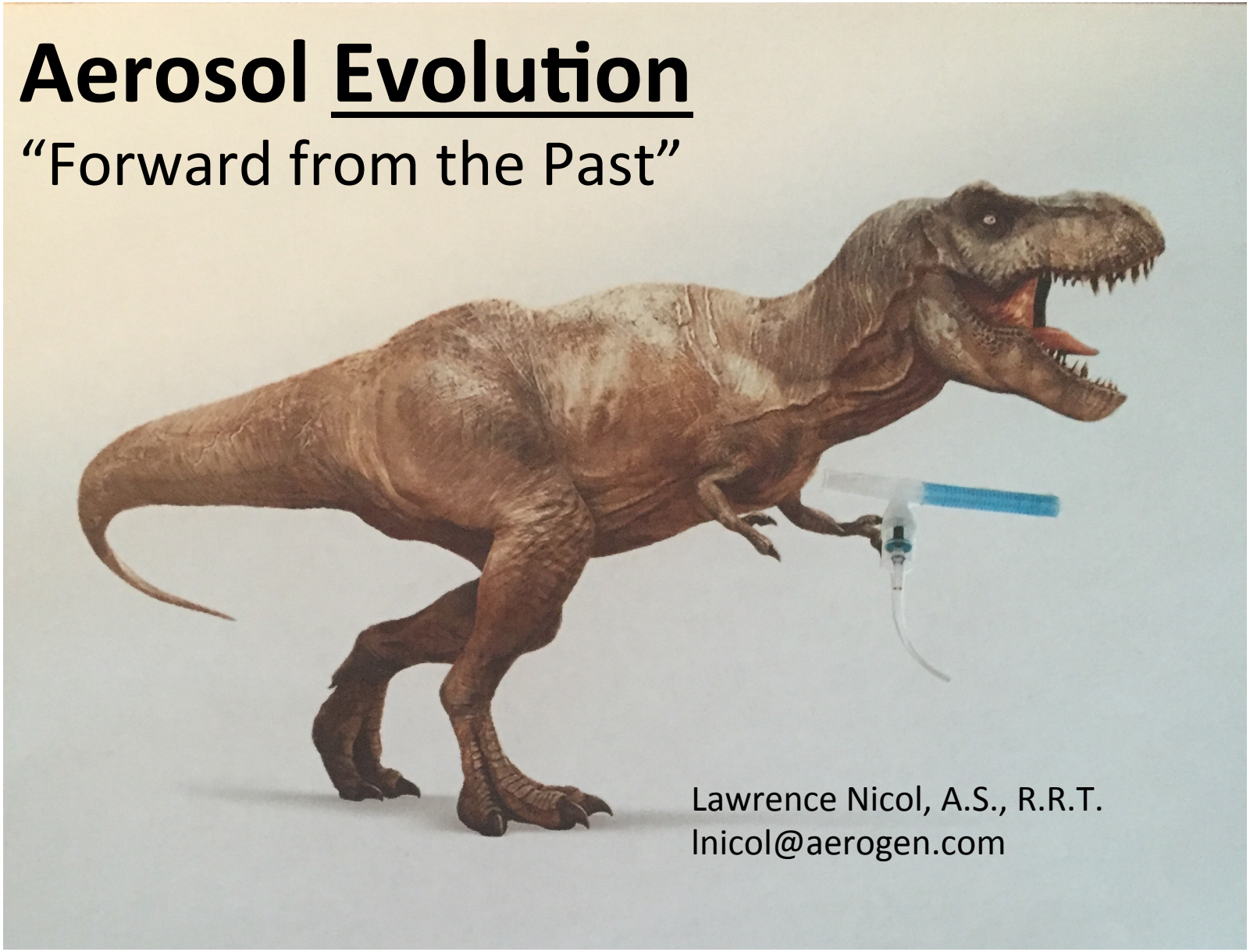
Aerosol Evolution

"Forward from the Past"



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Disclosures

Medical Science Liaison (February 2014-present)

Aerogen Ltd, Galway, Ireland

The opinions expressed during this presentation are those of the speaker, and not necessarily those of the organizing committee, association or sponsor.

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Aerosol Science Objectives

Understand basic aerosol science

Know the most recent research based information regarding aerosol delivery

Demonstrate proper placement of aerosol delivery devices for optimal aerosol delivery

Summary

Overview of Aerosols

Application of Aerosol Concepts

Aerosol Generating Devices

Ideal Nebulizer Placement

Evidenced Based Research

Non-Conventional Ventilation Nebulizer Placement

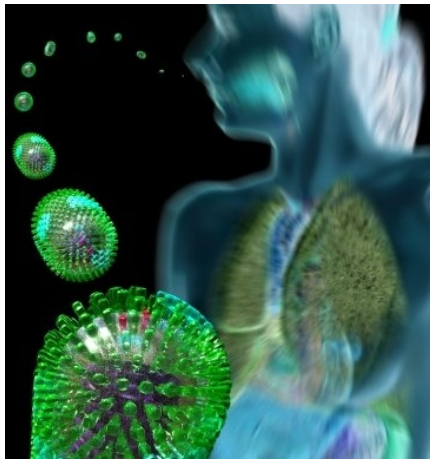
What is an Aerosol?

An aerosol can be defined as a system of solid or liquid particles suspended in air or other gaseous environment.

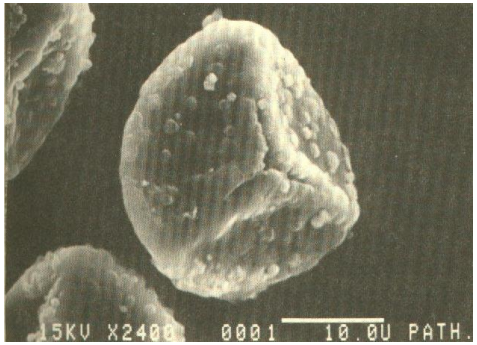
Types of Aerosols

Sneeze

Cigarette Smoke



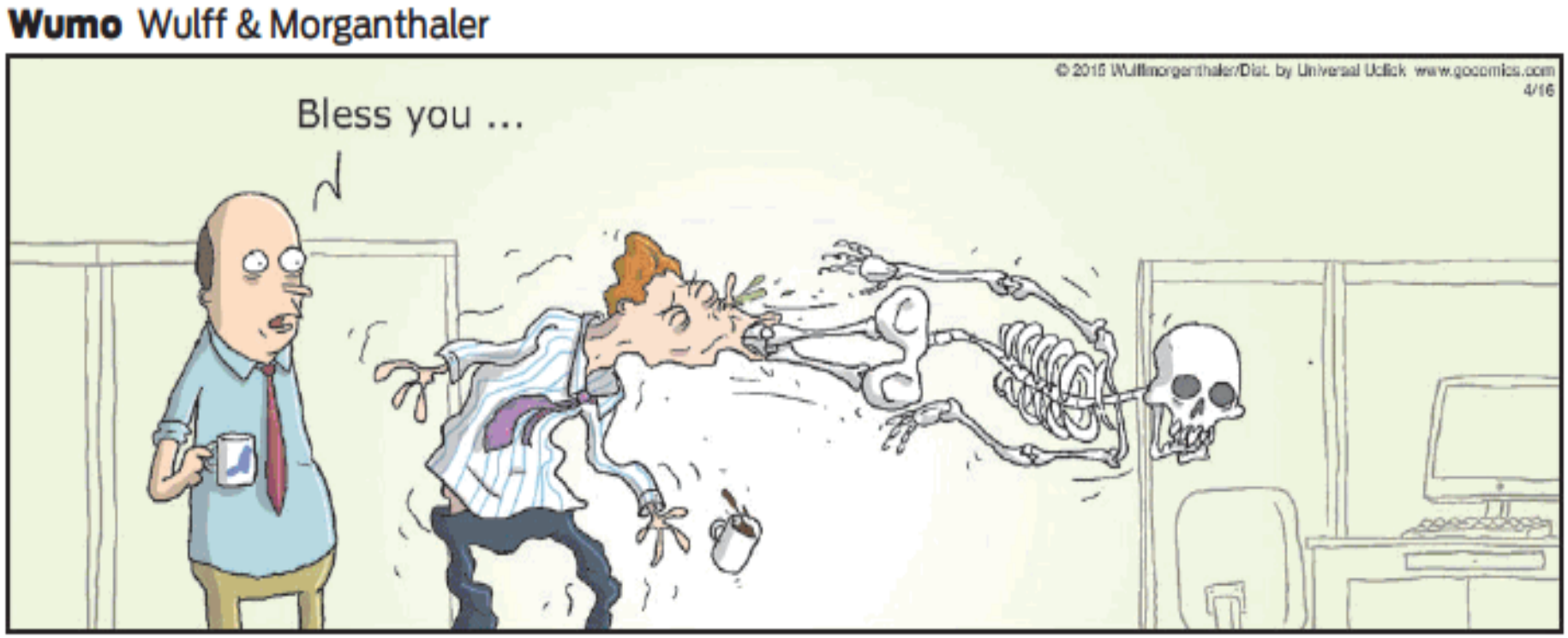
Flu Virus



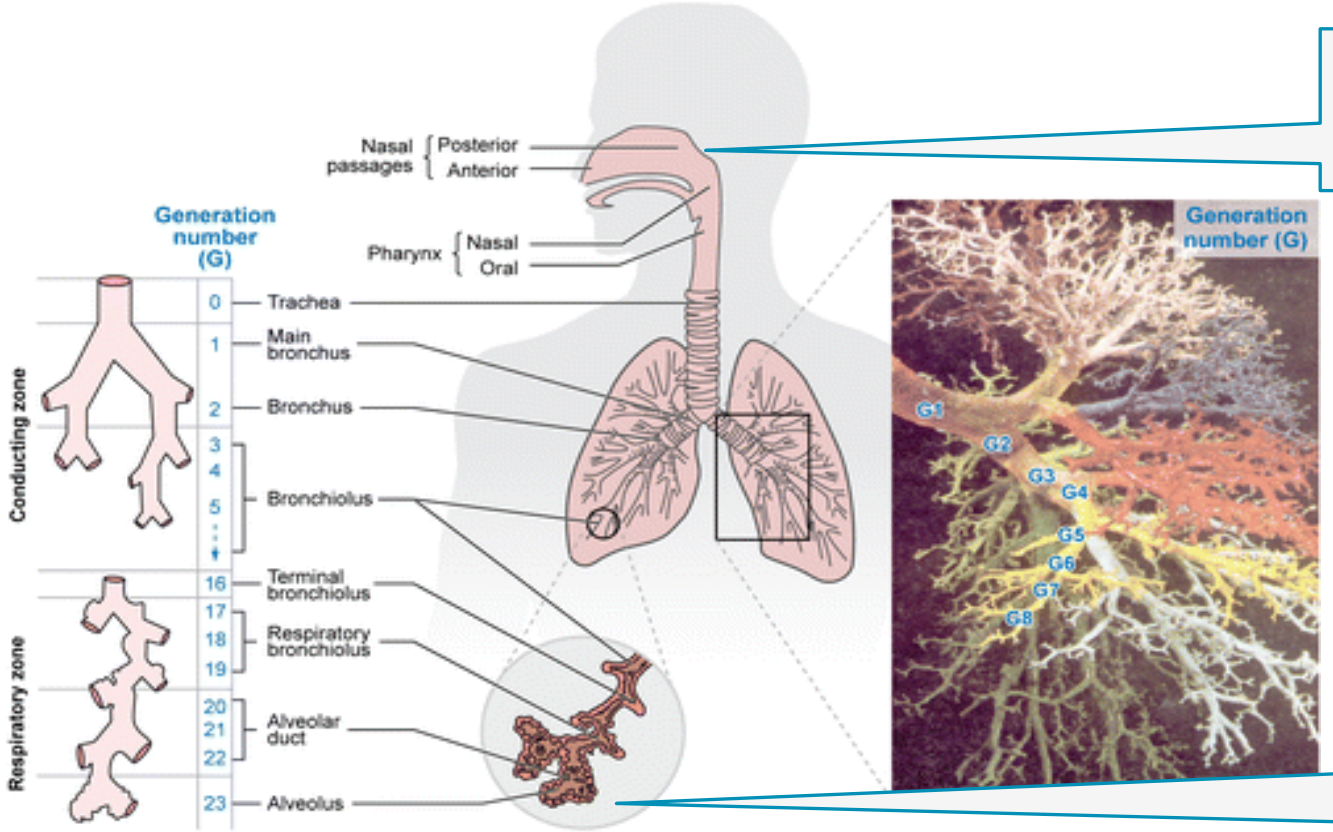
Plant Spores

Dust

“Large particle aerosol" ☺



Why particle size important?

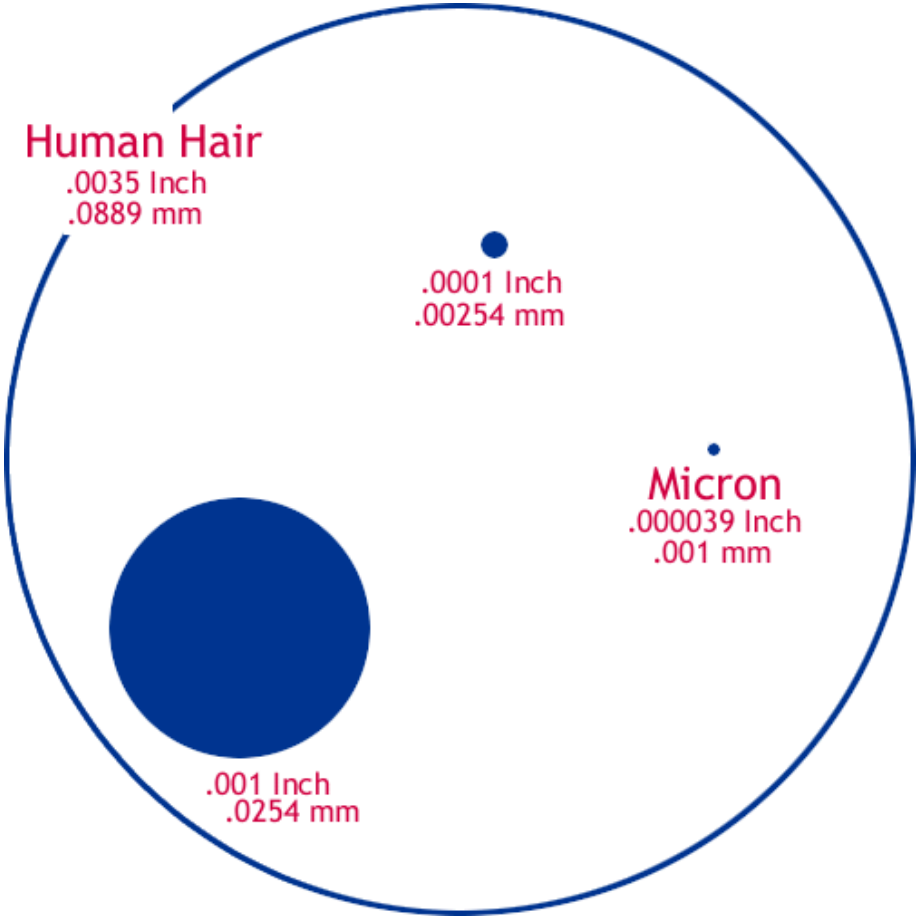


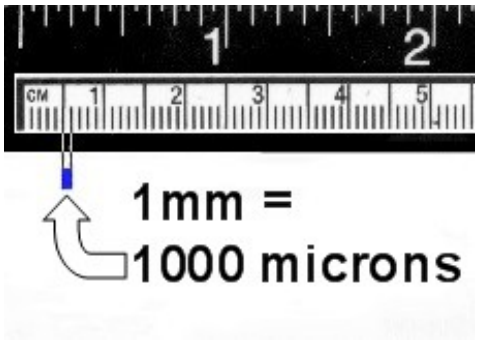
Kleinstreuer C, et al. 2008.
Annu. Rev. Biomed. Eng. 10:195–220.

Oro-pharyngeal
>6 μm

Alveolar, 23rd generation
0.5-3 μm

The Micron in Context

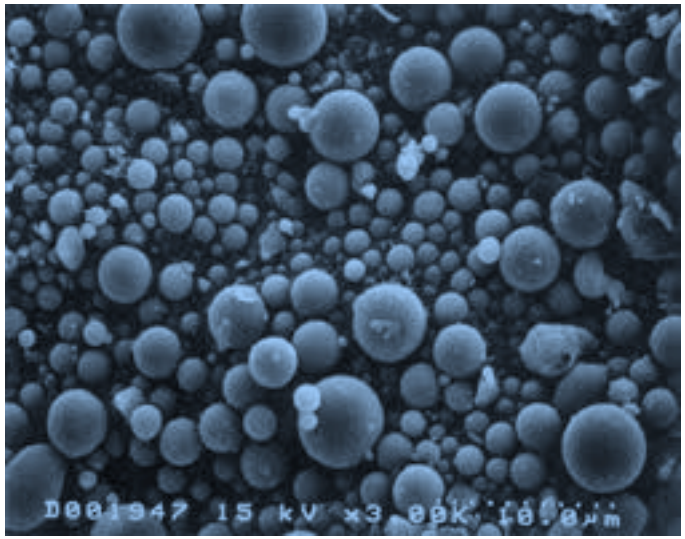




Particles less than 2 µm stay suspended in air

Mass Median Aerodynamic Diameter

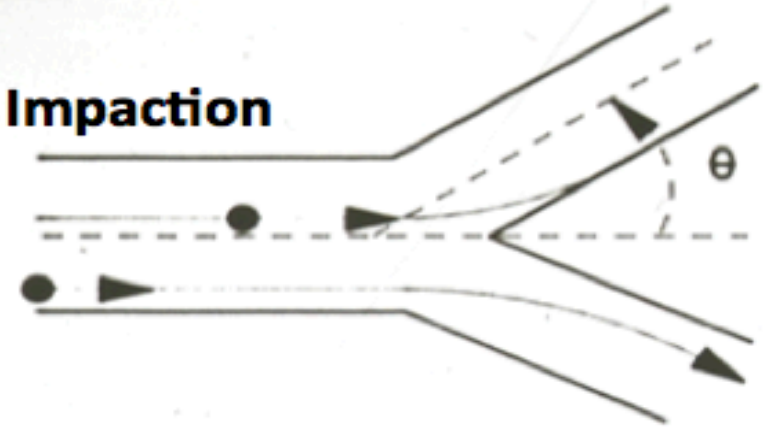
Mass Median Aerodynamic Diameter (MMAD) is defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller. MMAD expressed as μm.

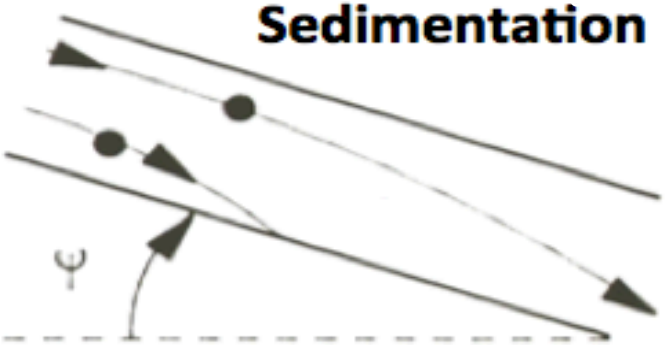


Factors that affect aerosol deposition

- Aerosol Physics – particle size, shape, density, mechanisms of particle distribution, electrostatic charge, humidity
- Anatomy of the Respiratory Tract – length, diameter, gravity, branching angles
- Airflow Patterns – velocity, laminar vs. turbulent, breathing patterns
- Other – aerosol device, application, interface, patient cooperation, patient age

Deposition Mechanisms





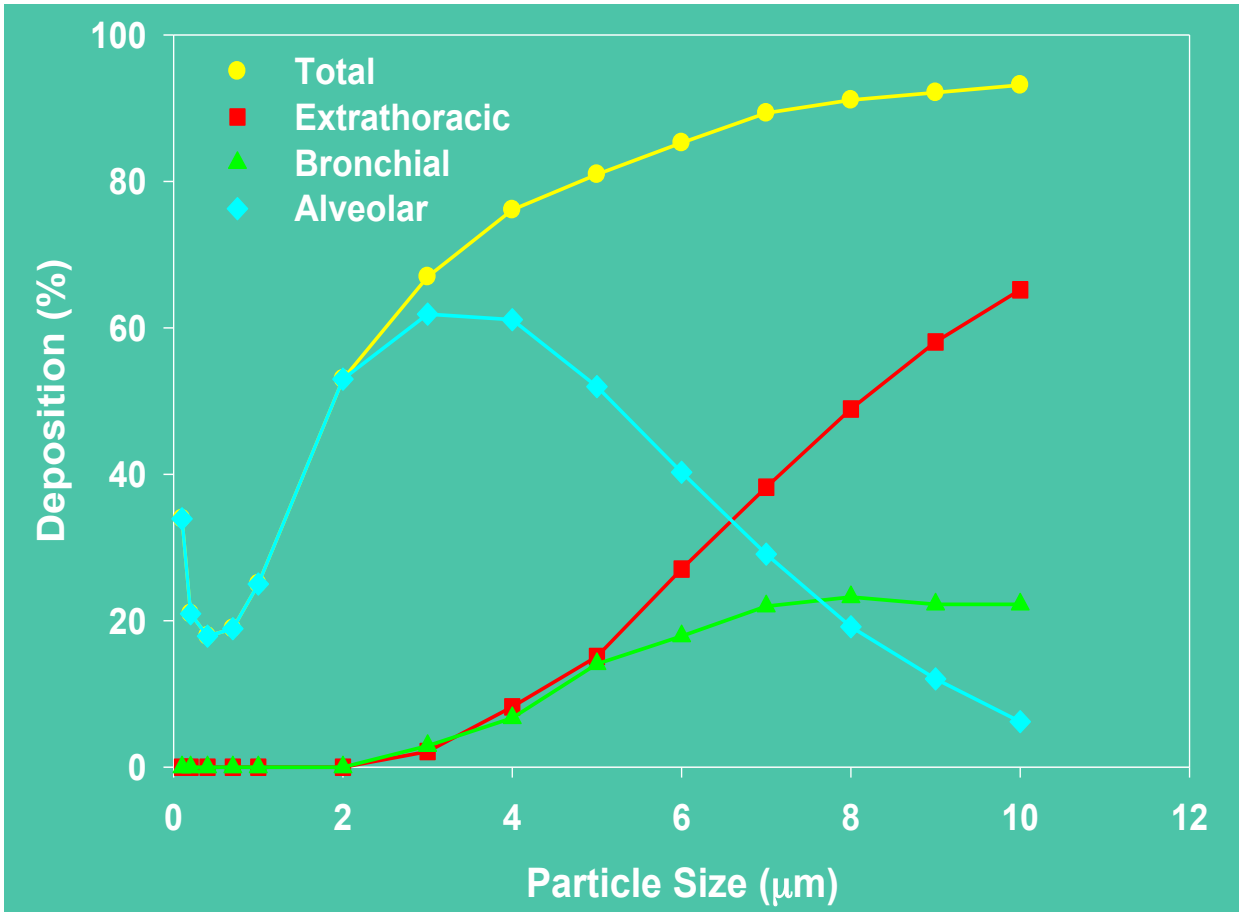
In vivo deposition

Inspiratory Flow Rate =

15 L/min (250 mL/sec)

Tidal Volume =

1000 ml



J Heyder et al J Aerosol Sci 1986;17:811-825.

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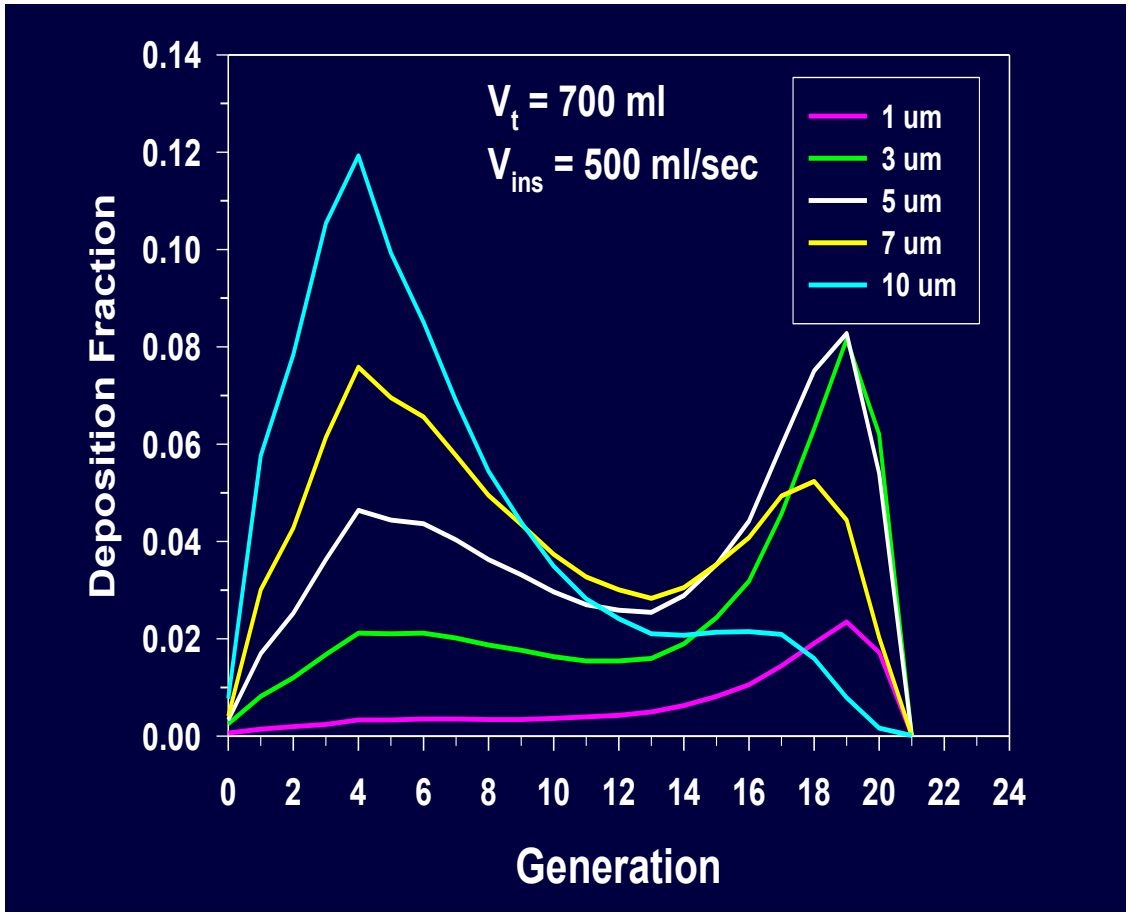


T Gerrity In: Respiratory Drug Delivery 1991.

Factors that affect aerosol penetration

- Inspiratory pattern and volume (slow deep inhalation with a breath hold provides optimal penetration of aerosol)
- Particle size
- Presence of lung disease (airway obstruction)
  - Bronchoconstriction
  - Mucosal edema
  - Quantity and characteristics of secretions

Factors Influencing Inhaled Dose in Infants

Summary:

- Increased dose with CPAP, larger Vt in MV, larger Ti and larger ETT and dry gas.
- Increased dose with MMAD 1-3 um, small residual volume, MDI with VHC, synchronized actuations.
- Increased dose with aqueous solutions and temps 36 degrees centigrade.

Mazela and Polin Eur J Pediatr 2010

Anatomical Age Differences

	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

Fink JB. Clin Ther. 2012; 34 (11): S36-45.

Aerosol therapy in young children

- Lower aerosol lung deposition than adults
- Young children cannot perform an inhalation maneuver
- 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 or BAN until age 5 – 6 years

Janssens et al, "Aerosol Therapy, The Special Needs of Young Children", Paediatric Respiratory Review, 2006 Vol 7, Supplement 1, pp S83-S85

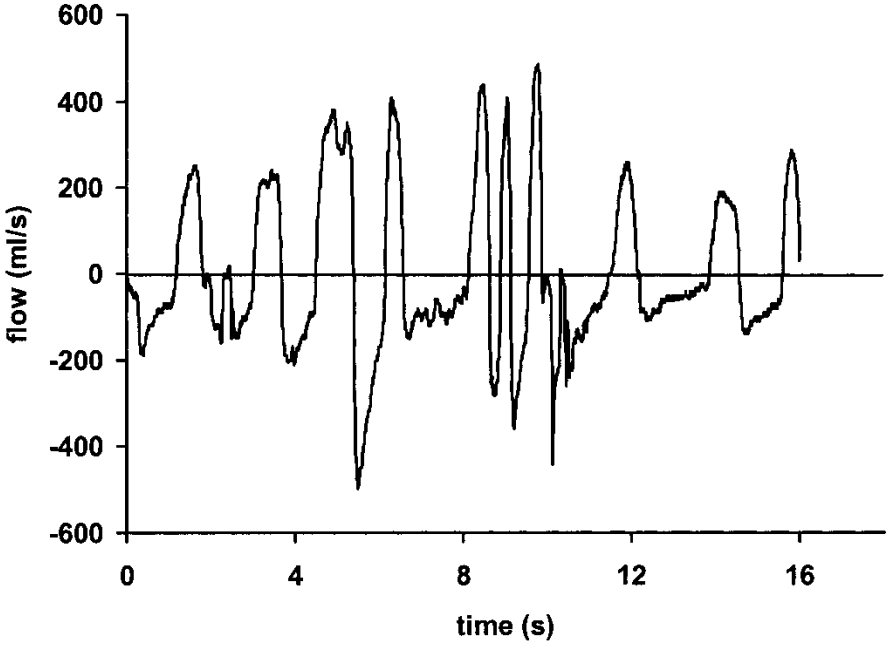
Crying Child – Aerosol Deposition

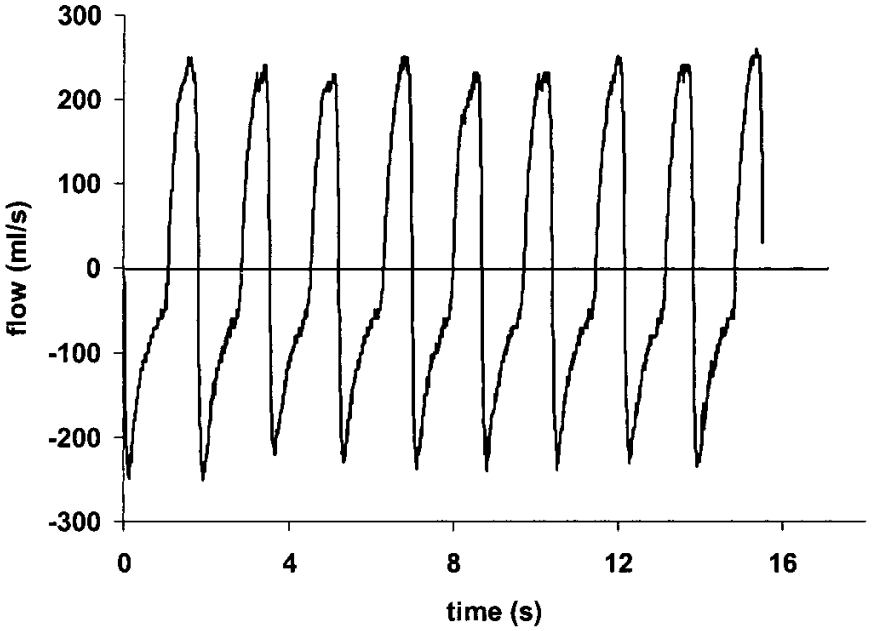
Murakami et al, administered a radio tagged aerosol to infants while crying (left) and during quiet breathing (right). When crying aerosol is primarily deposited in the upper airway, esophagus, and stomach. During quiet breathing there is greater deposition and distribution of aerosol throughout the lungs.

Silent Nebulization, does not disturb the child = Effective Drug Delivery
With no need for air flow, the Aeroneb Solo Adapter offers totally silent aerosol drug delivery

Murakami G, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M, Yoshizumi A, Okada T. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Annals of allergy*. 1990;64:383-387

*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

History Of Nebulization

1858 First Compressed Air Nebulizer

1930 Electric table top compressors

1955 MDI

1960 Portable Ultrasonic

2000 Pro Vibrating Mesh

2012-2015

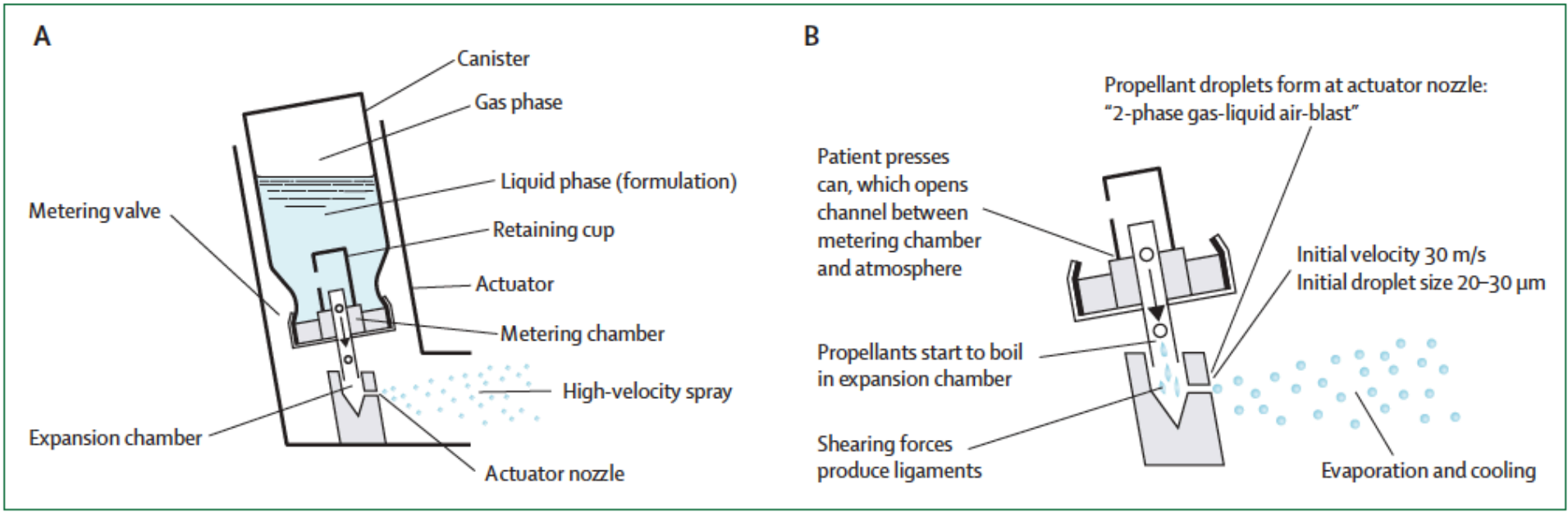
Nebulizers

Nebulizers are used for administering large doses of drug to patients with poor lung function.

- Historically very inefficient drug delivery (jet nebulizer)
- Requires higher doses of medication
- Typically pneumatic (gas) power source
- Breath enhance technologies developed to improve efficiency

J. Rau, "The Inhalation of Drugs: Advantages and Problems", Respiratory Care, March 2005 Vol 50, No 3, pp 377

Pressurized Metered-Dose Inhaler



- Provides uniform particle dispersion and dose
- Requires ability to actuate canister and coordination of actuation and breath
- Drug inhalation is extremely technique dependent

1. Clark AR. MDIs: Physics of Aerosol Formation. 1996 J Aerosol Med: 9:S-19-26
2. Rau's Respiratory Care Pharmacology 9th edition 2016, Chapter 3 Administration of Aerosolized Agents (31-64).

Pressurised Metered-Dose Inhaler (pMDI)

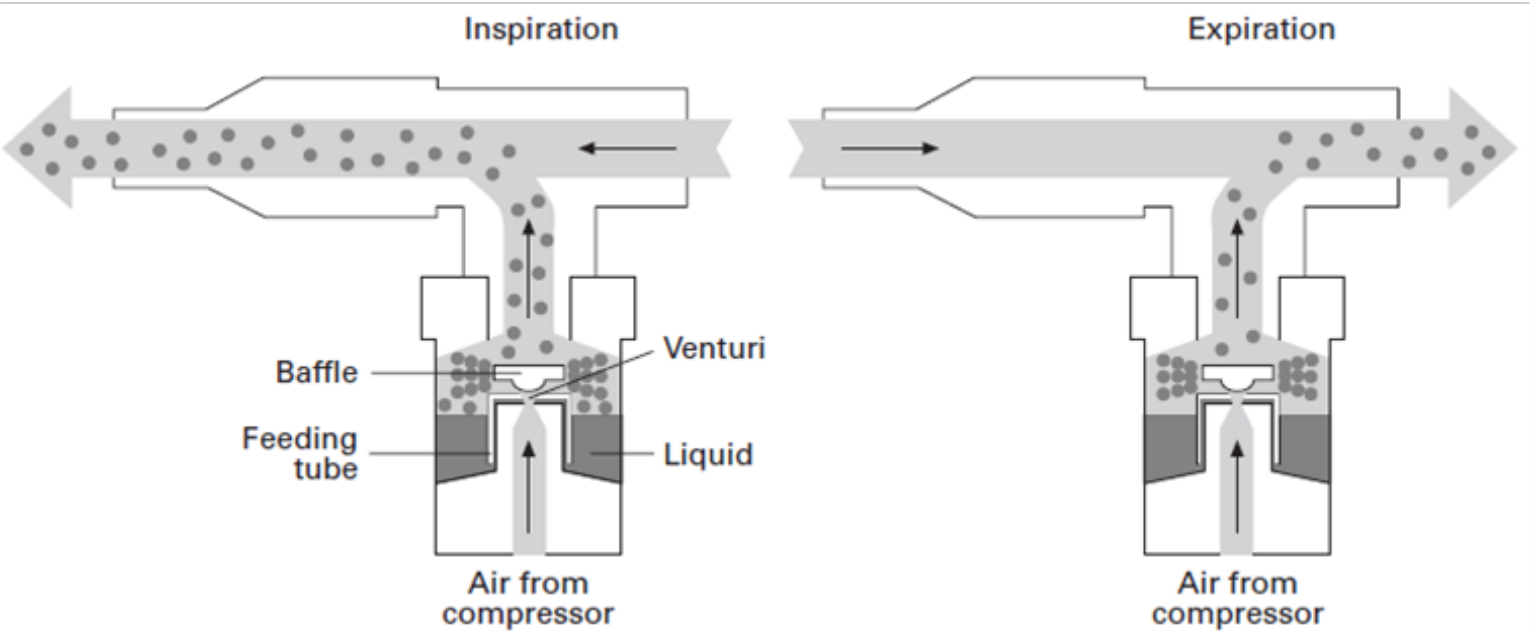
- Convenient, light weight, and portable.
- Limited availability of formulations.
- Relative lower cost (except in US).
- Solid drug particles blended with lactose and dissolved in propellant.
- Propellant provides energy for dispersion.
- Dose limited to <0.5mg per actuation.
- Highly variable dose delivery dependent on technique.

S. Newman, “Principles of Metered Dose Inhaler Design”, Respiratory Care, September 2005, Vol 50, No 9, pp 1181-1183

Dry Powder Inhalers (DPI) have a larger dose range

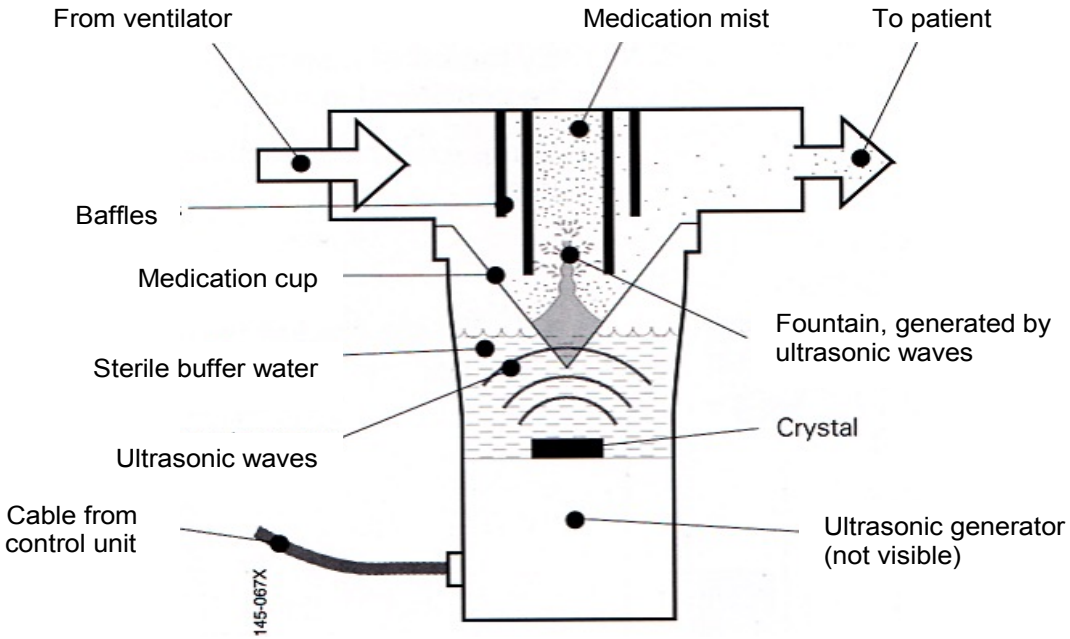
- Formulation typically consists of drug particles mixed with large lactose particles (to enhance dispersion)
- Patient's inhalation provides energy for dispersion
- Becoming more popular in US (e.g. Advair™)
- Typically not labeled for use in children
- Medium cost per dose
- **Dose limited to < 5 mg**
- Dose typically integrated in inhaler
- Dispersion dependant on inhalation flow rate (therefore not good for children, or patients with severely compromised lung function)
- Inhaler forms significant part of brand image
- No harmful propellants

Jet Nebuliser



- Require compressed air or oxygen to create aerosol
- Jet nebulizers use baffles to aerodynamically to sort out the correct particle size
- Large residual volume – 0.8 – 1.2 mL

Ultrasonic Nebuliser

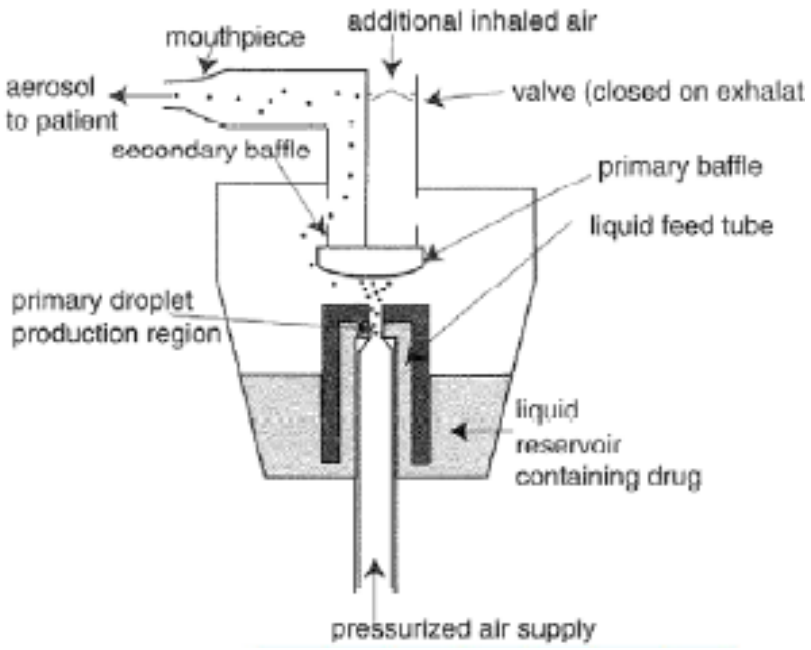


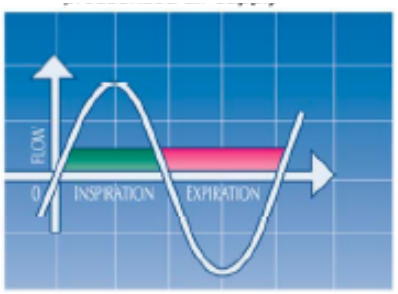
- Ultrasonic disruption of liquid surface
- > 20 Degree C Temperature increase
- Unsuitable for suspensions

Breath Actuated Nebulizer

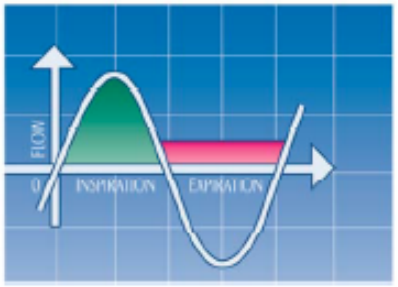
- Produce aerosol only during inspiration
- Require 15-20 L/min inspiratory flow to trigger mechanism of aerosol delivery
- Small children and patients in respiratory distress may not be able to trigger the mechanism
- Treatment times can be up to 40 minutes for patients in respiratory distress

Breath Enhanced Nebuliser



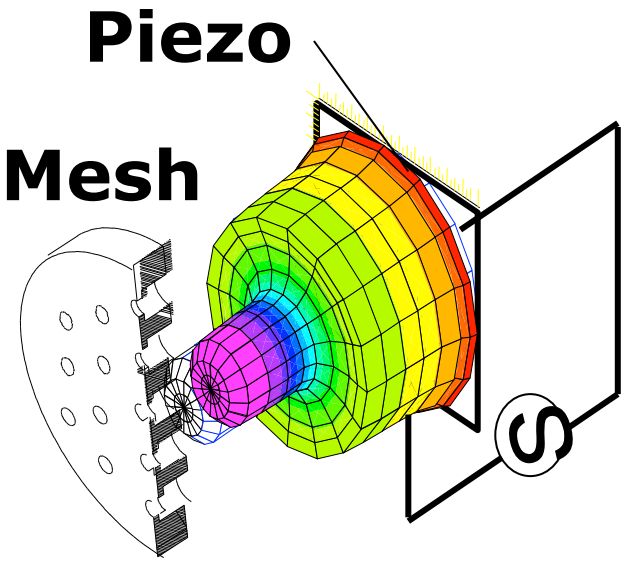


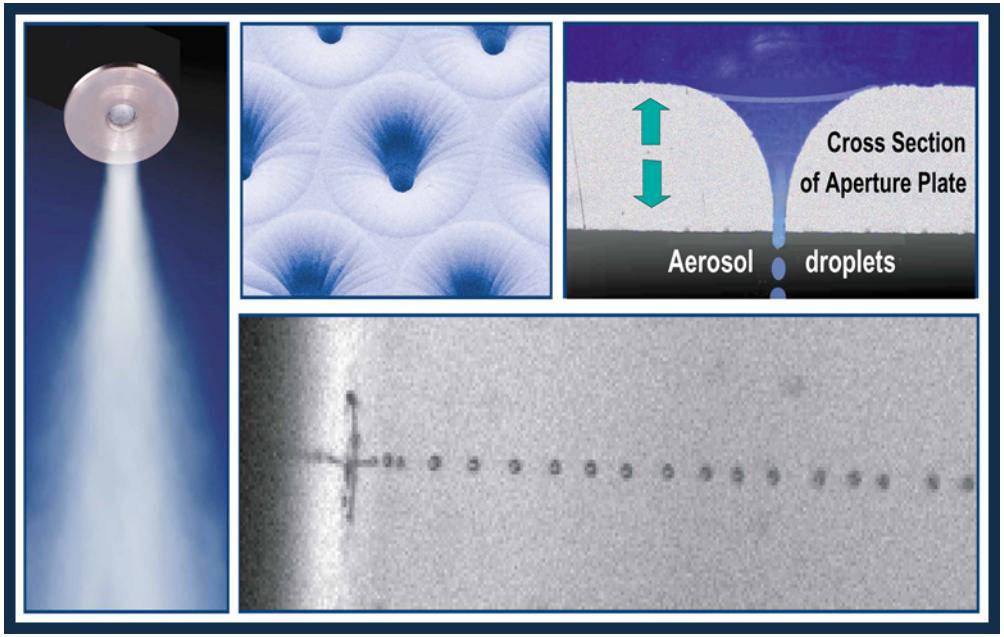
Traditional "T" Nebulizer



- Shorten treatment time by directing the inhaled air through the primary droplet production region
- Increased the droplet production rate during the inhalation phase
- Faster and deliver more drug to the lungs

The Vibrating Mesh in Context



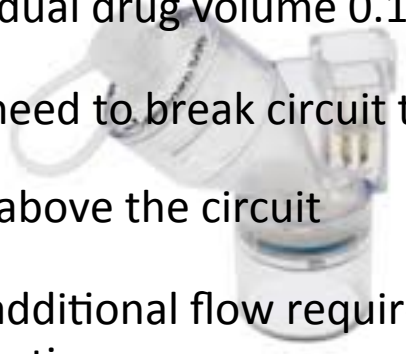


- Static and dynamic
- Aperture plate
- Input will be great

Vibrating Mesh vs Jet Nebuliser

Vibrating Mesh

- Deliver 5-9 x more drug than jet nebulizers[1, 2]
- Residual drug volume 0.1- 0.5 ml mL[3]
- No need to break circuit to nebulize
- Sits above the circuit
- No additional flow required during operation



Small Volume (Jet) Nebulizers

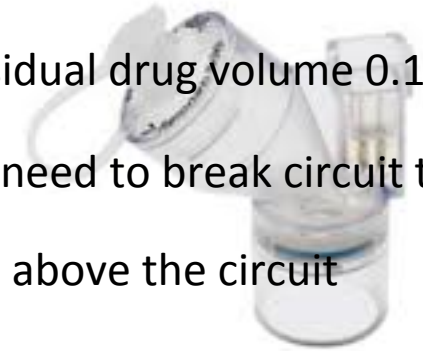
- Drug waste- delivers less drug than vibrating mesh
- Residual drug typically 0.8 - 1.4 ml of dose un-nebulized[3]
- Can require a break in circuit
- Sits at the lowest point of the circuit
- Adds flow- need to adjust ventilator settings and alarms

1. Ari et al. 2010 Evaluation of Aerosol Generator devices at 3 Locations in Humidified and Non-humidified Circuits During Adult Mechanical Ventilation.
2. Berlinski A, Willis JR. Albuterol delivery by 4 different nebulizers placed in 4 different positions in a pediatric ventilator in vitro model. Respiratory care. 2013;58:1124-1133
3. Ari et al. 2012 Inhalation Therapy in Patients Receiving Mechanical Ventilation: An Update.

Vibrating Mesh vs Ultrasonic Nebuliser

Vibrating Mesh

- Deliver 5-9 x more drug than jet nebulizers[1, 2]
- Residual drug volume 0.1- 0.5 ml mL[3]
- No need to break circuit to nebulize
- Sits above the circuit
- No additional flow required during operation



Ultrasonic Nebulisers

- Bulky
- Expensive
- Ultrasonic disruption of liquid surface
- > 20 Degree C Temperature increase
- Unsuitable for suspensions

1. Ari et al. 2010 Evaluation of Aerosol Generator devices at 3 Locations in Humidified and Non-humidified Circuits During Adult Mechanical Ventilation.
2. Berlinski A, Willis JR. Albuterol delivery by 4 different nebulizers placed in 4 different positions in a pediatric ventilator in vitro model. Respiratory care. 2013;58:1124-1133
3. Ari et al. 2012 Inhalation Therapy in Patients Receiving Mechanical Ventilation: An Update.

Vibrating Mesh vs pMDI

Vibrating Mesh

- Easy to Operate 'plug and play'
- Propellant free operation
- Delivers more drug per dose[1]

pMDI

Technique dependent- timed with inspiration

HFA propellants

Delivers less drug than vibrating mesh per dose [1]

1. Alhamad BR, Fink JB, Harwood RJ, Sheard MM, Ari A. Effect of aerosol devices and administration techniques on drug delivery in a simulated spontaneously breathing pediatric tracheostomy model. Respiratory care. 2015

Nebuliser Comparison Summary

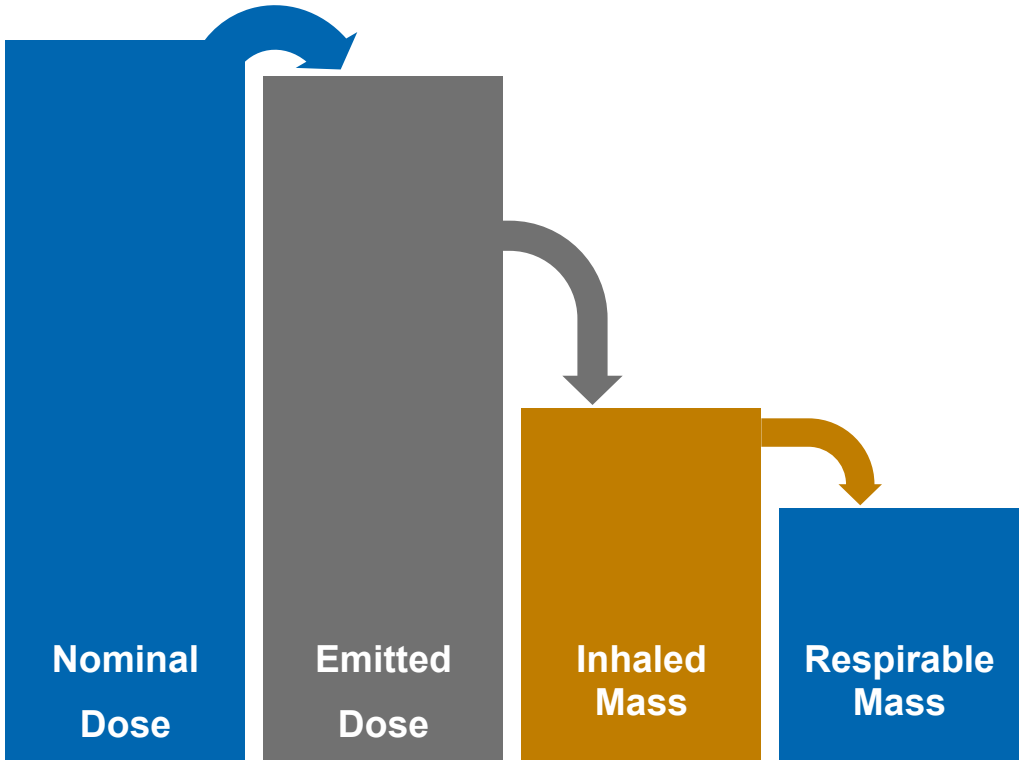
	Jet	Ultrasonic	Vibrating mesh
Features			
Power source	Compressed gas or electrical mains	Electrical mains	Batteries or electrical mains
Portability	Restricted	Restricted	Portable
Treatment time	Long	Intermediate	Short
Output rate	Low	Higher	Highest
Residual volume	0·8–2·0 mL	Variable but low	≤0·2 mL
Environmental contamination			
Continuous use	High	High	High
Breath-activated	Low	Low	Low
Performance variability	High	Intermediate	Low
Formulation characteristics			
Temperature	Decreases*	Increases†	Minimum change
Concentration	Increases	Variable	Minimum change
Suspensions	Low efficiency	Poor efficiency	Variable efficiency
Denaturation	Possible‡	Probable‡	Possible‡
Cleaning	Required, after single use	Required, after multiple use	Required, after single use
Cost	Very low	High	High

*For jet nebulisers, the temperature of the reservoir fluid decreases about 15°C during nebulisation because of evaporation. †For ultrasonic neubulisers, vibration of the reservoir fluid causes a temperature increase during aerosol generation, which can be as high as 10–15°C. ‡Denaturation of DNA occurs with all the nebulisers.

DOLOVICH, M. B. & DHAND, R. 2011. Aerosol drug delivery: developments in device design and clinical use. Lancet, 377, 1032-45.

Quantifying Nebulizer Efficiency

Aeroneb® Go as example



reservoir volume	Nominal Dose minus Residual Dose	Emitted Dose x T_i/T_{tot}	Inhaled Mass x FPF
3.0mL	2.7mL	1.1mL	0.8mL
	(3.0mL – 0.3mL)	(2.7mL x 0.4)	(1.1 x 70%)
100%	90%	36%	25%

Residual Dose
Volume of medication remaining in device at end of nebulisation.

Emitted Dose
Amount of aerosol that leaves device.

T_i/T_{tot}
Ratio of total inspiratory time to total breath cycle (0.4 in this example).

Inhaled Mass
Amount of aerosol available for inhalation to the patient.

Fine Particle Fraction (FPF)
Percentage of particles within the respirable range (1-5 microns Mass Median Aerodynamic Diameter).

Respirable Mass
Amount of aerosol available for inhalation to the patient that is within the respirable range (FPF).

VM vs SVN - Estimated Lung Dose

Dosage Comparison Chart for Aerosolized Medication				
Drug	Dosage	SVN via off vent (12%)	SVN on vent (3%)	VM on vent (17%)*
Tobi BID	300 mg	36 mg	9 mg	**51 mg**
Pulmozyme BID	2.5 mg @1 mg/m	300 µg	75 µg	425 µg
Pulmicort BID	0.5 mg	60 µg	15 µg	85 µg
Mucomyst QID 2 ml@10%	200 mg	24 mg	6 mg	34 mg
Mucomyst QID 2 ml@20%	400 mg	48 mg	12 mg	68 mg
Duo-Neb QID	0.5 mg ipratropium 2.5 mg albuterol	60 µg ipratropium 300 µg albuterol	15 µg ipratropium 75 µg albuterol	85 µg ipratropium 425 µg albuterol
Albuterol QID	2.5 mg	300 µg	75 µg	425 µg

*(Ari, et al. 2010)

Aerosol Research

Bruce K Rubin, Aerosol Medications for Treatment of Mucus Clearance Disorders
Respir Care, June 2015 60:825-832

Aerosolized or instilled sodium bicarbonate can produce an effective cough, this is presumed to be caused by airway irritation. Bicarbonate is not effective in breaking down secretions or promoting secretion clearance.

Despite extensive study, dornase has not been shown to be effective in diseases other than CF.

There are no randomized controlled trials demonstrating a benefit of inhaled N-acetylcysteine or similar mucolytic medications in the treatment of any airway diseases, and therefore, these drugs are not recommended for clinical use.

The order of aerosol administration guidelines are lacking empiric data from randomized controlled trials, and many of these guidelines recommend that aerosol medications be given in a sequence that is quite different from other guidelines.

ISAM 2013 Surfactant Study

Summary:

Surfactant administered via mask, prongs, and tracheal tube.

Curosurf given with the Pari eFlow nebulizer.

Piglets were used in the study.

Conclusions:

The in-vitro and in-vivo lung delivery deposition patterns are similar.

This in-vitro set-up may be useful in studying drug delivery to the lung.

We believe that the surfactant deposition we found with this nebulizer may be sufficient for treatment of RDS.

*Surfactant is not currently approved for inhalation. Efficacy studies are needed to prove this hypothesis.

Nebulizing Poractant Alfa Versus Conventional Instillation: Ultrastructural Appearance and Preservation of Surface Activity

Stefan Minocchieri, MD et al. Pediatric Pulmonology 49:348–356 (2014)

Conclusion: The similarity of surfactant characteristics of nebulized surfactant via a tube and the non-nebulized surfactant suggests that vibrating membrane nebulizers are suitable for surfactant nebulization.

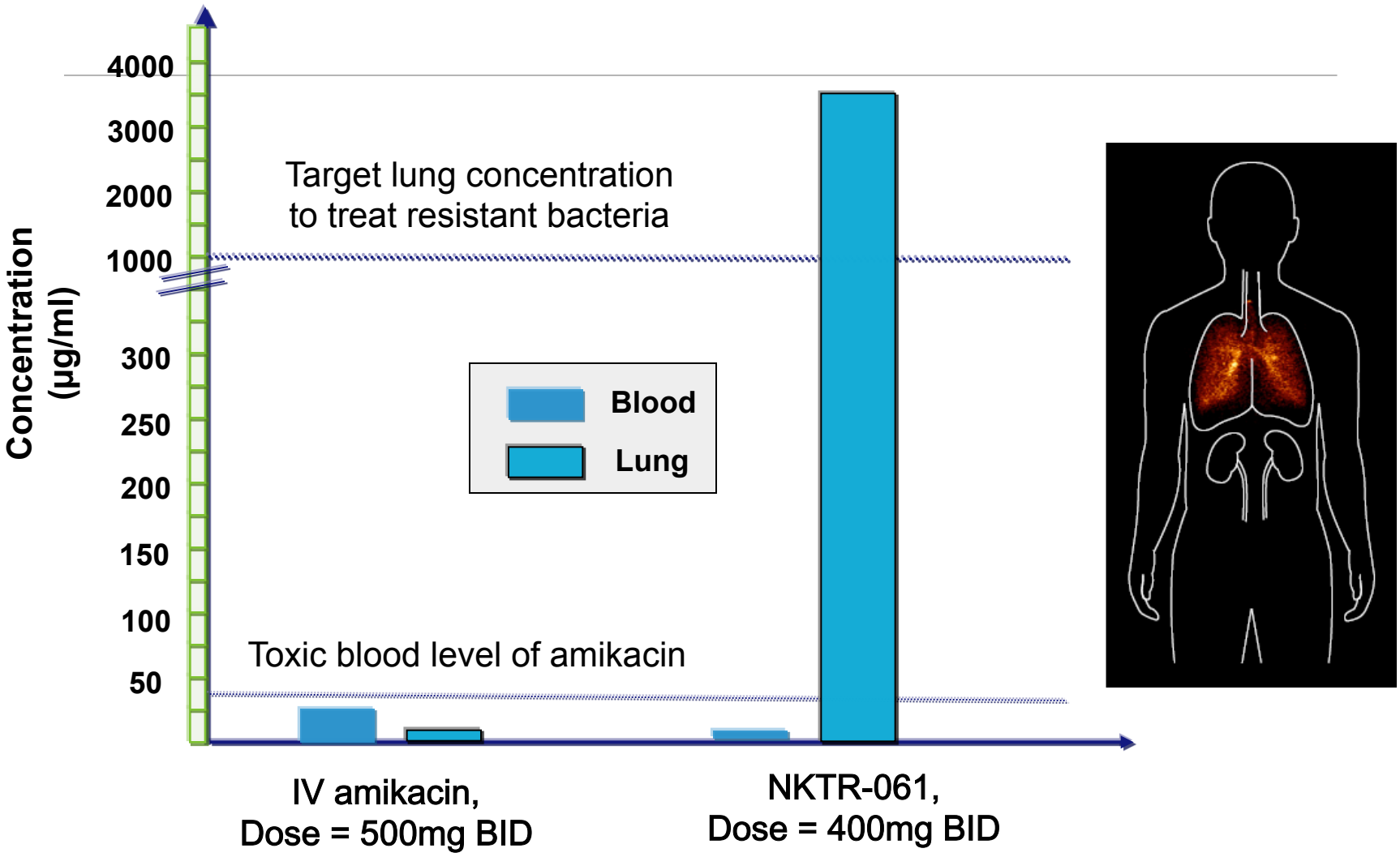
Note: Surfactant is not currently approved for inhalation.

Douglas F Willson, **Aerosolized Surfactants, Anti-Inflammatory Drugs, and Analgesics** Respir Care, June 2015 60:774-793

- Aerosolization of surfactant avoids hypoxia and hypotension consequent to instilling a large volume of liquid down the endotracheal tube.
- Aerosolization may allow surfactant to be administered without the need for an artificial airway, and may result in less of the drug being needed.
- Certain nebulizers may inactivate some surfactants, so demonstration of surface activity after nebulization is imperative.
- Most animal studies suggest that distribution is more homogeneous with aerosolization compared with instillation.

  It is important to recognize that aerosolization may change not only drug onset and effect but also dose. Effective dose may be related to particle size, the patient interface with the aerosol device (eg, spacers), and patient coordination or effort.
- Aerosolization makes the most sense for drugs where the lung is the primary target organ such as with surfactant, inhaled corticosteroids, and increasingly antibiotics.

Delivery to serum and lung of IV and inhaled aminoglycoside



*Amikacin is not currently approved for inhalation; testing is in progress.

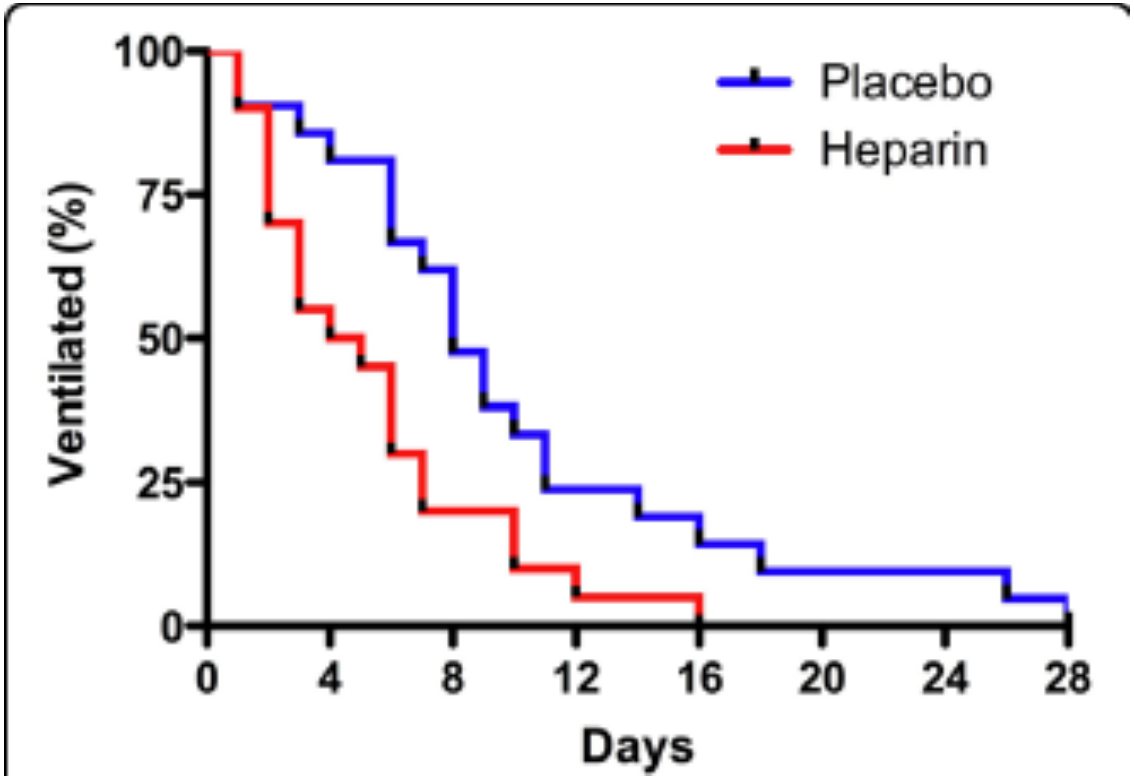


Figure 3 Rate of freedom from mechanical ventilation. Over the first 28 days among surviving patients, the rate of freedom from mechanical ventilation was higher in patients administered heparin. Median times of ventilation were 5 days in the heparin group ($n = 20$) and 8 days in the placebo group ($n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

Dixon et al. 2010

* Heparin is not currently approved for inhalation.

Steroids

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Oxford University Hospitals NHS
NHS Trust

USE OF A NEW-GENERATION ELECTRONIC MICROPUMP NEBULISER TO DELIVER BUDESONIDE IN CHRONIC LUNG DISEASE: A FEASIBLE ALTERNATIVE TO SYSTEMIC DEXAMETHASONE?

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Results

- 7 babies with severe or worsening CLD were treated with nebulised budesonide
- At commencement, 6 had already accumulated median 33 (range 10-49) days of dex treatment **(Table 1)** and remained on concurrent oral dex
- All but one had lower FiO_2 needs within 10 days of starting nebulisers (**Table 2)**
- Budesonide nebulisation permitted successful weaning off systemic steroids within 8 (0-20) days in the six dex-dependent babies and avoided need for dex in another (*case 4*)
- No baby needed a subsequent oral dex course before discharge/ back transfer

Fig 1: ***Aeroneb Pro-X vibrating mesh electronic nebuliser***

Conclusions

- **Topical airways delivery of inhaled drugs to infants with CLD on nasal high flow therapy is feasible with this new electronic micropump vibrating mesh nebuliser**
- **Nebulised budesonide delivery may permit weaning off systemic dexamethasone and may avoid the need for systemic dexamethasone**
- **The safety and efficacy topical steroid delivery in CLD using this new device requires formal evaluation in clinical trials**

ACKNOWLEDGEMENT:
SJ wishes to thank Aerogen Ltd for a small travel bursary that assisted the international presentation of this work. The authors have no other actual or potential conflicts of interest to declare in relation to this work.

CHARACTERIZATION OF RIBAVIRIN WITH SMALL PARTICLE AEROSOL GENERATOR AND MICROPUMP AEROSOL TECHNOLOGIES.

Brian K. Walsh et al.
RESPIRATORY CARE Paper in Press. Published on March 01, 2016 as DOI: 10.4187/respcare.04383

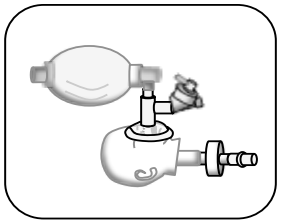
The authors set out to determine if delivery by a newer generation nebulizer (vibrating mesh micropump) was as effective as the standard of care SPAG system .

Results: Ribavirin was found to be stable in both 0.9% aq NaCL and sterile water with an R2 of 0.96, identical coefficients of variation with no difference in drug concentration pre and post nebulization with the micropump. The SPAG MMAD (1.84 mm) was smaller than the micropump (3.63; p=0.02). but there was no significant difference in proportion of drug mass in the 0.7 to 4.7 mm particle range. Inhaled drug delivery was similar with SPAG and VMM in both spontaneously breathing (p=0.77) and mechanical ventilation (p=0.48) models.

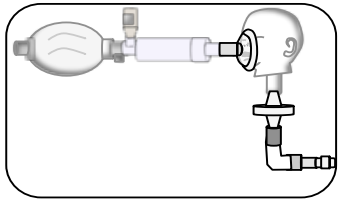
Conclusion: the Author's findings support that the vibrating mesh micropump nebulizer may provide an effective alternative to the SPAG in administration of Ribavirin both on and off the ventilator.

*Note: the Author mentioned in his AARC presentation that it was likely his hospital would be trialing the VM nebulizer on their Ribavirin patients.

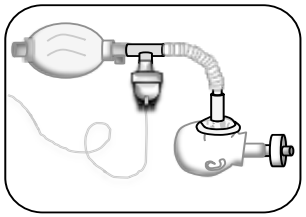
Aerosol to Infants with Ambu Bag: Passive and Active



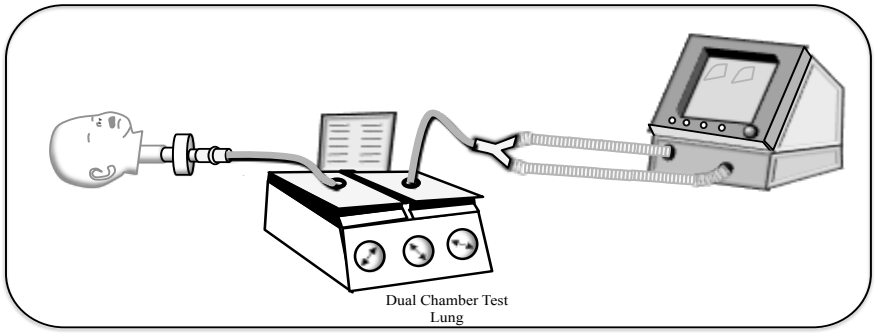
Vibrating Mesh Nebulizer



pMDI/VHC



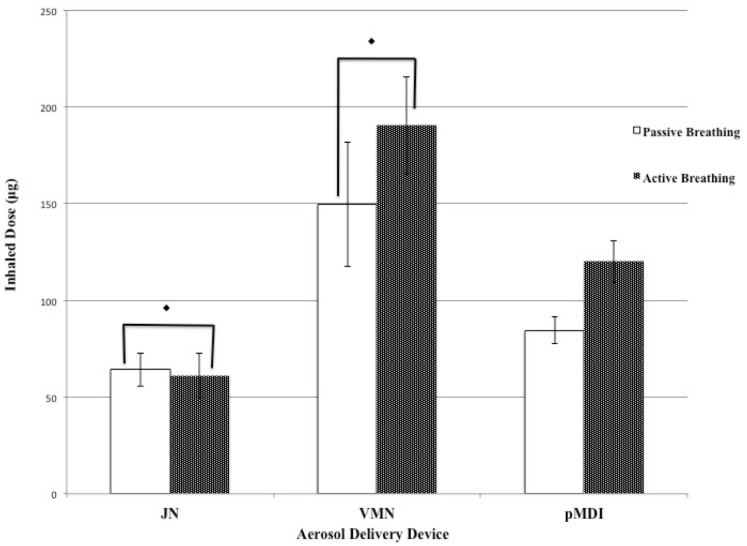
Jet Nebulizer



Dual Chamber Test Lung

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

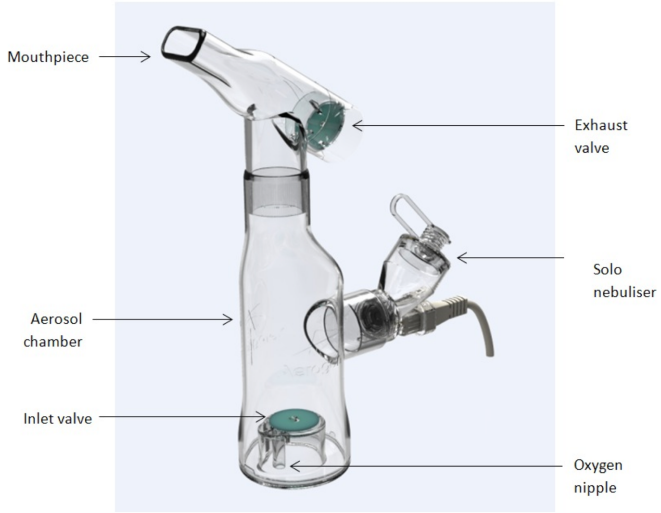
Aerosol Device	Passive Breathing	Active Breathing	*p*-values
JN (%)	2.57 ± 0.34	2.45 ± 0.46	0.729
VMN (%)	5.99 ± 1.28	7.62 ± 1.01	0.157
pMDI/VHC (%)	19.55 ± 1.60	27.84 ± 2.52	0.013
p-values	0.0001	0.0001	

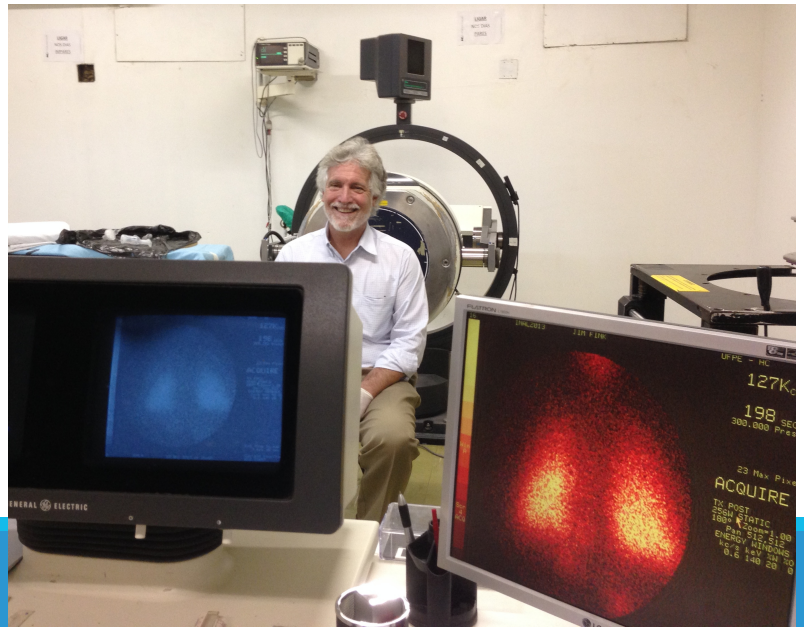


Huriah H. Al Sultan

Spontaneous

Deposition Distribution with VM with the Aerogen Ultra/Adapter





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

Deposition of radioaerosol with jet and mesh nebulizers in healthy adults

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[a] Department of Physical Therapy and Nuclear Med[b], Universidade Federal de Pernambuco , Recife, Pernambuco, Brazil. Georgia State University, Atanta, USA.

BACKGROUND: Mesh nebulizers (MN) have lower residual volume and increased inhaled dose compared to jet nebulizers (JN) per in vitro and animal models. The aim of this study was to compare radio-aerosol deposition using MN and JN in healthy subjects, using 2-D planar scintigraphy.

METHODS: A randomized trial in 6 normal subjects (4 female, 2 male) inhaled 99mTc-DTPA with an activity of 1 mCi with the normal saline to a total dose of 4 mL with JN (Misty Max, Air Life, Yorba Linda, USA) oxygen flow of 8 L / min and 1.5 mL with MN (Aerponeb Solo with Ultra adapter; Aerogen Galway, Ireland). Scintigraphy was used to determine distribution of deposition and mass balance between compartments.

RESULTS: Distribution between compartments with JN and MN shown in table.

	Jet Nebulizer	Mesh Nebulizer	p-value
Lung	3.4±1.2	25.7±9.3	0.004
Upper airway	1.3±0.3	3.4±2.6	NS
Stomach	0.7±0.3	4.0±2.2	0.010
Adapter	9.2±4.8	46.8±17.9	0.037
Nebulizer	53.9±3.6	8.9±11.1	0.004
Expiratory filter	32.5±8.6	10.4±17.8	NS

CONCLUSIONS: Mesh with adapter was more efficient than jet nebulizer with higher radio-aerosol deposition in the lung and decreased residual drug in the nebulizer.

Sponsored Research- This study was funded by a grant CNPq-PVE-400801/2013-2, FACEPE APQ 0234-4.08/12.

“Analysis of Deposition Radioaerosol Nebulizers Membrane in Healthy Subjects” Alcoforado et. al.

Summary:

Radioaerosol Deposition in 6 healthy adults was **22.8%** with the mesh nebulizer (with Ultra) compared to **4.5%** with the jet nebulizer.

Dose given was **1.5ml** for the mesh nebulizer compared to **4ml** (with 8LPN flow added) for the jet nebulizer.

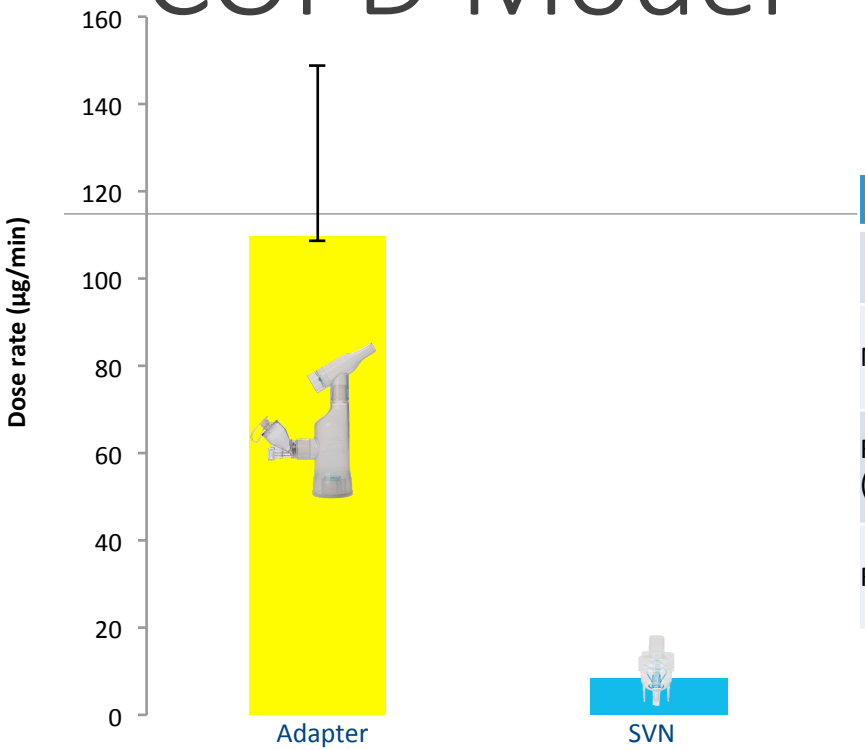
Conclusions:

The jet nebulizers had a lower performance than the mesh.

In healthy voluntaries, radioaerosol pulmonary deposition with the mesh nebulizers was more efficient than the jet nebulizer.

There is a greater residual volume with the jet nebulizers resulting in lower delivery to patient.

COPD Model

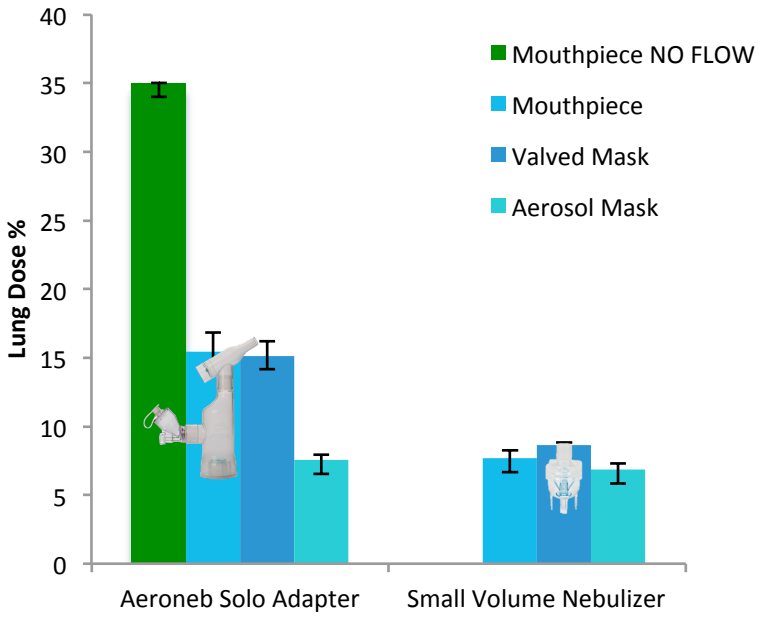


COPD breathing pattern		
	Aerogen Solo Adapter	SVN
Nebulisation time (mins: secs)	4:38	8:50
Respirable dose (% of total dose)	12.6	1.6
Residual volume (%)	0.9	42.9

Vibrating Mesh with Adapter delivers 8 times the drug in half the time in a COPD model

Hickin S, Mac Loughlin R, Sweeney L, Tatham A, Gidwani S. Comparison of mesh nebuliser versus jet nebuliser in simulated adults with chronic obstructive pulmonary disease. Poster at the College of Emergency Medicine Clinical Excellence Conference. 2014

4.5 fold higher aerosol dose than regular nebulizer



Adult model	No Flow	2lpm	
	Adapter	Adapter	SVN
Inhaled dose [1]	35	15.4	7.7

Inhaled dose achieved with 2 lpm supplemental oxygen

Vibrating mesh with adapter achieves 4.5 fold higher inhaled dose than a standard small volume nebuliser: Adult model

1. Ari A, Dornelas de Andrade AF, Sheard M, Fink J. Aerosol delivery with jet and mesh nebulizers using different masks in spontaneously breathing infants: An in-vitro study. Presentation Abstract at the American College of Chest Physicians 2014

A Case Study: Use of Vibrating Mesh with a Valved Adapter in a Pediatric Patient with a Severe Asthma Exacerbation

Tina Thayer, RRT et al Respiratory Therapy Vol. 11 No. 1 Winter 2016

10 y.o. with severe persistent asthma, CAS of 6

Received two 5mg albuterol txs with mesh neb and open aerosol mask without relief, 02 sat 90%

Refused BiPAP or HFNC

Received one 5mg albuterol with mesh neb and valved adapter (Aerogen Ultra) by mouthpiece without added oxygen

02 sat > to 98% and CAS decreased to 2

Transferred to PICU and received Q2 mesh tx with valved adapter and he continued to improve

LOS from ER to discharge was 21 hours and he has not been readmitted

The team concluded that choosing of the mesh with mouthpiece and valved adapter prevented the escalation of care

AEROSOL DELIVERY WITH JET AND MESH NEBULIZERS USING DIFFERENT MASKS IN SPONTANEOUSLY BREATHING INFANTS: AN IN-VITRO STUDY

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2. Universidade Federal de Pernambuco, Department of Physical Therapy, Recife, Brazil

Background

Drug delivery to infants varies with type of nebulizer and interface used during aerosol therapy.

The purpose of this study was to quantify aerosol deposition with a jet nebulizer (JN) and mesh nebulizer (MN) with a proprietary adapter using different types of masks in a simulated spontaneously breathing infant.

Methods

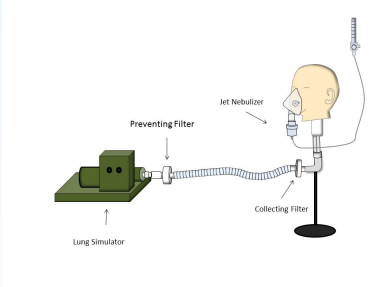
Lung Model: A lung model using a teaching manikin connected to a sinusoidal pump via a collecting filter at the level of the trachea simulating a spontaneously breathing infant/toddler (Vt 150 mL, RR 25 bpm and I:E ratio 1:2).

Dose, Nebulizers, & Masks: Albuterol sulfate (2.5 mg/ 3 mL) was aerosolized with JN (Mistymax 10, Airlife) or MN with adapter (Aeroneb Solo Adapter which facilitates use of the Aeroneb Solo with mouthpieces and masks, Aerogen Ltd, Galway, Ireland) using the dragon mask, aerosol mask, and valved-mask. The adapter specifically designed for MN was attached to all the interfaces used in this study and with supplemental oxygen of 2 lpm. A valved-mask was prepared by modifying a non-rebreathing oxygen mask with one-way valves on ports on both sides of the mask. The JN was run at 10 lpm based on the manufacturer's guideline.

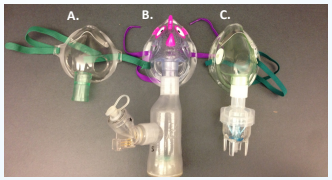
Data Collection and Analysis: Drug was eluted from the filter and analyzed via spectrophotometry. Descriptive statistics, dependent t-test and one-way analysis of variance were used for data analysis at the significant level of 0.05.

Methods

Experimental Set-up of the Lung Model.



Masks and Nebulizers Used in This Study.



A. Aerosol Mask **B.** Dragon Mask **C.** Valved Mask

Results

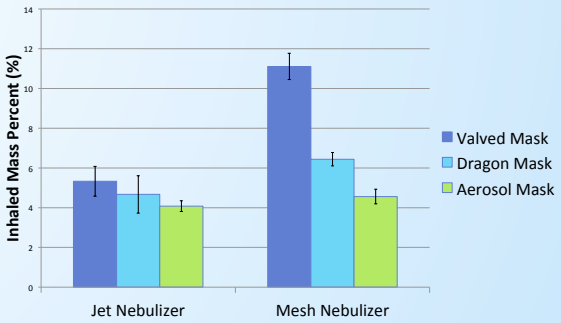
JN was less efficient in drug delivery than MN using valved-mask, dragon mask and aerosol mask ($p=0.002$, $p=0.066$ and $p=0.355$, respectively). While no significant difference was found among valved-mask, dragon mask and aerosol mask using JN ($p>0.05$), drug delivery with MN via valved-mask was greater than the dragon mask ($p= 0.002$) and aerosol mask ($p=0.002$). The dragon mask was more efficient than the aerosol mask using MN ($p=0.009$).

Results

The table below shows mean ± SD for inhaled mass delivered distal to the trachea.

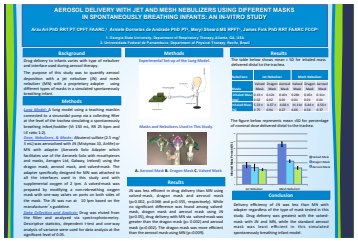
Nebulizers	Jet Nebulizer			Mesh Nebulizer		
Masks	Valved Mask	Dragon Mask	Aerosol Mask	Valved Mask	Dragon Mask	Aerosol Mask
Inhaled Mass (mg)	0.13 ± 0.02	0.12± 0.02	0.10± 0.01	0.28± 0.01	0.16± 0.01	0.11± 0.01
Inhaled Mass (%)	5.33 ± 0.75	4.67 ± 0.94	4.08 ± 0.27	11.11± 0.66	6.44 ± 0.34	4.56 ± 0.37

The figure below represents mean ±SD for percentage of nominal dose delivered distal to the trachea.



Conclusion

Delivery efficiency of JN was less than MN with adapter regardless of the type of mask tested in this study. Drug delivery was greatest with the valved-mask with JN and MN, while the standard aerosol mask was least efficient in this simulated spontaneously breathing infant model.


AEROSOL DELIVERY WITH JET AND MESH NEBULIZERS USING DIFFERENT MASKS IN SPONTANEOUSLY BREATHING INFANTS: AN IN-VITRO STUDY

Background

Methods

Results

Conclusion

Drug delivery was greatest with the valved-mouthpiece and mask with JN and MN.

The standard aerosol mask was least efficient in these simulated spontaneously breathing adult and pediatric lung models.

Delivery efficiency of JN was less than MN in all conditions tested in this study except in the aerosol mask.

The use of a mouthpiece or a valved mask provides more aerosol delivery than the open port standard aerosol mask.

Continuous (Volumetric) Nebulization

How does volumetric dosing work?

Liquid medication is in a syringe or bag

Drug passes from a tubing set into the nebulizer

Vibrating mesh is on “continuously”

Medication drips onto the aperture plate

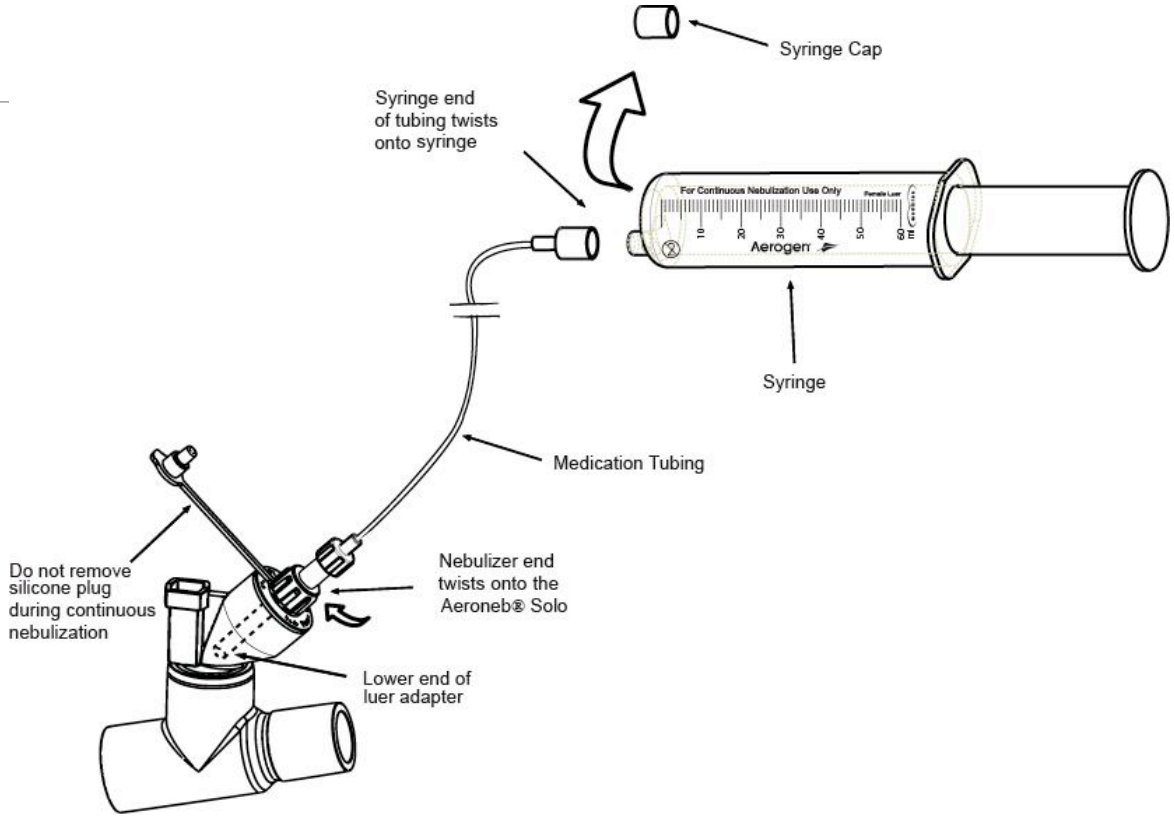
Aerosol produced from each drop

No aerosol until the next drop

Rate of the infusion pump = the output of the Aerogen Solo

Looks different then what we are used to seeing. This is a new paradigm in aerosol delivery

Volumetric Continuous Dosing



Video clip of volumetric dosing with the Aerogen Solo mesh nebulizer

Volumetric Dosing with Salbutamol

Albuterol 0.5% = 5 mg/ml solution (undiluted)					
Dose (mg/hour)	5 mg	7.5 mg	10 mg	15 mg	20 mg
Infusion rate = Aerosol output rate	1 ml	1.5 ml	2 ml	3 ml	4 ml

No added saline required

Delivery rate of infusion = aerosol output rate

Easy titration available to allow quick response to clinical needs of the patient

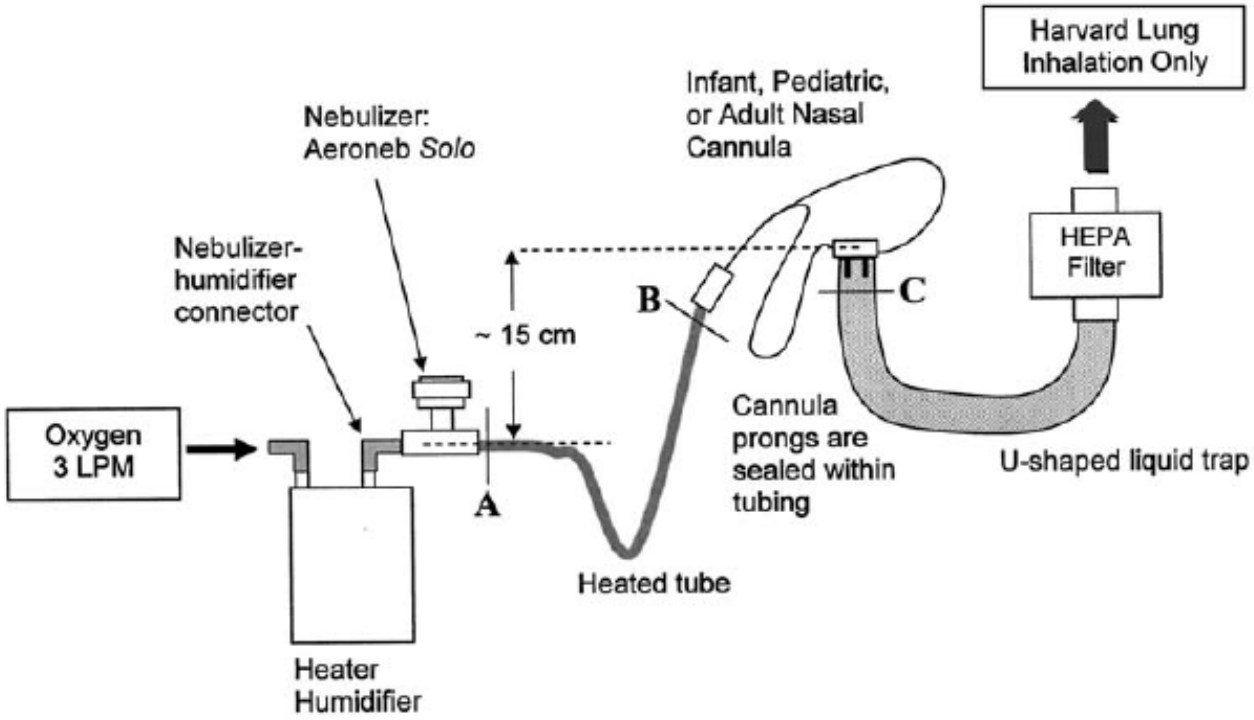
Save clinician time

Reduce medication waste (use one concentration of medication)

(Example only. Diluted Medications can also be used.)

Where is the best nebulizer placement in a HFNC circuit?

Aerosol Delivery via Nasal Cannula



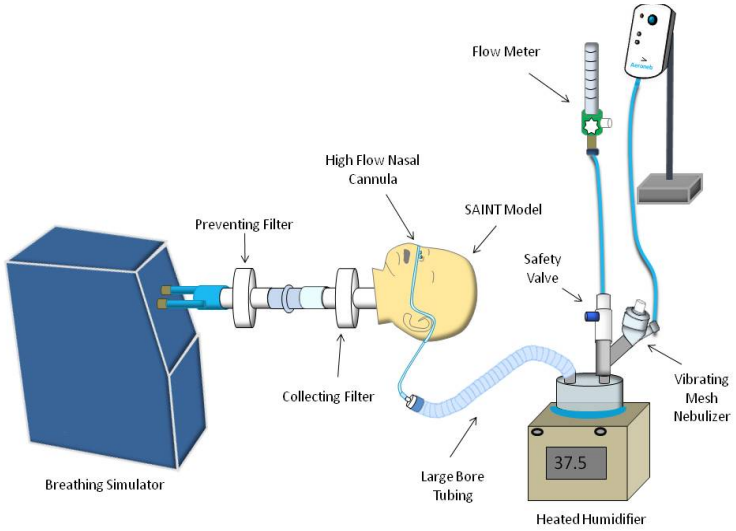
	Infant cannula		*Pediatric cannula*		*Adult cannula*	
	No Harvard lung	*Harvard lung*	*No Harvard lung*	*Harvard lung*	*No Harvard lung*	*Harvard lung*
Aerosol output dose (%)	8.4 ± 2.3	18.6 ± 4.0	18.1 ± 4.2	25.4 ± 1.7	25.1 ± 5.0	26.9 ± 4.9
delivery time (min)	13.1 ± 2.5	10.8 ± 0.7	13.0 ± 0.0	10.9 ±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

Bhashyam et al. JAM 2008

Aerosol Delivery to Trachea of Neonate Model

Vt – 8 mL
RR – 50 BPM

Cannula size impacts Aerosol Delivery

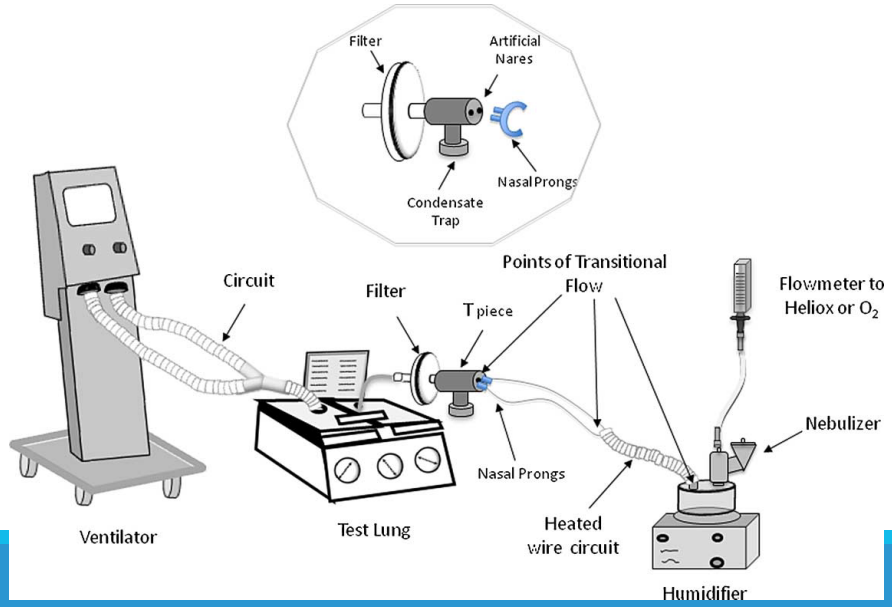


	INFANT CANNULA		PEDIATRIC CANNULA	
	3 LPM	6 LPM	3 LPM	6 LPM
Fisher Paykel	5.69 ± 0.77	4.78 ± 1.13	13.2 ± 3.29	9.06 ± 2.75
Hudson RCI	4.66 ± 1.10	4.52 ± 0.73	5.75 ± 0.54	4.14 ± 0.38
Vapotherm	4.88 ± 0.42	6.10 ± 1.10	7.17 ± 0.22	7.05 ± 1.10

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 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%

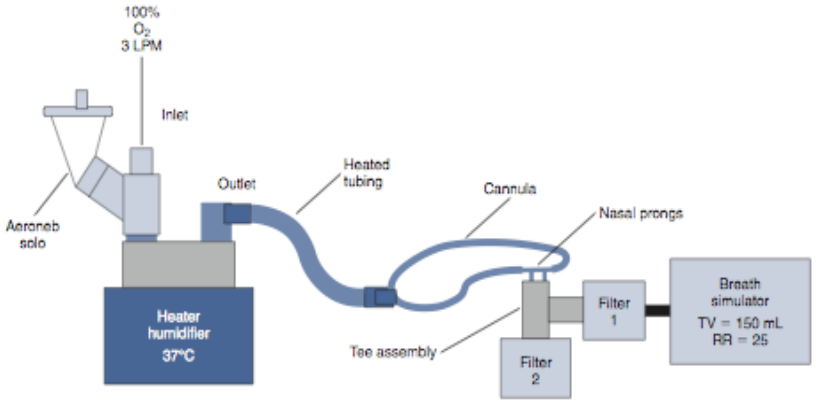
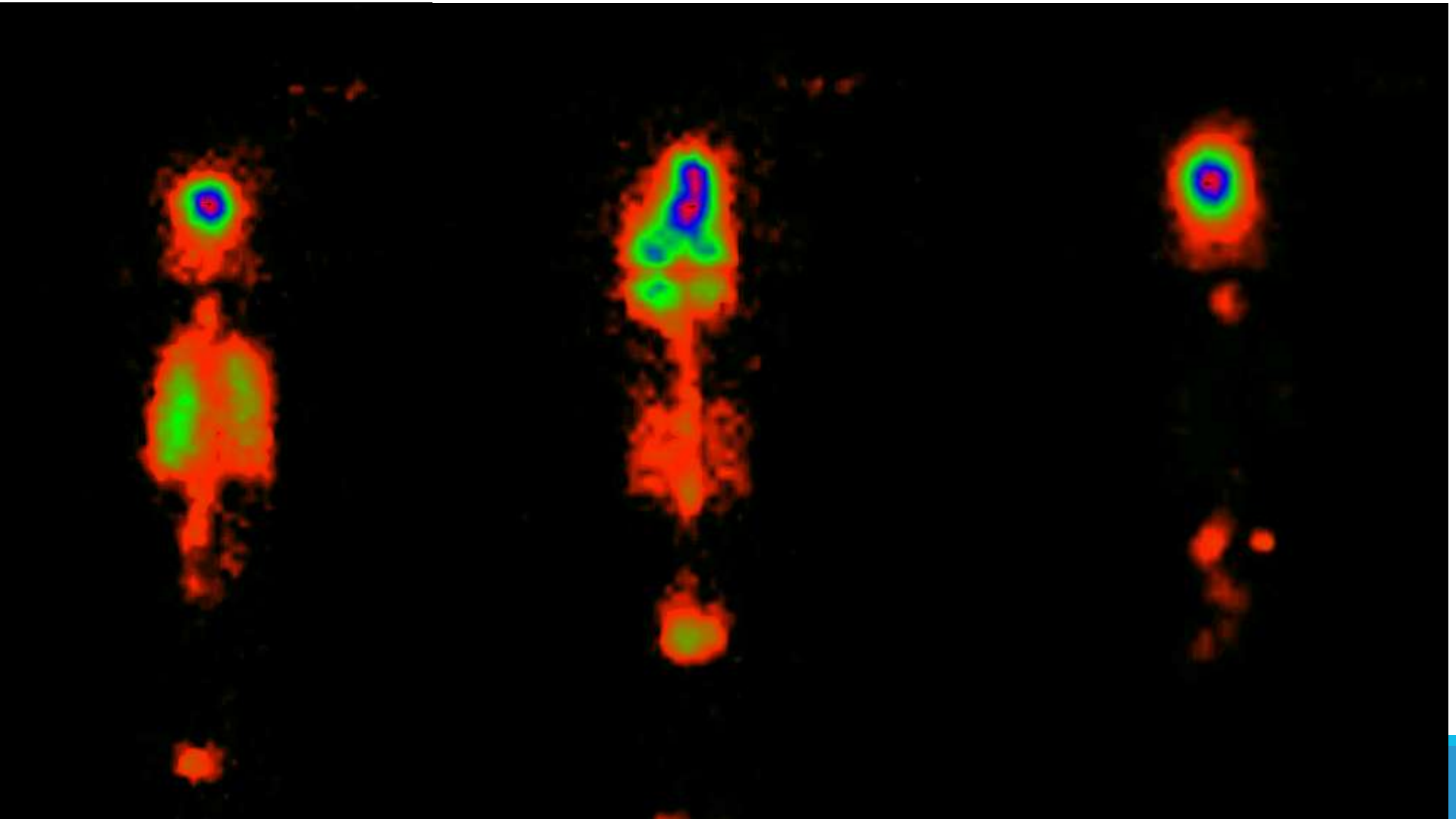


FIGURE 4-44 In vitro setup for testing aerosol delivery with a heated humidifier through a nasal cannula. The nebulizer is placed at the inlet of the humidifier, and the cannula is attached to a T-piece that allows aerosol to collect on filter 1 and condensate to collect on filter 2. This device can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

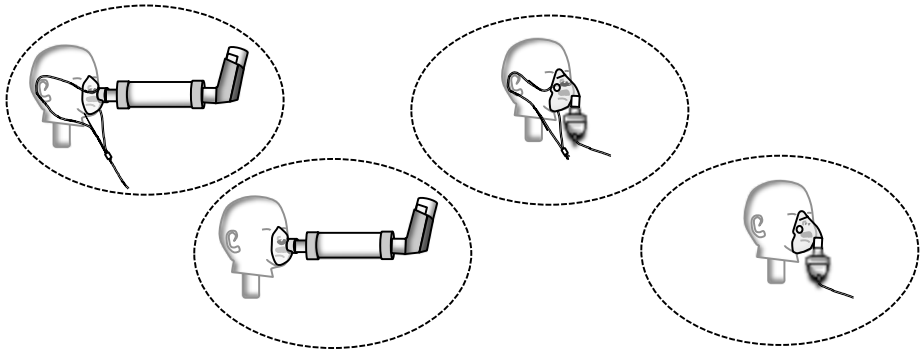
Ari, Dailey, Fink 2009

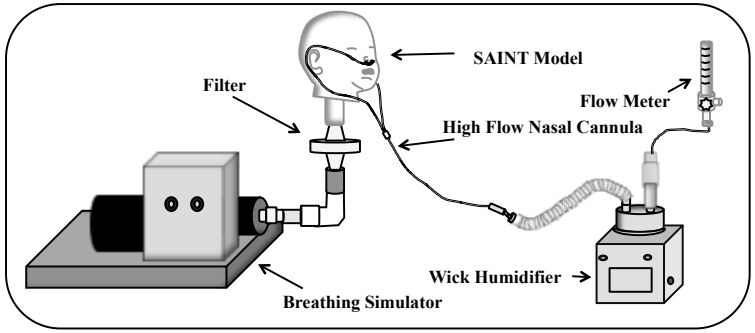
Feasibility study
Nebulization by nasal canula with standard vibrating mesh

2 L/min **4 L/mi** **8 L/min**



Aerosol to infants with and without HFNC



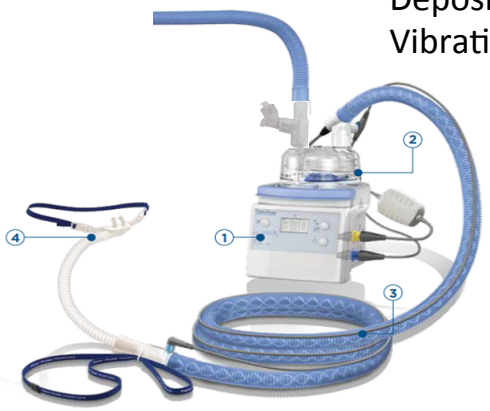


Vt of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4.

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	

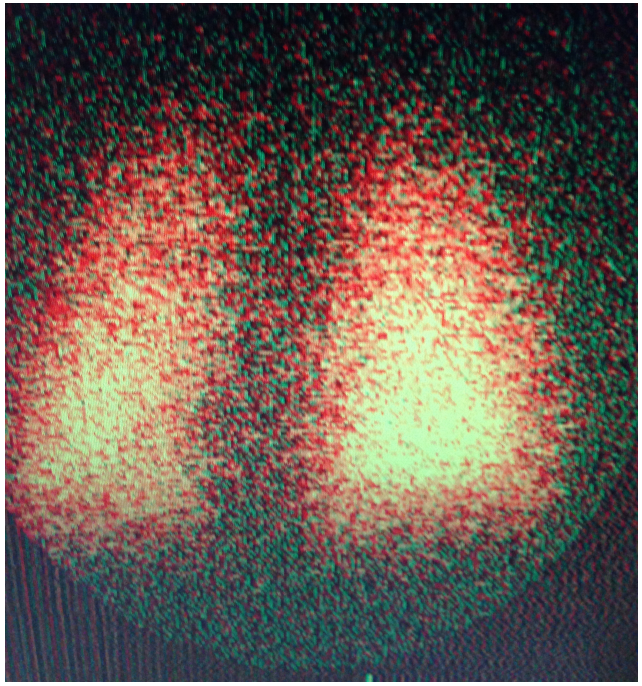
Mahmood Ahmed Alalwan 2011

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



Deposition with High Flow Nasal Cannula in an adult using 1 mL total dose with Vibrating Mesh nebulizer with 10 L/min Oxygen

Total Lung Deposition
15.4%



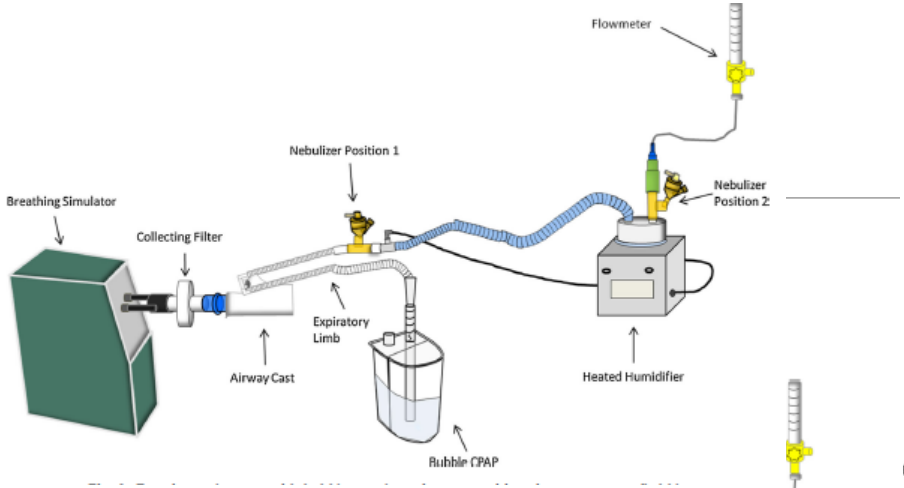
In Vitro Comparison of Aerosol Delivery Using Different Face Masks and Flow Rates With a High-Flow Humidity System

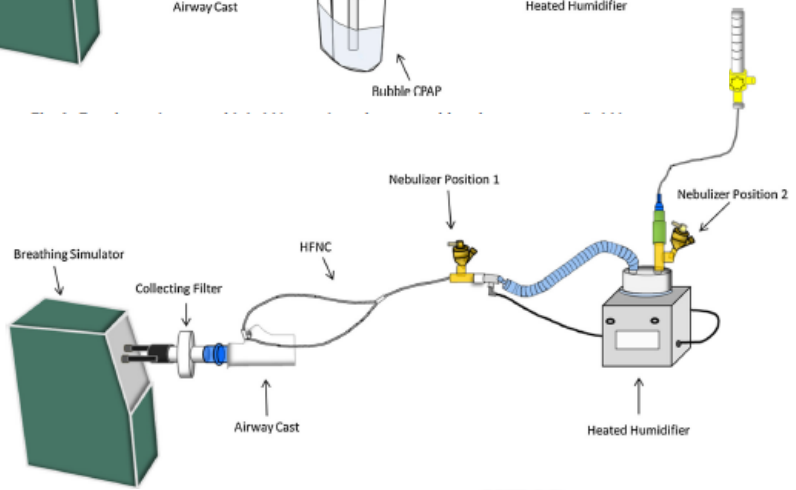
Hui-Ling Lin et al. RESPIRATORY CARE Paper in Press. Published on December 09, 2014 as DOI: 10.4187/respcare.

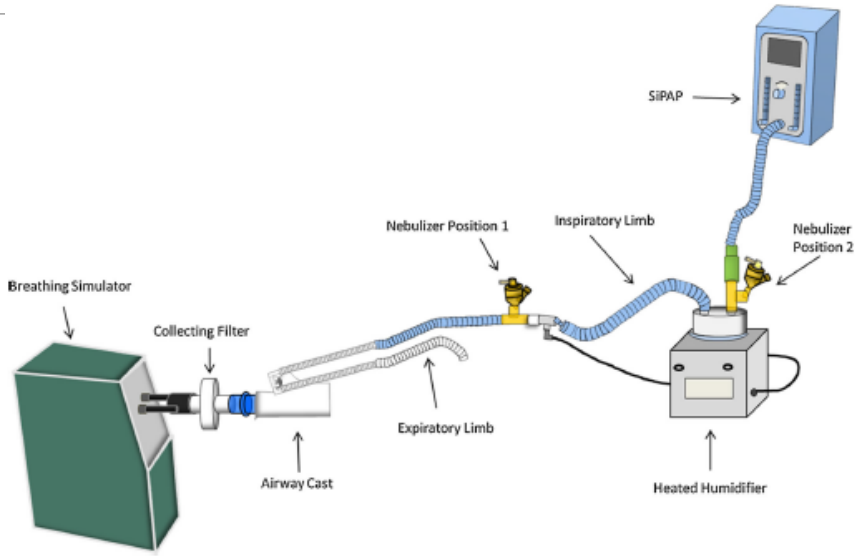
CONCLUSIONS: The flows of gas entering the mask and breathing patterns influence aerosol delivery, independent of the face mask used. Aerosol delivery through a high-flow humidification system via mask could be effective with both infant and pediatric breathing patterns.

Where is Ideal Nebulizer Placement with CPAP (fixed flow)?

Sunbul FS, Pediatric Pulmonology 2014







	HFNC	Bubble CPAP	SiPAP	*P*-values
Proximal to the patient (ug)	22 ± 6.5	17 ± 4.0	14 ± 4.9	0.101
Prior to the humidifier (ug)	32 ± 4.5	30 ± 6.1	19 ± 2.7	0.002
P-values	0.43	0.007	0.130	
Proximal to the Patient (%)	0.90 ± 0.26	0.70 ± 0.16	0.59 ± 0.19	0.098
Prior to the humidifier (%)	1.30 ± 0.17	1.24 ± 0.24	0.79 ± 0.11	0.002
P-values	0.43	0.03	0.13	

Pediatric Pulmonology

Where is Ideal Nebulizer Placement with CPAP (variable flow)?

In Vitro Evaluation of Radio-Labeled Aerosol Delivery Via a Variable-Flow Infant CPAP System

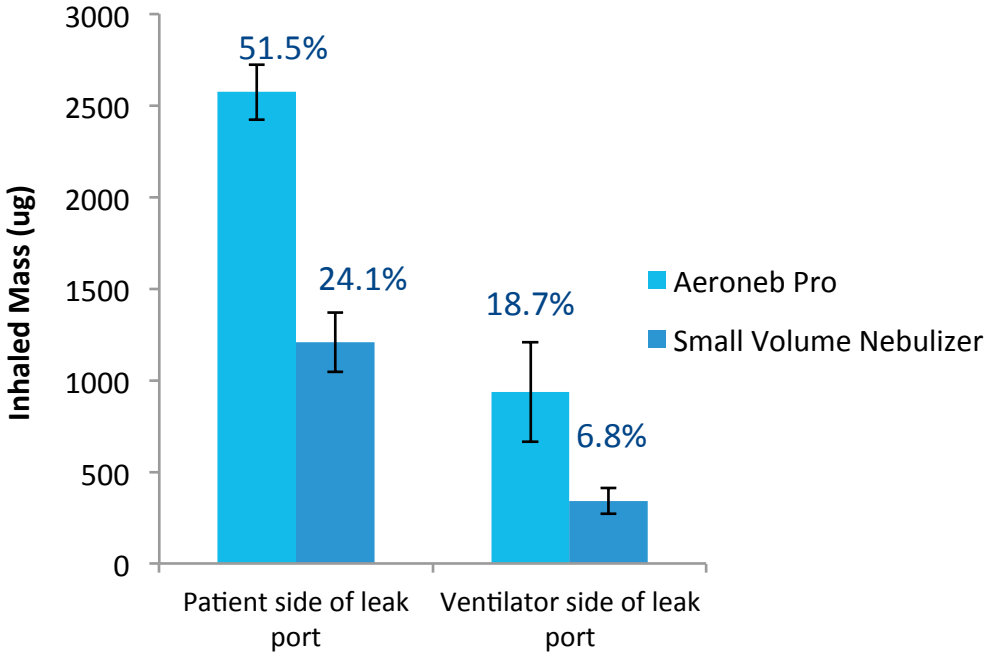
Kimberly D Farney et al. Respir Care 2014;59(3):340 –344

Isotope delivery from an aerosol generator placed near the humidifier on variable-flow nasal CPAP was negligible in this in vitro setup 0.3 +/- 0.4%; however, such delivery was significantly improved by locating the aerosol generator closer to the nasal CPAP interface 21+/- 11%.

The authors stated higher bias flows for the CPAP and smaller tidal volumes may be the reason delivery is better in variable flow CPAP with the nebulizer near the patient.

Where is the best nebulizer placement in a single limb BiPAP/NIV circuit?

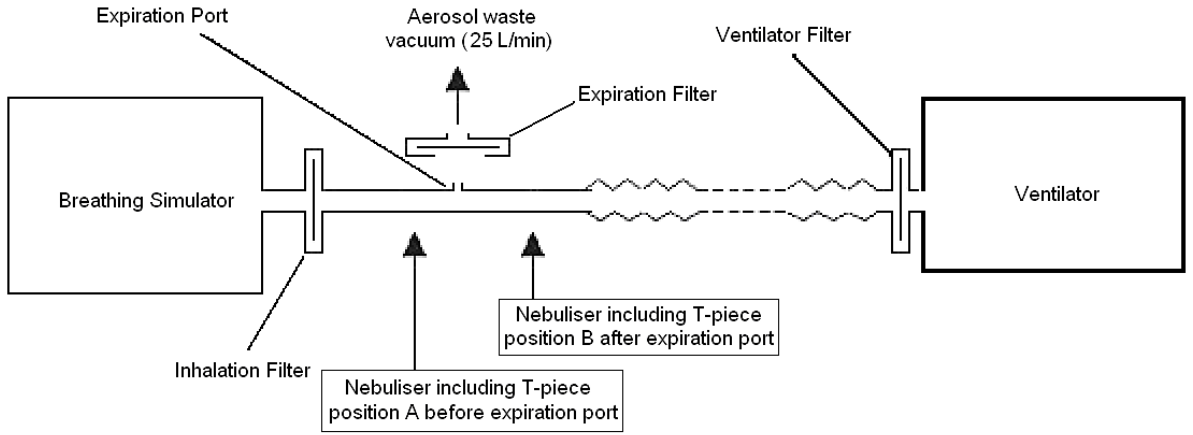
NIV / CPAP – Abdelrahim (in vitro)



2 fold more drug mass inhaled compared to a small volume nebuliser during NIV

Abdelrahim ME, Plant P, Chrystyn H. In-vitro characterisation of the nebulised dose during non-invasive ventilation. The Journal of pharmacy and pharmacology. 2010;62:966-972

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.

Radioaerosol Pulmonary Deposition Using Mesh and Jet Nebulizers During Noninvasive Ventilation in Healthy Subjects

Valdecir C Galindo-Filho PhD, Maria Eveline Ramos PT, Catarina SF Rattes MSc, Antoˆnio K Barbosa MSc, Daniella C Brandã˜o PhD, Simone Cristina S Brandã˜o PhD, James B Fink PhD FAARC, and Arme`le Dornelas de Andrade PhD

RESPIRATORY CARE Paper in Press. Published on June 23, 2015 as DOI: 10.4187/respcare.03667
RADIOAEROSOL PULMONARY DEPOSITION DURING NIV IN HEALTHY SUBJECTS

CONCLUSIONS:

- **During NIV in healthy subjects, vibrating mesh nebulizers delivered 2-fold more radiolabeled drug (with less residual drug volume) into the respiratory tract compared with conventional jet nebulizers.**

- **Additional studies are recommended in subjects with asthma, COPD, bronchiectasis, and cystic fibrosis to better understand differences in both aerosol delivery and response.**

Mechanical Ventilation

To Achieve Target Lung dose on the Ventilator

1 treatment with VM

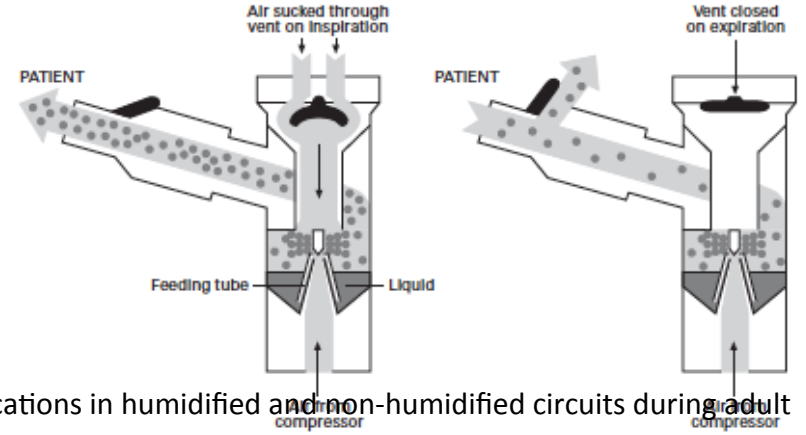
=

> 4 treatments with standard SVN

- **VM on vent delivers 17%**
- **SVN on vent delivers 3%**

Example Tobi:

- Antibiotic approved for use with jet nebulizer, delivering 12% lung dose[1]
- To achieve same effect on vent SVN requires **4** times **MORE** drug[2]

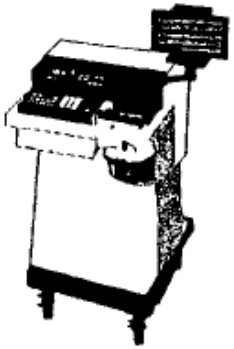


1. Geller Pari
2. Ari A, Areabi H, Fink JB. Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. *Respiratory care*. 2010;55:837-844

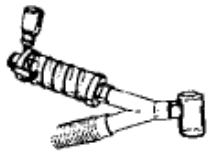
Factors that influence aerosols during mechanical ventilation

BASIC TECHNIQUES FOR AEROSOL DELIVERY DURING MECHANICAL VENTILATION

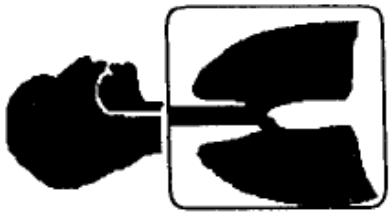
Ventilator-Related
- Ventilation mode
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath-triggering mechanism



Device-Related - MDI
- Type of spacer or adapter
- Position of spacer in circuit
- Timing of MDI actuation
- Type of MDI



Drug-Related
- Dose
- Formulation
- Aerosol particle size
- Targeted site for delivery
- Duration of action



Device-Related - Nebulizer
- Type of nebulizer
- Fill volume
- Gas flow
- Cycling: inspiration vs continuous
- Duration of nebulization
- Position in the circuit

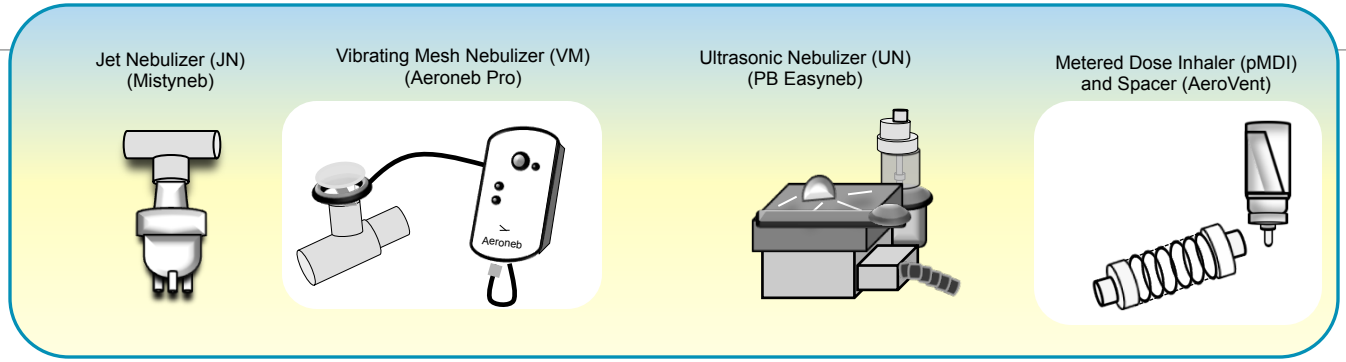
Patient-Related
- Severity of airway obstruction
- Mechanism of airway obstruction
- Presence of dynamic hyperinflation
- Patient-ventilator synchrony

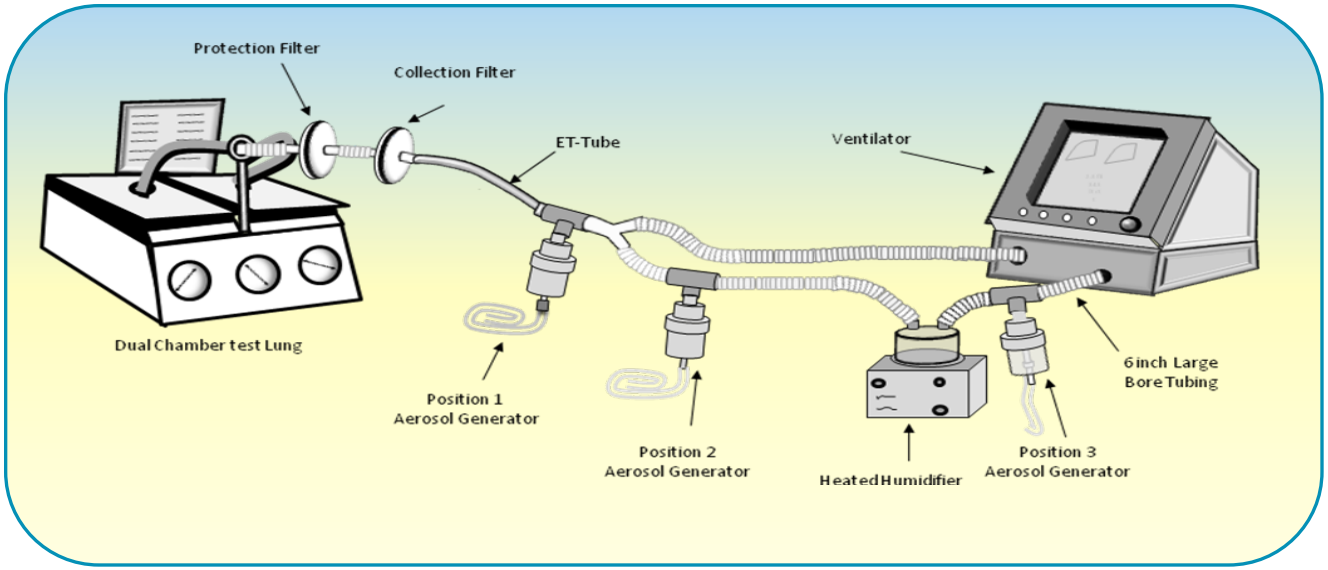
Circuit-Related
- Endotracheal tube size
- Humidity of inhaled gas
- Density of inhaled gas

Dhand, R. Basic techniques for aerosol delivery during mechanical ventilation.Respir Care 200449(6);611-622

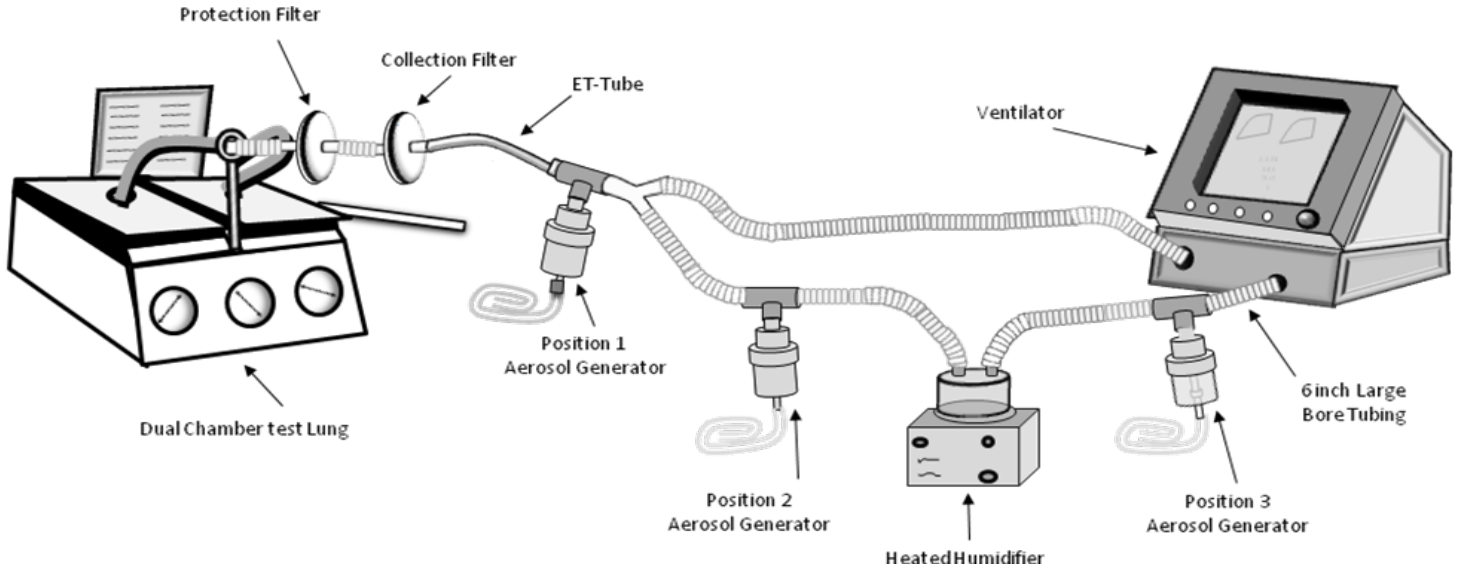
Where is the best nebulizer placement in a ventilator without bias flow?

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





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

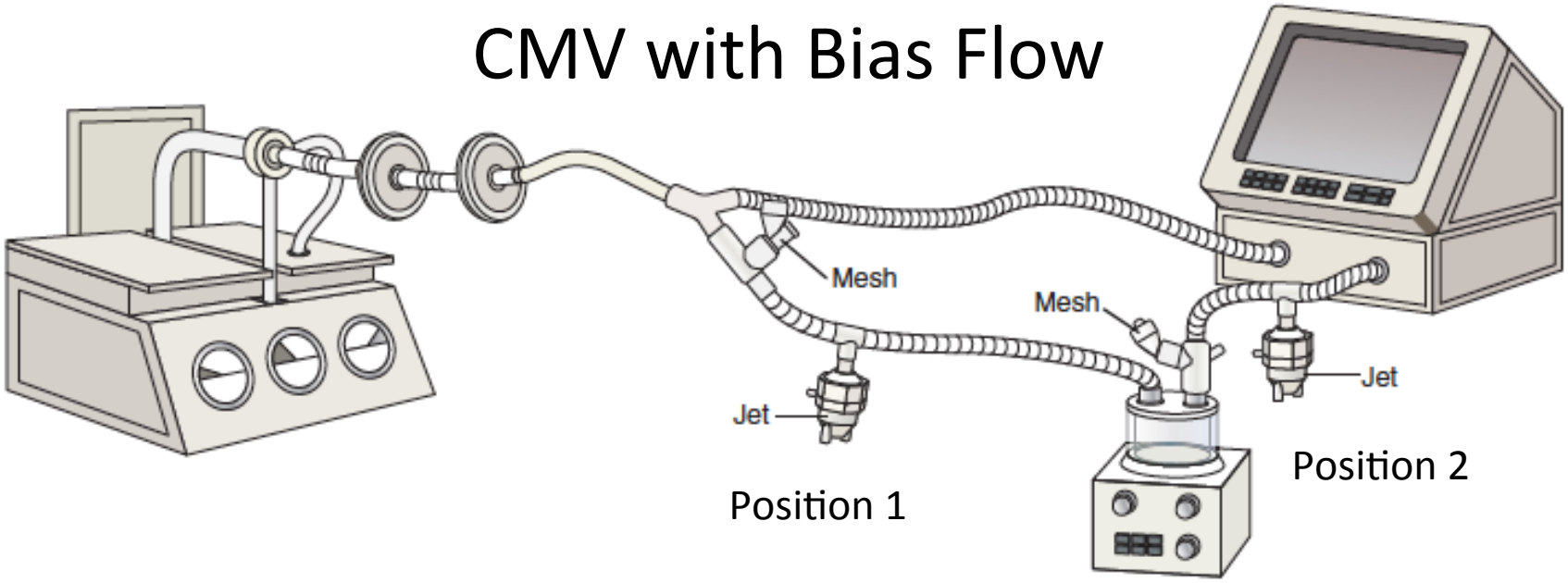


Neb Position	Pos 2 - 6 in from Y	
Ventilator Circuit	Heated	
JN	**3.61 (0.2)**	
VM	**16.79 (2.6)**	
UN	**16.53 (4.3)**	
pMDI	**17 (1.0)**	

Ari et al, Respir Care 2010

Where is the best nebulizer placement in a ventilator with bias flow?

CMV with Bias Flow



	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.

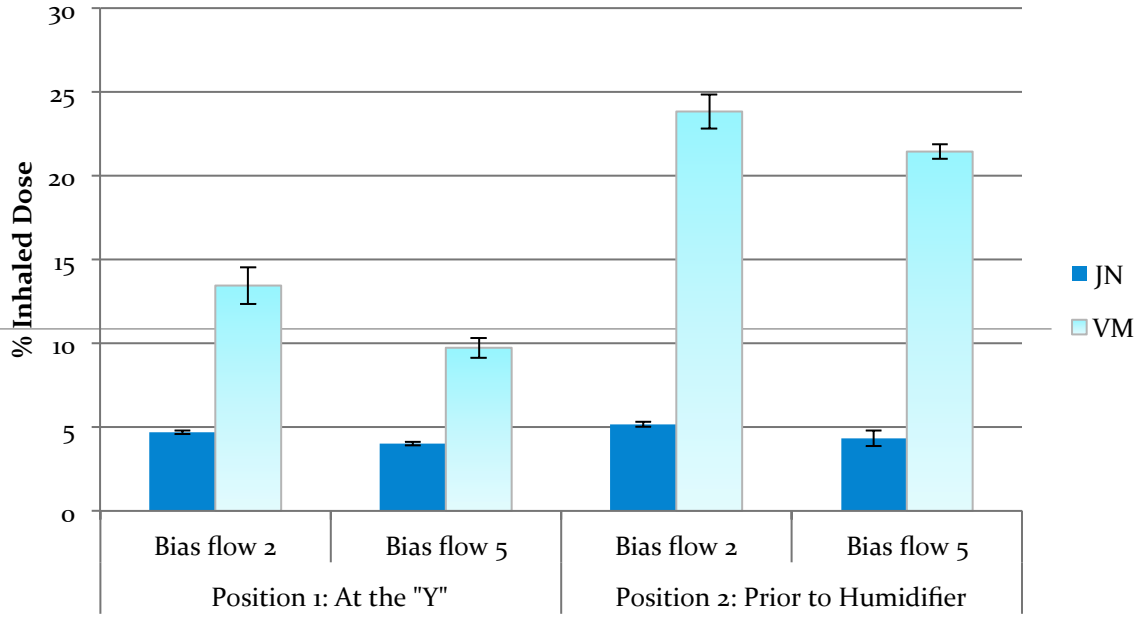
With Bias Flow

VM and JN more Efficient Placed Prior to Humidifier

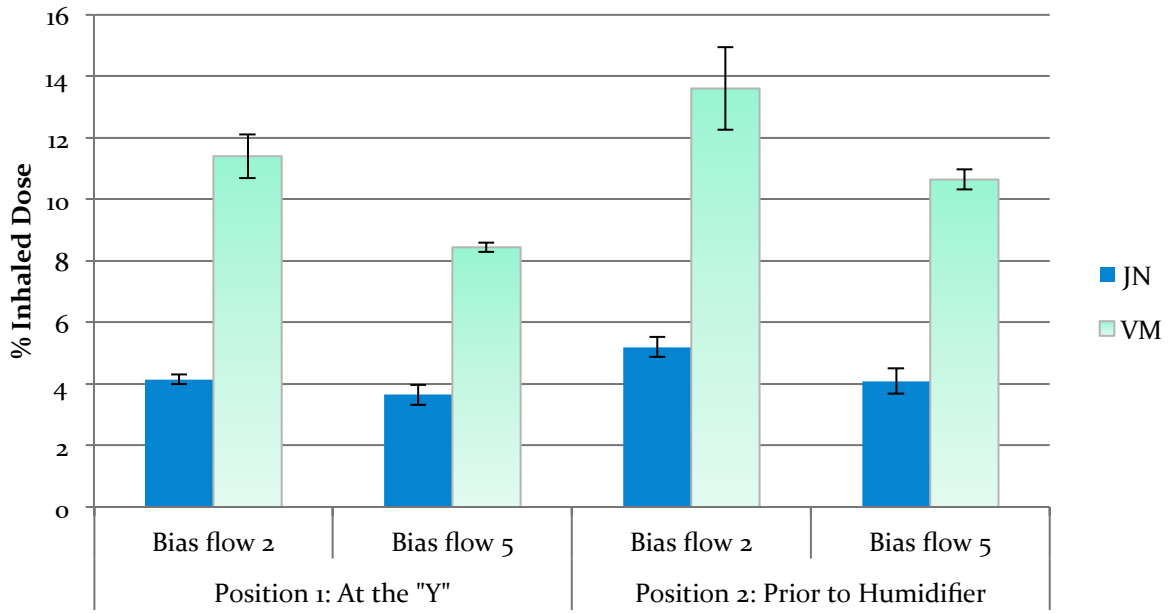
As Bias flow Increases deposition decreases

VM > JN

Adult



Peds



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

4 Nebulizers in 4 Positions of Pediatric Vent

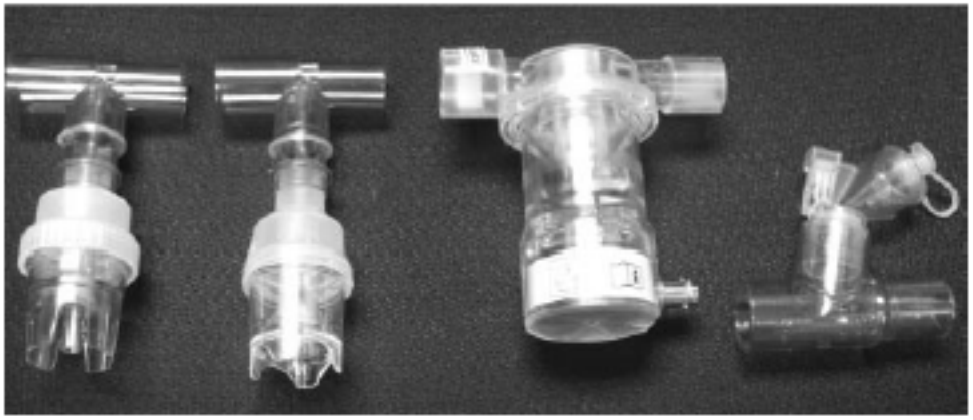
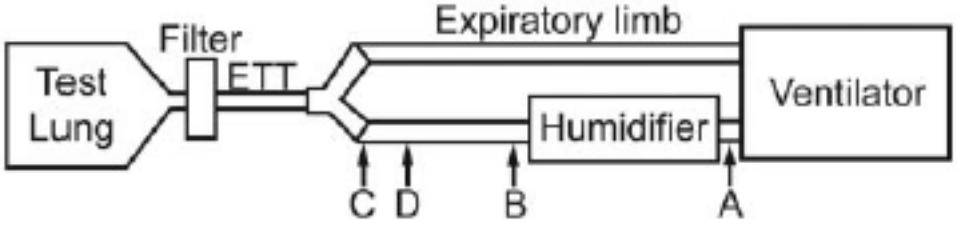


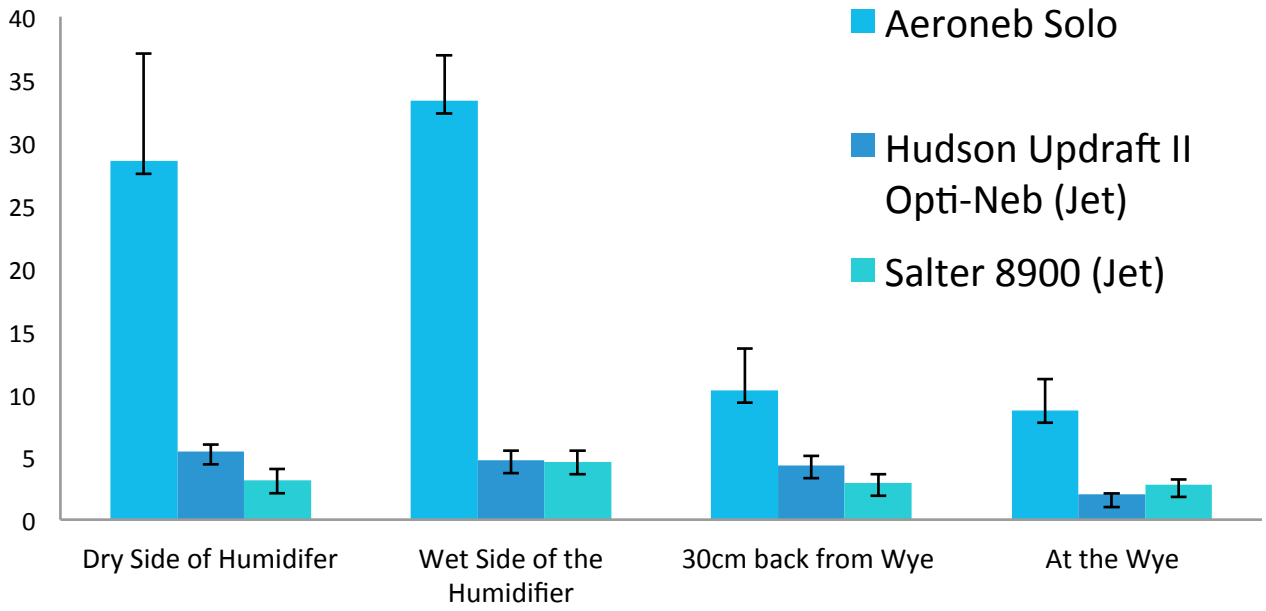
Fig. 1. Nebulizers tested. From right to left: Aerogen Solo, Maquet Ultrasonic model N06302595E400E, Salter 8900, and Hudson Updraft II Opti-Neb.



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 Respiratory Care

Mechanical Ventilation – Berlinski (in vitro)

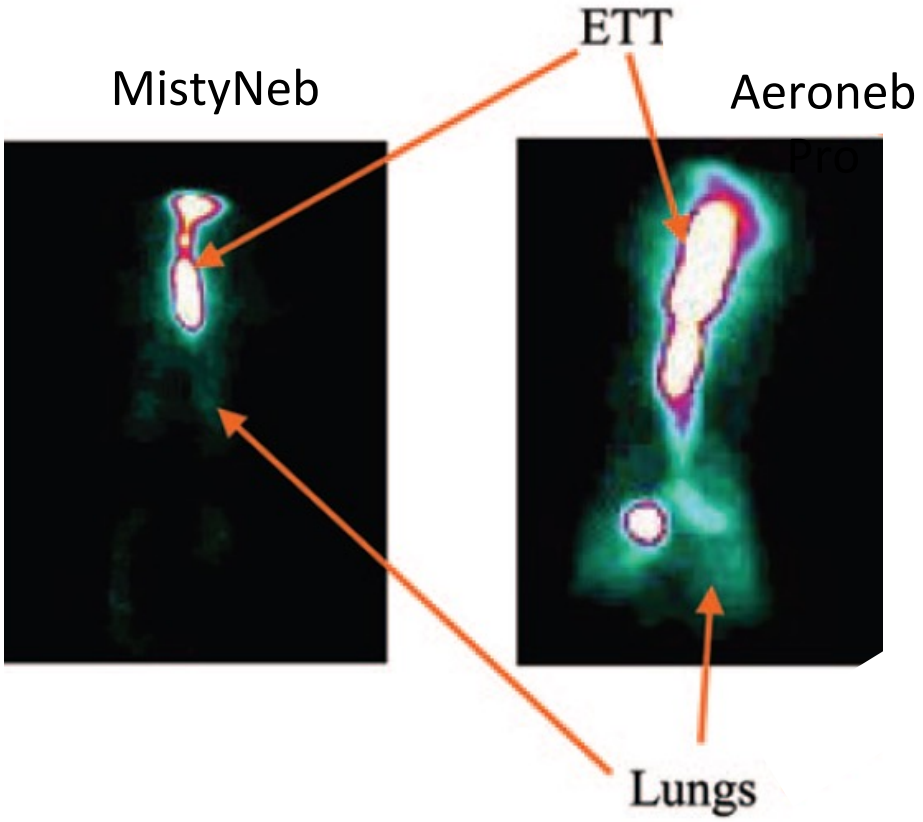


- Pediatric simulated model of aerosol delivery during mechanical ventilation (Bias flow 2L/min)
- Vibrating mesh performance was superior regardless of the position in the ventilator circuit

5-9 times more aerosol delivered by vibrating mesh on dry side of the Humidifier

Berlinski A, Willis JR. Aerosol delivery by 4 different nebulizers placed in 4 different positions in a pediatric ventilator in-vitro model. Respir Care 2013;58(7):1124-1133.

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

INHALED TREPROSTINOL DELIVERY USING A VIBRATING MESH NEBULIZER IN MECHANICALLY VENTILATED ADULT, PEDIATRIC, AND INFANT LUNG MODELS

Parker DK[1], Shen S[3], Zhiang J[3], Ivy DD[2,5], Yung D[3], DiBlasi RM[3,4]

[1] Children's Hospital Colorado Respiratory Care Department , [2] Hospital Colorado Heart Institute , [3] Seattle Children's Hospital and Research Institute , [4] Seattle Children's Hospital Respiratory Care Department, [5] University of Colorado Department of Pediatrics, University of Washington Department of Pediatrics

Original Abstract

BACKGROUND: Tyvaso® (treprostinil) Inhalation Solution (iTre) is a prostacyclin analogue approved for treatment of Pulmonary Arterial Hypertension in adults. It has also been shown to be effective in pediatric patients. iTre is FDA approved for delivery using the Tyvaso Inhalation System (TIS) which consists of an OPTINEB® ir (NEBUTEC, Elsenfeld, Germany) programmed for intermittent medication delivery. While there have been reports of the TIS being adapted for use in mechanically ventilated patients and delivery of iTre using a standard jet nebulizer; neither of these systems is ideal. Vibrating Mesh Nebulizers (VMN); used in many institutions for delivery of inhaled medication to mechanically ventilated patients, have been shown to provide greater drug delivery in ventilated patients than jet nebulizers and do not affect ventilator function. This study was designed to test the hypothesis that there were no differences in medication delivery at two nebulizer circuit locations during conventional ventilation (CMV) and one during high frequency oscillatory ventilation (HFOV).

METHOD: A test lung (ASL 5000, Ingmar Medical) configured for neonatal, pediatric, and adult, models was attached to an ETT with a filter placed on the distal end. The test lung was ventilated for each model with a Servo-i® (Maquet, Solna, Sweden) for CMV and Sensormedics Oscillator A & B (Carefusion,Yorba Linda, CA) for HFOV. The Aeroneb® Solo nebulizer was placed in 2 different positions in CMV; proximal to the patient wye and distal inlet of the humidifier. With HFOV it was placed between the patient wye and the ETT. 1 ml (660mcg) of iTre was nebulized. Each condition was repeated in triplicate with 3 different nebulizers. The treprostinil mass was quantified using high pressure liquid chromatography. Differences between mean treprostinil mass were compared at each condition using ANOVA with Tukey post-hoc tests. RESULTS: Under all testing conditions HFOV provided greater drug delivery than CMV (p<0.05). During CMV, greater drug delivery was obtained with the nebulizer placed prior to the humidifier during pediatric and adult ventilation (p<0.05). There were no differences in position during neonatal ventilation.

DISCUSSION/CONCLUSIONS: Tyvaso drug delivery is best achieved when the nebulizer is placed proximal to the patient-wye during neonatal ventilation and prior to the humidifier with pediatric and adult ventilation. Drug delivery appears to be adequate when using iTre with HFOV.

Introduction

Tyvaso® (treprostinil) Inhalation Solution (iTre) is a prostacyclin analogue approved for treatment of Pulmonary Hypertension in adults. It has also been shown to be effective in pediatric patients (*AM J Cardiol, 2012*). ITre is FDA approved using the Tyvaso Inhalation System (TIS) which consists of an OPTINEB® ir (NEBUTEC, Elsenfeld, Germany). This system must be activated on inhalation and is cumbersome to use during ventilation. While there are reports of TIS being adapted for use in mechanically ventilated patients and also using a standard jet nebulizer; neither of these systems is ideal. Vibrating Mesh Nebulizers (VMN) have been shown to provide greater drug delivery in ventilated patients than jet nebulizers and do not affect ventilator function. This study was designed to test the hypothesis that there were no differences in medication delivery at two nebulizer circuit locations during conventional ventilation (CMV) and one during high frequency oscillatory ventilation (HFOV).

Tables and Figures

Table 1. Lung model configuration and settings for conventional mechanical ventilation

Condition	HFOV Neonate	HFOV Pediatric	HFOV Adult
Ventilator	3100A	3100A	3100B
ETT	3.5	4.5	7.5
Amplitude	36	46	66
MAP	14	20	30
Hz	10	8	6
I:E	1:2	1:2	1:2
FIO_2	1.0	1.0	1.0
IT%	33	33	33
Flow (LPM)	15	20	30
Resistance	50	25	5
Compliance	4	20	70
Tyvaso Dose	162 µcg	162 µcg	162 µcg

Table 2. Lung model configuration and settings for high frequency oscillator Ventilation

Condition	CMV Neonate	CMV Pediatric	CMV Adult
Ventilator	Servo i	Servo i	Servo i
Mode	PRVC	PRVC	PRVC
VT (ml)	24	140	560
RR	30	20	15
It (sec)	0.4	0.75	1.0
I:E	1:4	1:3	1:3
FIO_2	1.0	1.0	1.0
PEEP	5	5	5
Bias Flow (LPM)	0.5	2	2
Resistance	50	25	5
Compliance	4	20	70
Tyvaso Dose	270 µcg	216 µcg	216 µcg

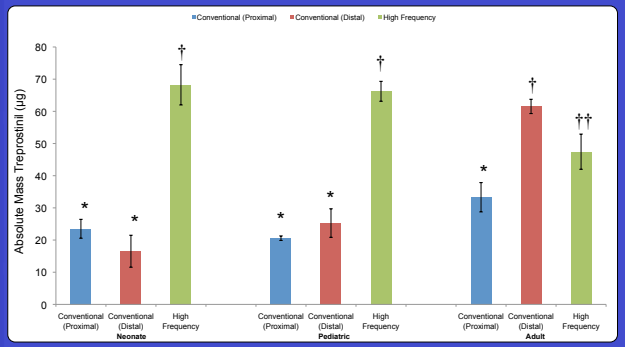


Figure 1. Values represented as mean±SD; Values not sharing similar symbols are different, *P*<0.05

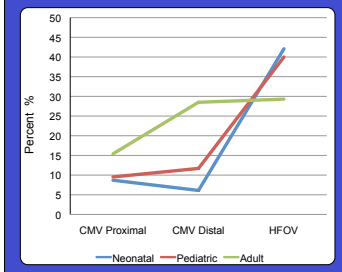


Figure 2. Percent nominal dose of Tyvaso

Methods

A test lung configured for neonatal, pediatric, and adult, lung models (Table 1 and 2) was attached to an ETT with a filter placed on the distal end. The test lung was ventilated for each model with a Servo-i® for CMV and SensorMedics Oscillator A & B for HFOV. The Aeroneb® Solo nebulizer was placed in two different positions in CMV; proximal to the patient wye and distal inlet of the humidifier. It was placed between the patient wye & the ETT during HFOV. The dose of iTre was nebulized based on I:E ratio (Table 1 and 2). Each condition was repeated in triplicate with 3 different nebulizers. The treprostinil mass was quantified using HPLC. Differences between mean treprostinil mass were compared at each condition using ANOVA with Tukey test.

Results

HFOV provided greater drug delivery than CMV ($p<0.05$) in all conditions, except adult conventional in distal location. During CMV, greater drug delivery was observed with the nebulizer placed prior to the humidifier during adult ventilation ($p<0.05$). There were no differences in position during neonatal and pediatric ventilation (Figure 1 and 2).

Conclusions / Discussion

Tyvaso drug delivery is best achieved when the VMN nebulizer is placed prior to the humidifier during adult ventilation. Drug delivery appears to be adequate when nebulizing iTre with a VMN during HFOV.

Disclosures

This Research was supported though a grant from United Therapeutics Corp.Silver Spring, Md). The University of Colorado receives fees for Dr. Ivy to be a consultant for Actelion, Gilead, Pfizer and United Therapeutics Ms Parker has received consulting /advisory board fees from Ikaria and research funding from United Therapeutics. Mr Diblasi has received funding from Draeger, Ikaria, Monaghan, Vapotherm & United Therapeutics

This shows that for neonates the optimal nebulizer placement is proximal to the patient. Pediatric circuit is a little better distal and adult is definitely distal.

Where is Ideal Nebulizer Placement with High Frequency Oscillatory Ventilation?

High Frequency Oscillatory Ventilation Siemens 3100AB

AEROSOL LUNG DEPOSITION USING A VIBRATING MESH NEBULIZER DURING HIGH FREQUENCY OSCILLATORY VENTILATION IN AN ADULT LUNG MODEL OF ARDS

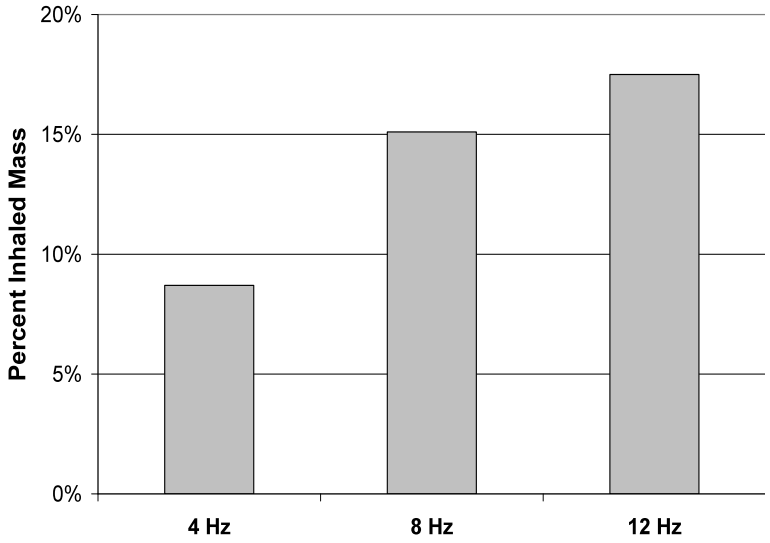
Mark Siobal BS, RRT, FAARC[1] Arzu Ari PhD, RRT, PT, CPFT[2], Jim Fink PhD, RRT, FAARC, FCCP[2]
[1] UCSF Dept of Anesthesia, San Francisco, CA, [2] Div. Resp Therapy, Georgia State University, Atlanta, GA

Background: Lung deposition of aerosolized medication during high frequency oscillatory ventilation (HFOV) in adults has not been thoroughly quantified. We measured simulated lung deposition in an adult lung model during HFOV using a vibrating mesh nebulizer (VMN).

Method: A VMN (Aeroneb Solo, Aerogen) was placed between the 3100B (Viasys) ventilator "Y" and a Ballard Trach Care double swivel elbow inline suction catheter. The suction catheter was connected to a 7.5mm endotracheal tube inserted into a bifurcated trachea model and the cuff was inflated. Bacteria filters were positioned at the distal ends of each bronchial lumen and connected via a "Y" adapter to a single compartment of a test lung (TTL, Michigan) set at a compliance of 20 mL/cm H20. The ventilator was set to amplitude of 90 cm H2O, mean airway pressure of 34 cm H2O, 33% inspiratory time, with bias flow of 40 L/min. The VMN was filled with a 3 mL (2.5 mg) dose of albuterol and nebulized continuously until empty. A total of 3 runs each were performed at frequencies of 4 Hz, 8 Hz, and 12 Hz. Albuterol was eluted from the filters and analyzed with UV spectrophotmetry (276 nm) and reported as percent of total dose.

Results: The percent of albuterol delivered distal to the mainstem bronchi in a bifurcated trachea model was 8.7 ± 0.78 % at 4 Hz, 15.1 ± 6.9 % at 8 Hz,frequency. The average deposition across all frequencies tested was 13.8%.

Conclusion: During HFOV in an adult lung model of ARDS, simulate lung deposition of drug aerosolized with the VMN is consistent with th range of dose efficiency reported with conventional ventilation (Ari et a Resp Care July 2010). During HFOV, drug delivery appears to increase wit higher frequencies. Further investigation of lung deposition, penetration, an clinical response to aerosol medication delivery during HFOV in adu patients with ARDS is warranted.

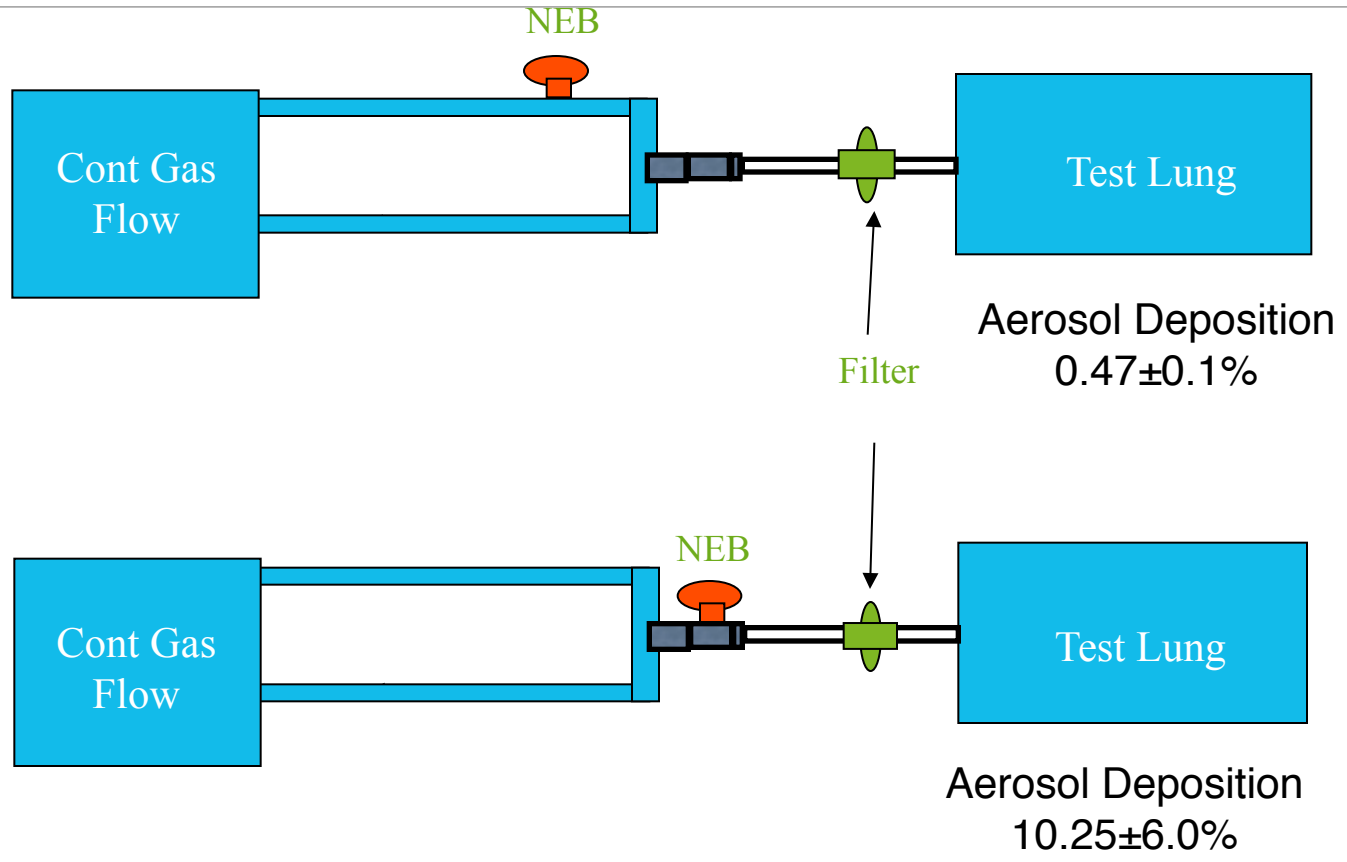


OF-2010

Deposition increased as frequency increased from 4-12 hz.

Deposition increased from 8.7-18%..

Effect of Nebulizer Position on Aerosol Delivery with HFOV



Demers et al. ATS San Diego, 2005

Aerosol Delivery Using Jet Nebulizer and Vibrating Mesh Nebulizer During High Frequency Oscillatory Ventilation: An In Vitro Comparison

Tien-Pei Fang, Hui-Ling Lin et al, JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY Volume 29, Number 0, 2016

"This is the first report comparing aerosol delivery efficiency with JN and VMN during HFOV in infant, pediatric, and adult models. We demonstrated that aerosol can be efficiently delivered by VMN placed proximally to the ETT, between the ETT and the ventilator circuit, during HFOV, while little or no aerosol (</= 3%) was delivered with the JN."

In the proximal position the mesh nebulizer delivered 23%, 17%, and 9% from the adult, pediatric, and neonate circuit compared to 3%, 2.8%, and 0.1% for the jet nebulizer. In the distal position the % deposition was 0.6% or less in all circuits. Further clinical studies are desired to determine pharmaceutical responses to a broad range of drugs during HFOV.

Evaluation of aerosol delivery through high frequency oscillatory ventilation

Hui-Ling Lin MSc RRT RN FAARC- Department of Respiratory Therapy, Chang Gung University

Shu-Hua Chiu BS RRT, Tien-Pei Fang MS RRT- Department of Respiratory Therapy, Chiayi Chang Gung Hospital

Background:

High frequency oscillatory ventilation (HFOV) is used with critically ill patients with failed oxygenation on respiratory distress syndrome or acute respiratory distress syndrome as a rescue therapy. However, the efficiency of aerosol delivery during HFOV has not been tested extensively with different devices.

Objective:

The purpose of this *in vitro* study was to determine aerosol delivery by various devices on HFOV with adult, pediatric, and neonate lung models.

Ventilator settings

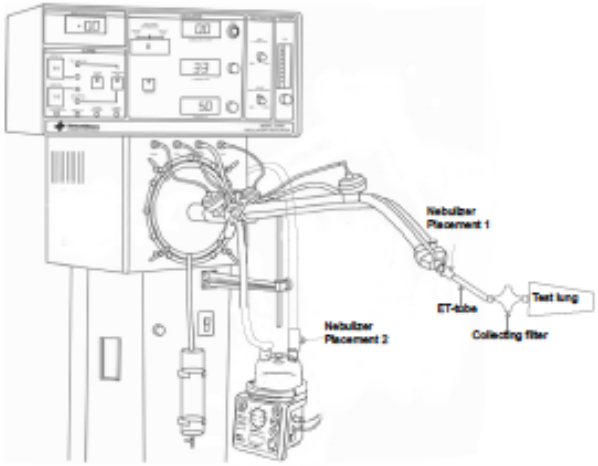
Parameter	Neonate	Pediatric	Adult
MAP (cm H_2O)	10	18	30
Bias flow (L/ min)	10	25	40
Frequency (Hz)	15	8	5
Inspiratory Time (%)	33	33	33
Power (cm H_2O)	3	7	8

Conclusion:

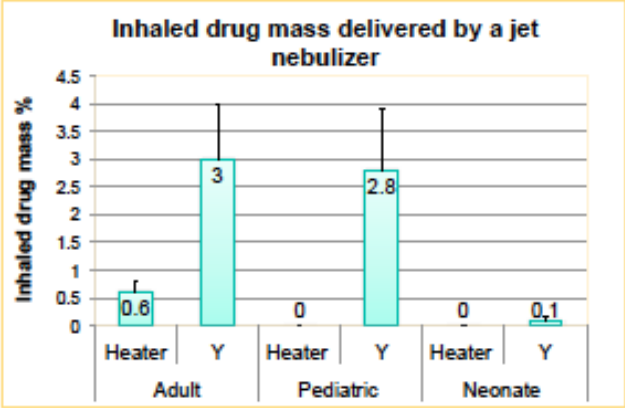
Aerosol delivery with a vibrating mesh nebulizer placed between the ETT and the ventilator circuit was more efficient than a jet nebulizer during high frequency oscillatory ventilation with infant, pediatric and adult settings.

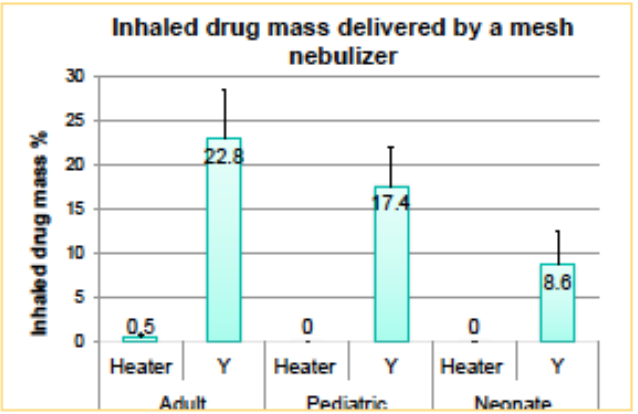
•There is no conflict of interest.

Methods:



Results: Figures below show Inhaled drug mass ± SD (%) among breathing patterns and locations between two devices.





Iloprost drug delivery during infant conventional and high-frequency oscillatory ventilation

Robert M. DiBlasi et al
Pulm Circ 2016;6(1):63-69. DOI: 10.1086/685080.

Drug delivery in proximal position was nearly threefold greater during HFOV than during conventional ventilation.

With the conventional ventilator drug delivery was 10.74% in the proximal position and 2.96% distal. With the HFOV ventilator drug delivery was 29.74% proximal and 0.96% distally.

In conclusion, iloprost drug delivery was best achieved when the nebulizer was placed proximal to the patient airway during neonatal mechanical ventilation. Drug delivery appears to be more efficient during HFOV than during conventional ventilation.

This is the first in vitro study of infant ventilation reporting a double digit percentage of the nominal dose of an aerosolized drug delivered distal to the ETT with both conventional ventilation and HFOV.

This is the first study to compare differences between two different forms of neonatal ventilation.

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

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ORIGINAL ABSTRACT

Infants with chronic lung disease (CLD) commonly require prolonged invasive ventilation extending beyond the 01. **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 Pro|ase®/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 those 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_2O and R: 50 cmH_2O/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

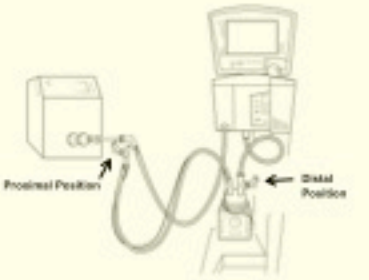


FIGURE 1. Schematic of experimental set-up during conventional ventilation

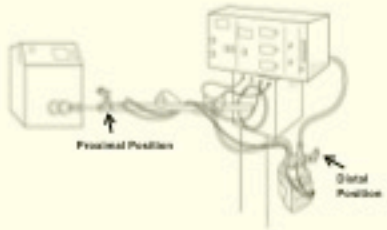
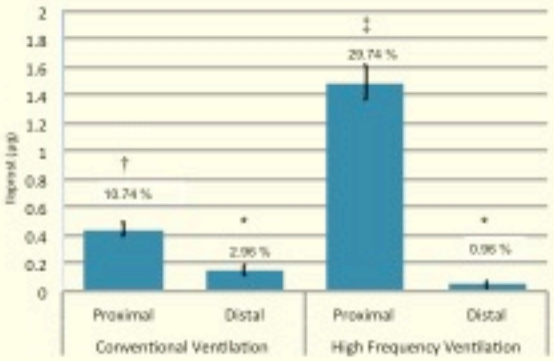


FIGURE 2. Schematic of Experimental Set-up during high-frequency oscillatory ventilation

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_2O and resistance: 50 cmH_2O/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.

Where is Ideal Nebulizer Placement with High Frequency Percussive Ventilation?

High Frequency Percussive Ventilation, Percussionaire VDR4

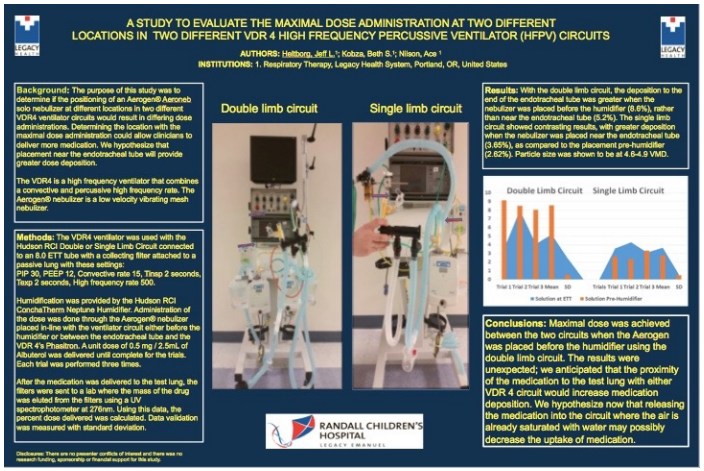
2014 AARC Poster: Jeff Heltborg et al. Randall Children's Portland Oregon

2 circuits, 2 neb positions for each circuit

Double limb circuit: 8.6% pre-humid, 5.2% at ETT

Single limb circuit: 2.6% pre-humid, 3.7% at ETT

More clinical trials are needed.



Where is Ideal Nebulizer Placement with High Frequency Jet Ventilation?

High Frequency Jet Ventilation, Bunnell Jet Ventilator

Aerogen bench tests show about 4% of drug is in aerosol form at the end of the ETT.

More clinical studies are needed.

Conclusion

Many inhaled drugs were approved based on studies in spontaneous breathing subjects with lung doses of 10 – 20%.

Lung dose with standard JN can deliver as little as 3% of dose to the lung.

Many of the devices used in Neonates, infants, children and adults can achieve >10% lung dose with conventional ventilation, NIV and HFNC.

Choice of aerosol generator, circuit placement, and interface makes a huge difference in drug delivery to the lung

Selection of Device and Drug Dose can Achieve Effective Lung Doses

Thank You

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