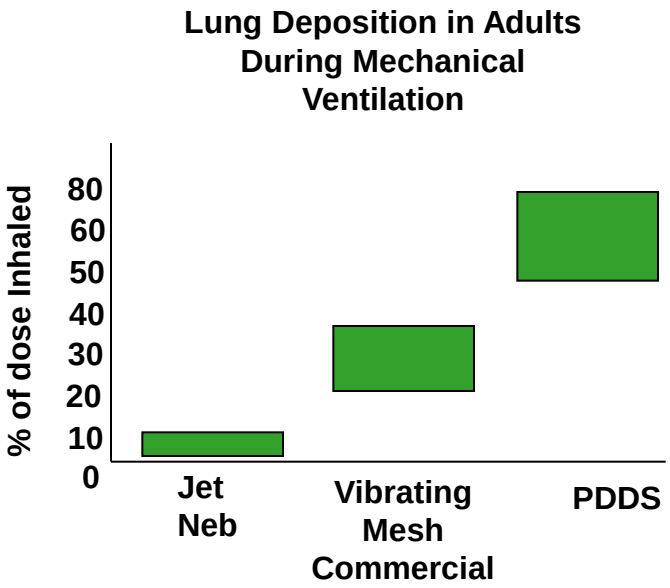
Source: [1,3] Chastre, Fagon, Am. Journal Critical Care Medicine, 2002, [2] AMR, [4] Rello, et al, Chest 2002

Delivery of inhaled amikacin during mechanical ventilation targets the lung without systemic toxicity



Pulmonary Drug Delivery System for Drug Development

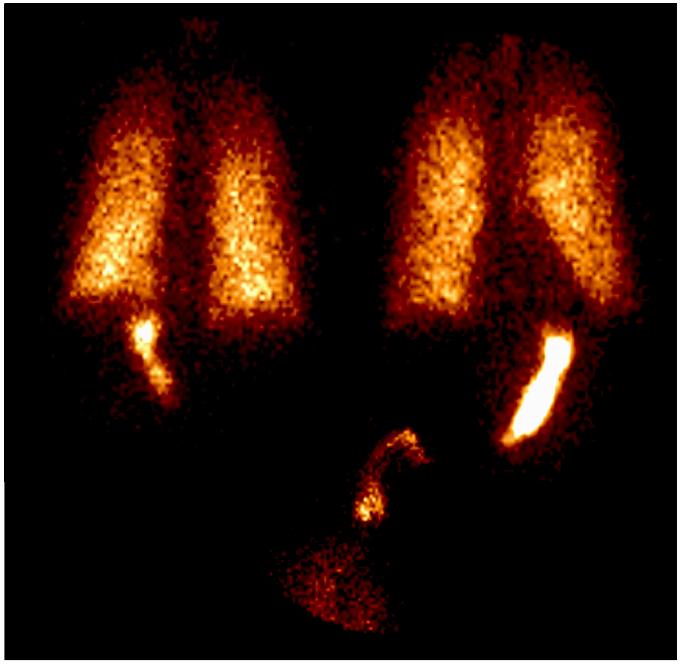




Invitro/ Invivo Correlation of Inhaled Amikacin During CMV with Jet Neb, Vibrating Mesh and PDDS

	Lung Dose In Vitro %	Sputum Conc (µg/mL/mg)	Amikacin Excretion/Dose
Jet Neb	7 ± 1	6.5 ± 9.5	1.9 ±1.2
Mesh	31± 4	31 ± 35	3.8 ± 1.6
PDDS	51± 11	54 ± 71	6.4 ±2

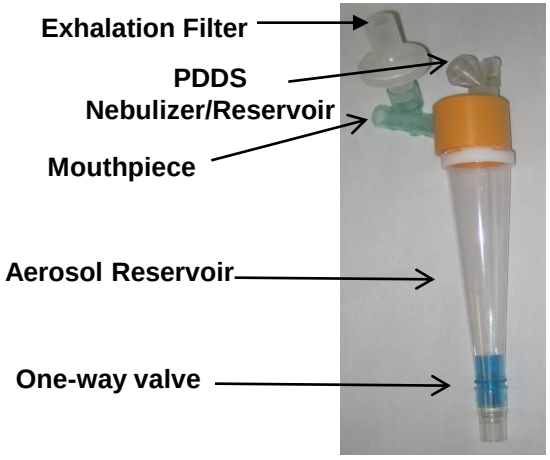
Gamma scintigraphy study with inhaled amikacin off ventilator



Posterior and anterior scintigraphic images

	Deposition	
	Mean	**S.D.**
Device	16.1	4.8
Oral	29.4	7.3
Lung	**43.0**	6.1
Exhaled	11.5	5.5

In-Vitro: ED = 87±2%
MMAD = 3.8 µm



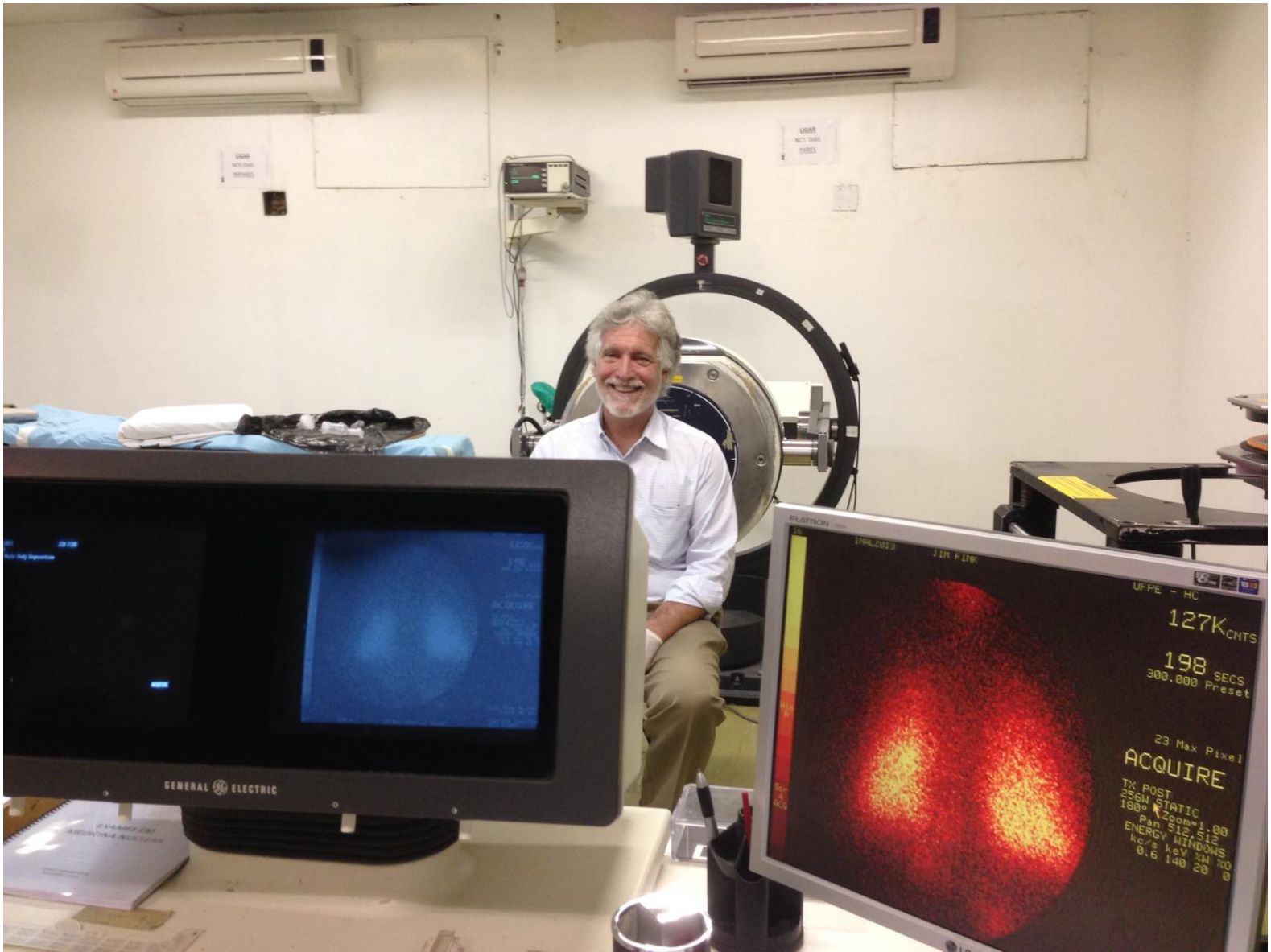
Hand-Held PDDS Nebulizer

Fink J et al: In-vitro in-vivo comparison of inhaled aerosol from a hand-held nebulizer for administration of amikacin. Presented at ISAM, Tours, FR, 2007.

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

Scintigraphy with Solo with Adapter



Deposition Distribution Solo with Adapter using valved Mouthpiece

Emitted Dose	31.35
Lung Deposition	16.1- 21 %
Head	8.93
Stomach	1.48
Neb	11.92
Reservoir	53.93
Expiratory Filter	9.56

Conclusion

Over the last decade aerosol delivery has changed in the ICU and Acute Care

Neonates, infants, children and adults can all get >10% lung dose with conventional ventilation.

Developments underway to approve aerosols for acute and critical care

Choice of aerosol generator and placement makes a huge difference.

Respiratory Therapist need to know so they can guide and educate the team

Aerogen®