NEW STRATEGIES IN AEROSOLIZED THERAPIES IN CRITCAL CARE

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Aerogen Pharmaceuticals
Chief Scientific Officer

Friday, January 18, 2019 –3:00 p.m. – 3:45 p.m.

Jim Fink, PhD, RRT, FAARC, FCCP, Currently serves as Chief Scientific Officer for Aerogen Pharma Corp in San Mateo, CA. Dr. Fink is an Adjunct Professor of Respiratory Therapy at Rush Medical School, Chicago, and Visiting Professor, Department of Physical therapy, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil (CNPq 400801/2013-2). A respiratory care clinician, supervisor, manager, educator and researcher for 45+ years with focus on understanding aerosol device/patient interface and design in both critical care and ambulatory settings.

New Strategies in Aerosolized Therapy in Critical Care

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CALIFORNIA THORACIC SOCIETY
NORTHERN CALIFORNIA
ANNUAL EDUCATIONAL CONFERENCE
FRIDAY JANUARY 18, 2019 -
SATURDAY JANUARY 19, 2019

What do we know?

- **In vitro data showing that different types of nebulizers perform differently (JN, USN, VM, etc.)[4,5,6]**
- **In vitro data demonstrating best placement for optimal aerosol delivery with different applications (MV, NIV, HFNC)[4,5,6,7,8]**
- **In vitro data with different interfaces[8]**
- **Imaging data with different applications comparing different nebulizers[9, 10, 11, 12, 14]**
- **Recent advances in aerosol generators have led to more efficient aerosol delivery**

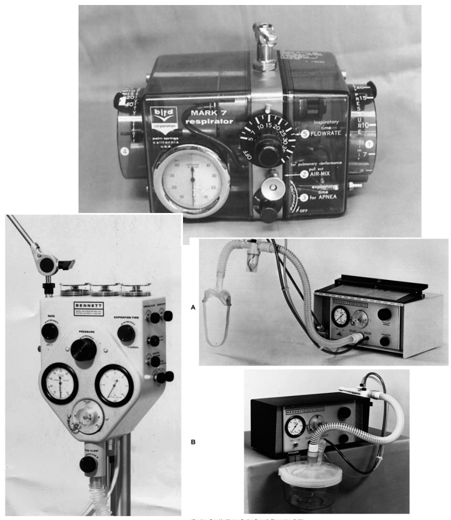
Gaps

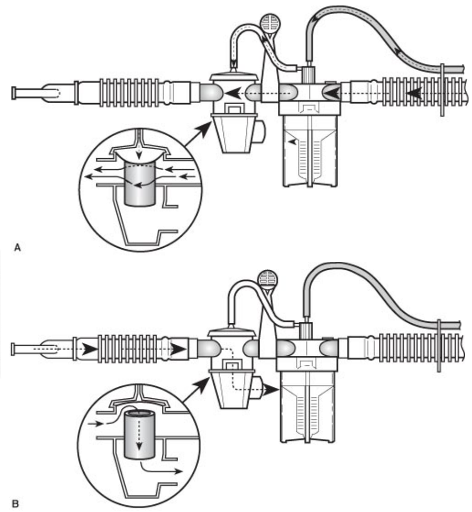
- No aerosol drugs approved for use in critical ill adults
  - Approvals based on ambulatory studies in patients with mild disease
- Aerosol delivery with JN is less efficient in critical care applications[1]
- Numerous factors effect performance[2]
- Lung deposition is a relatively low fraction of total aerosol dose.[3]
- Aerosol delivery with mechanical ventilation is limited and technique dependent[2]
- Newer applications such as HFNC require recommendations for aerosol delivery
- Wide range and variance in efficiency between different types of nebulizers across applications
- Little clinical data exists to support optimal aerosol delivery recommendations in critical care

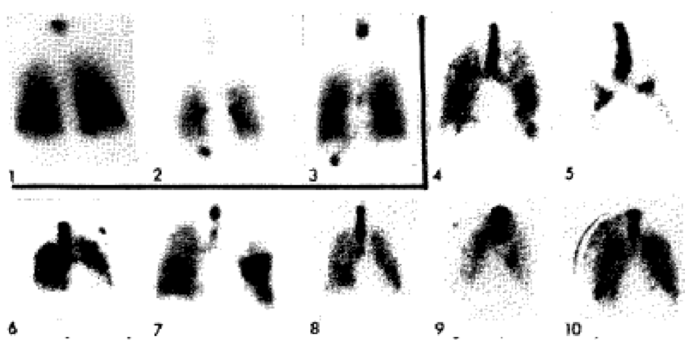
Medications via Aerosol to Acutely Ill Patients

- Bronchodilators
- Anti-infectives
- Prostanoids
- Anticoagulants - Heparin
- Diuretics
- Insulin
- Mucokinetics
- NOTE: Mucomyst (N-Acetylcystein) – no evidence of benefit by aerosol on or off the ventilator

Intermittent Positive Pressure Breathing (IPPB) – 30% Less Aerosol to lung than Neb Alone

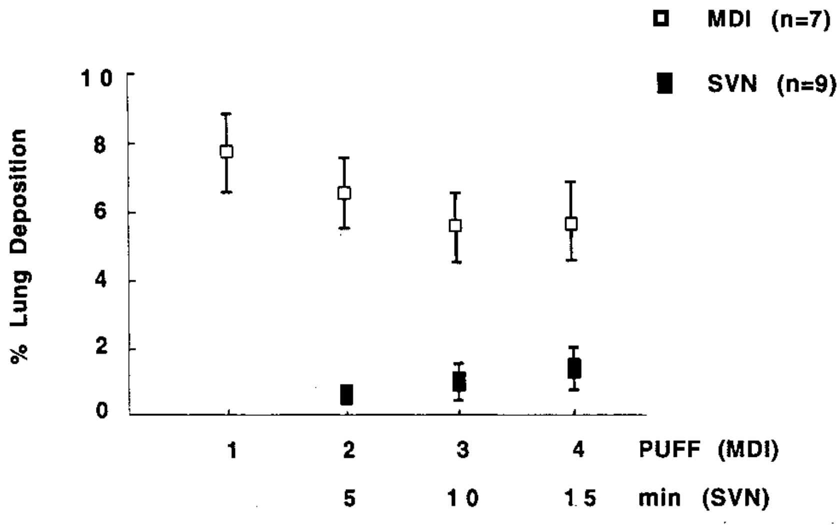






	Intubated Subjects	Nonintubated Subjects
Administered radioactivity	5.75 ± 1.3 mCi	6.53 ± 0.4 mCi
Percent of administered radioactivity in:		
Trachea (includes portion of endotracheal tube in intubated patients)	1.6 ± 1.1%[a]	0.3 ± 0.1%[a]
Lung parenchyma	2.9 ± 0.7%[b]	11.9 ± 2.2%[b]
Stomach	—	7.3 ±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

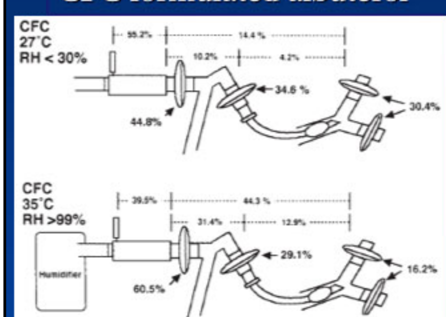
Macintyre Crit Cre Med 1985



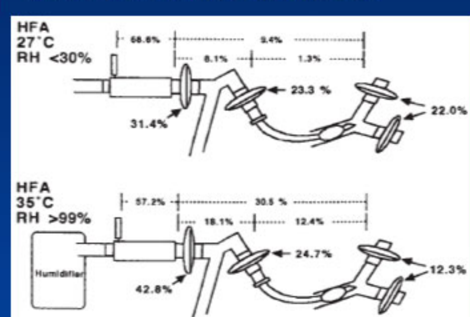
Fuller et al. 1990. ARRD 141:440-444.

Drug deposition

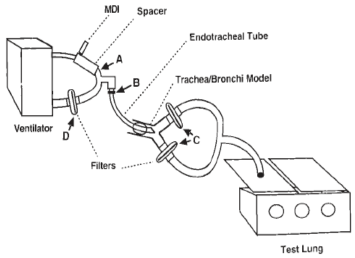
CFC formulated albuterol

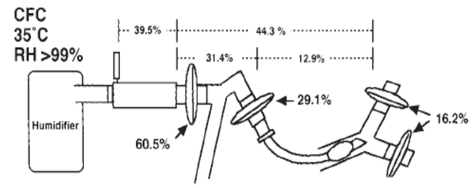


HFA formulated albuterol



Fink et al. AJRCCM 1999: 159; 63-67





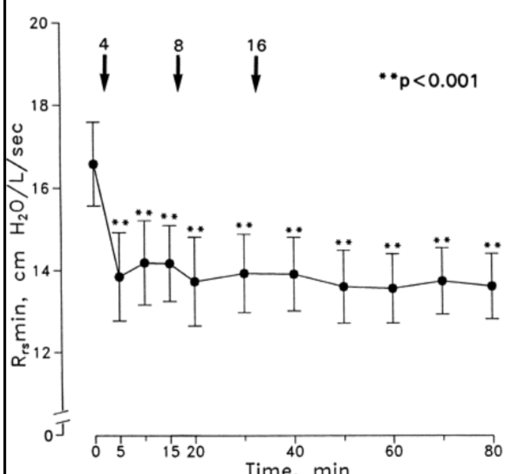
IN VIVO AND *IN VITRO* ESTIMATES OF EXHALED ALBUTEROL DURING CONTROLLED MECHANICAL VENTLATION

Patient No.	Sex	ETT (*mm*)	V_T (*L*)	Rate (*b/min*)	PIF (*L/min*)	T_I/T_{tot}	Albuterol on Expiratory Filter* *In Vivo*	*In Vitro*	Difference†
1	M	8.0	0.7	12.0	40	0.21	9.6	4.4	5.2
2	M	8.0	0.7	10.0	40	0.18	8.7	3.9	4.8
3	M	8.5	0.6	10.0	40	0.15	9.3	4.1	5.2
4	F	7.5	0.6	12.0	40	0.18	8.6	4.1	4.5
5	M	8.0	0.7	10.0	40	0.18	6.2	3.3	2.9
6	F	7.0	0.5	12.0	40	0.15	8.7	3.9	4.7
7	M	8.0	0.6	10.0	40	0.15	9.0	3.9	5.1
8	M	8.0	0.6	12.0	50	0.14	7.9	3.6	4.3
9	M	8.0	0.7	10.0	40	0.18	10.8	4.6	6.2
10	M	8.0	0.6	12.0	40	0.17	8.7	3.6	5.1
Mean		7.9	0.6	11.0	41	0.17	8.7	3.9	4.8
SD		0.4	0.1	1.1	3.2	0.02	1.2	0.4	0.8

Definition of abbreviations: ETT = endotracheal tube diameter; PIF = peak inspiratory flow; T_I/T_{tot} = duty cycle; V_T = tidal volume.
* Expressed as percent of nominal dose.
† The difference between *in vivo* and *in vitro* values, at similar settings of controlled mechanical ventilaton, is the estimate of the amount of aerosol exhaled by the patient.

AM J RESPIR CRIT CARE MED 1999;159:63–68.

Clinical response to pMDI during CMV



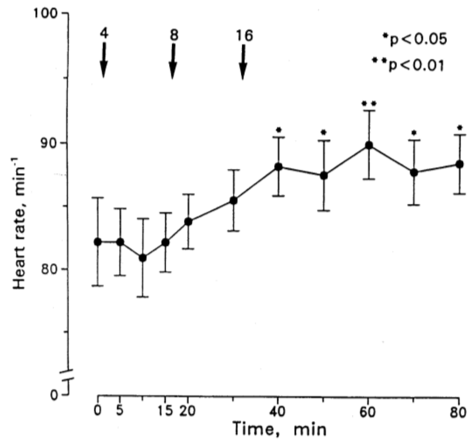
- Dose response in mechanically ventilated patients with COPD.
- MDI-spacer & albuterol
- Similar decline in airway resistance with 4, 8 and 16 puffs of albuterol.

Dhand R AJRCCM 154;388:1996

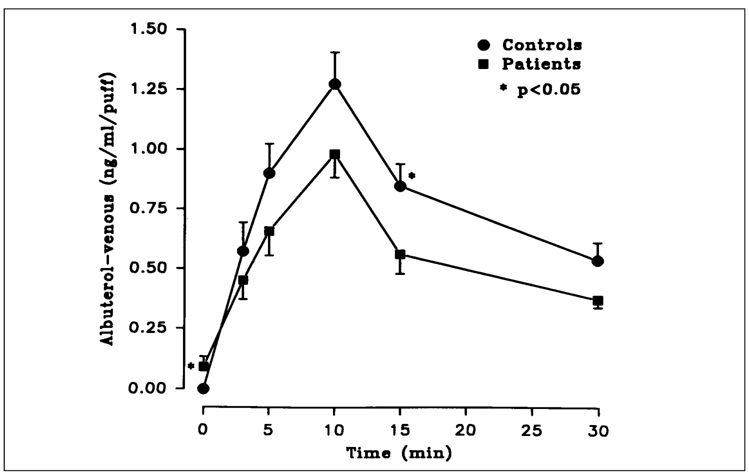
Toxicity

- Increase in heart rate after 28 puffs of MDI albuterol.
  AJRCCM 1996;154:388

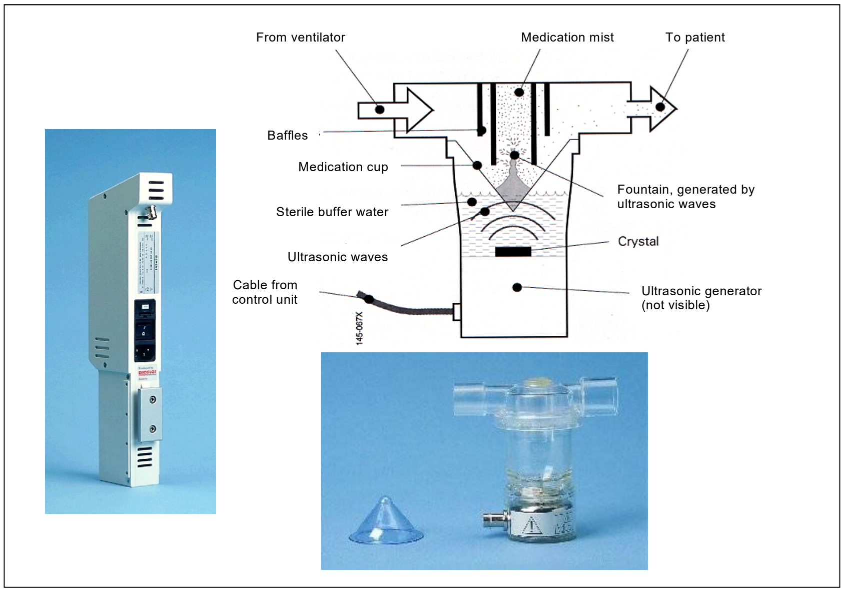
- Ventricular ectopy and SVT developed after 3-6 times normal nebulizer dose.
  Am Rev Resp Dis 1993;148



Comparison of Serum Albuterol Levels: Normal Controls and Intubated/Ventilated Subjects

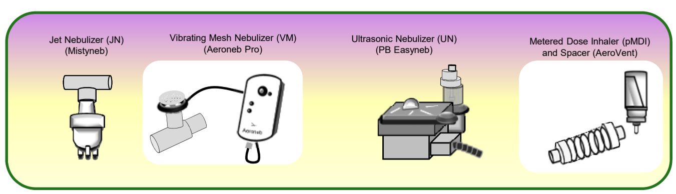


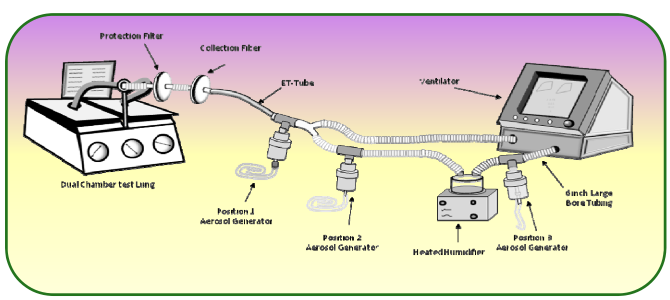
Duarte et al. 1996, AJRCCM



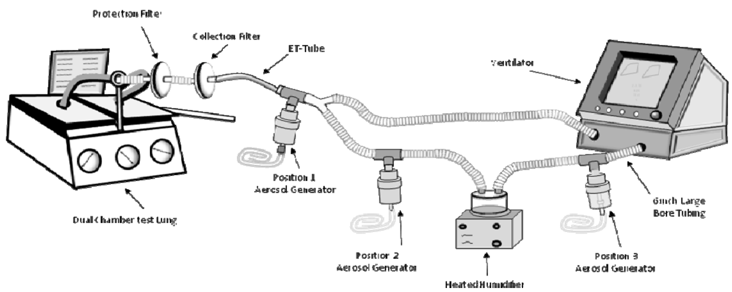
Maquet SUN 145 Ultrasonic Nebulizer with power control module.

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



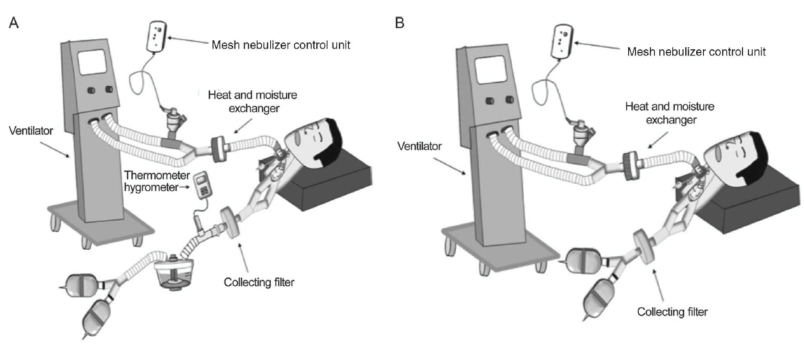


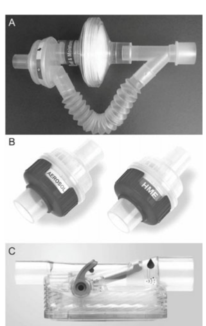
Ari et al. Respiratory Care 2010; 55 (7): 837-844.



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



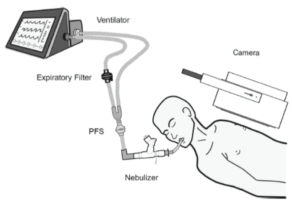


Exhaled Humidity	Dose Delivered (%)			
	Control	AirLife	CircuVent	Humid-Flo
With	10.8 ± 0.2	9.2 ± 0.7	9.8 ± 1.9	9.9 ± 1.1
Without	18.0 ± 0.7	12.0 ± 0.5	12.6 ± 0.8	15.3 ± 0.8

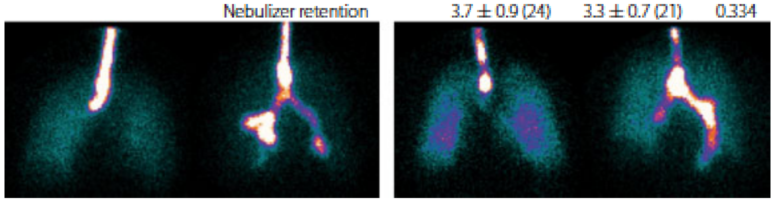
Results are mean ± SD.

Ari et al, Respir Care 2017

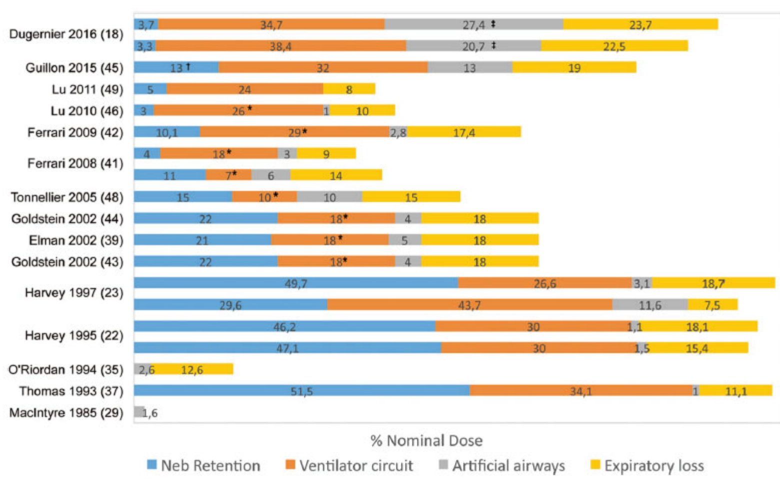
Aerosol Delivery During PSV and VCV

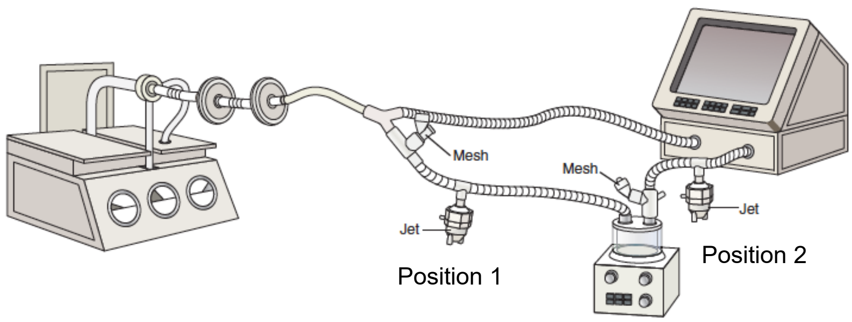


	PSV ($n = 8$)	VCV ($n = 9$)	p value
Pulmonary deposition (%)	*10.5 ± 3.0 (28)*	*15.1 ± 5.0 (33)*	*0.038*
Right lung	6.1 ± 1.9 (31)	10.6 ± 5.8 (55)	0.057
Penetration index	0.75 (0.30–0.94)	0.32 (0.16–0.77)	0.210
Left lung	4.1 (3.8–4.6)	4.5 (2.2–5.6)	0.885
Penetration index	0.67 (0.53–0.86)	0.74 (0.6–1.06)	0.211
Right/left lung ratio	1.39 (0.91–2.05)	3.33 (0.7–5.38)	0.336
Extrapulmonary deposition (%)	*89.5 ± 3.0*	*84.9 ± 5.0*	*0.038*
ETT and tracheal area	27.4 ± 6.6 (24)	20.7 ± 6.0 (29)	*0.043*
Expiratory filter	23.7 ± 5.3 (22)	22.5 ± 7.6 (34)	0.710
Ventilator circuit	34.7 ± 8.7 (25)	38.4 ± 12.3 (32)	0.486
Proximal pieces	32.0 ± 7.4 (23)	35.9 ± 12.5 (35)	0.451
Insp–expi tubing	2.7 ± 1.9 (70)	2.5 ± 1.7 (68)	0.833
Nebulizer retention	3.7 ± 0.9 (24)	3.3 ± 0.7 (21)	0.334



Dugernier Ann Critical Care 2016





	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.

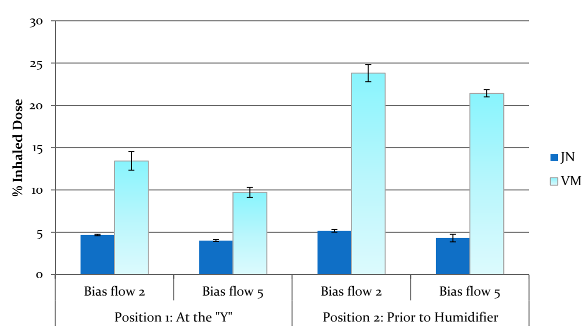
With Bias Flow

VM and JN more Efficient Placed Prior to Humidifier

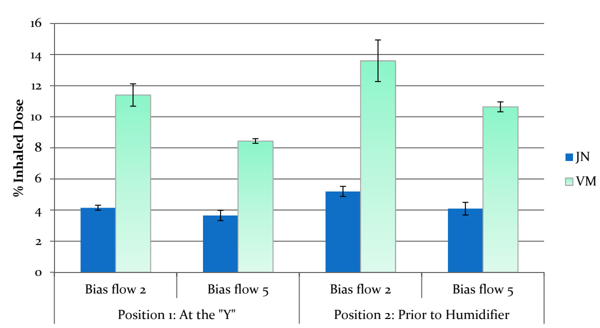
As Bias flow Increases deposition decreases

VM > JN

Adult



Peds



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

Is Nebulization with Inspiration Best?

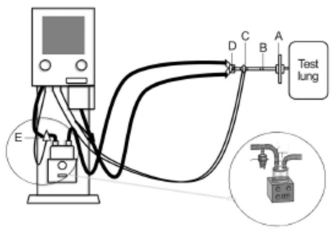
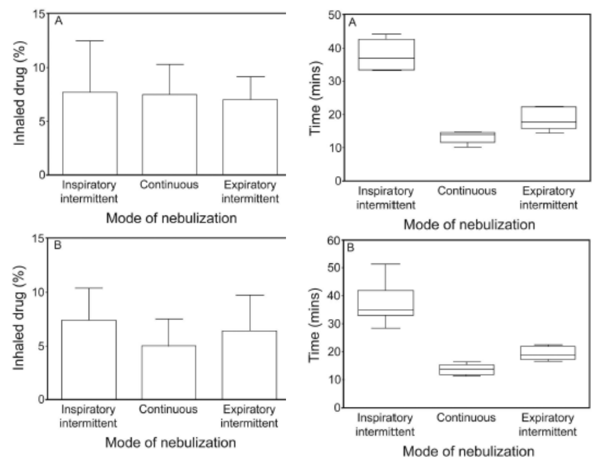


Fig. 1. Diagram of experimental apparatus. A jet nebulizer (E) powered by the ventilator nebulization function was placed in the ventilator outlet 15 cm from the heater, and a filter for aerosol collection (A) was placed distal to the endotracheal tube (B). Also shown are the flow sensor (C) and the Y-piece (D).



Wan et al, Respir Care 2014

Evaluation of aerosol delivery through high frequency oscillatory ventilation

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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.

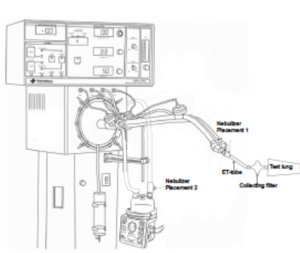
Ventilator settings

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

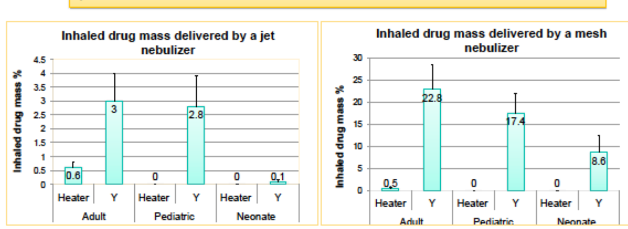
Conclusion:
Aerosol delivery with a vibrating mesh nebulizer placed between the ETT and the ventilator circuit was more efficient than a jet nebulizer during high frequency oscillatory ventilation with infant, pediatric and adult settings.

-There is no conflict of interest.

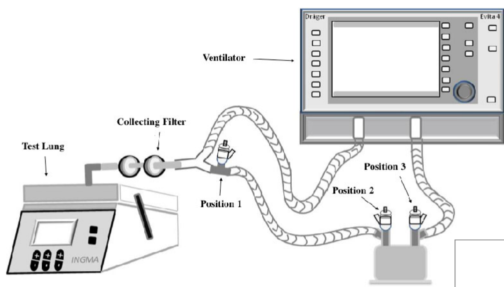
Methods:

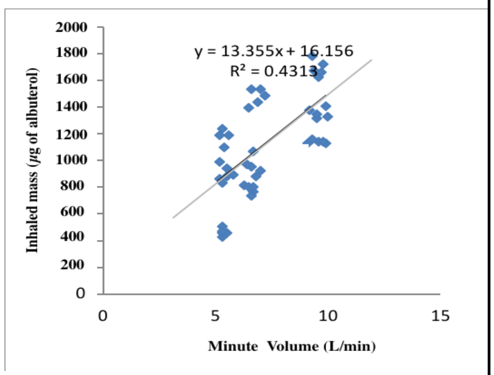


Results: Figures below show Inhaled drug mass ± SD (%) among breathing patterns and locations between two devices.



Aerosol Delivery with APRV





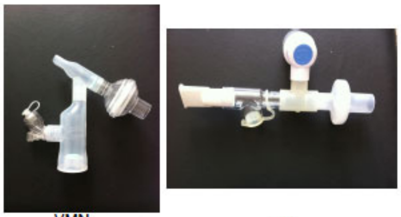
Hui-Qing Ge 2018

Aerosol Delivery with APRV

	μg of albuterol (mean ± SD) and percentage of nominal dose		
	Position 1 Insp limb at Y	Position 2 Humidifier outlet	Position 3 Humidifier inlet
PCV	796.9±13.9 (15.9%)	971.9 ± 69.4 (19.4%)	1490.6 ± 61.1 (29.8%)[a]
PCV_{BF6}	1046.88±27.1 (20.8%)[b]	1057.3 ± 52.9 (21.1%)	1182.3 ± 61.4 (23.6%)[ab]
APRV	475.0±28.4 (9.5%)	893.8± 40.4 (17.9%)	1153.1± 99.7 (23.1%)[ab]
APRVs	1153.1±13.1 [d] (23.1%)	1368.8±37.6 (27.4%)	1706.2±60.9 (34.1%)[ac]

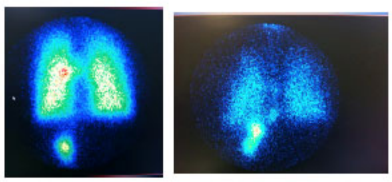
Hui-Qing Ge 2018

VMN with Adapter vs Jet Neb



VMN JN

Figure 1. Visual representation of the circuit



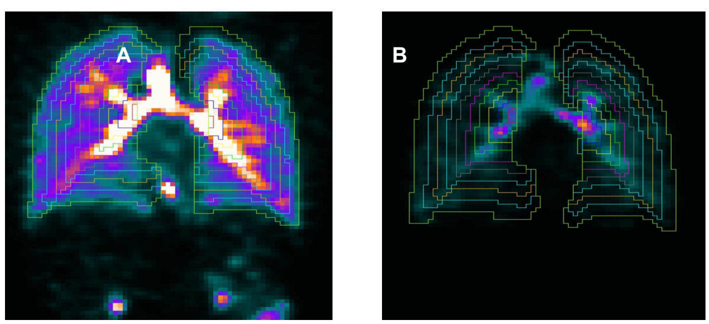
VMN JN

	Jet Neb	VMN/Ultra	p-value
Lung	4.5±1.35	22.8±9.83	0.004
Upper airways	1.7±0.51	3.3±2.08	NS
Stomach	0.9±0.38	3.7±2.18	0.010
Device	13.1±4.60	36.7±15.12	0.037
Nebulizer	75.0±4.46	10.4±9.93	0.004
Expiratory filter	41.4±14.18	18.2±23.22	NS

Alcofocado ATS2016

Mouthpiece Aerosol Delivery

6 Healthy Adults Vibrating Mesh with adapter vs Jet Neb

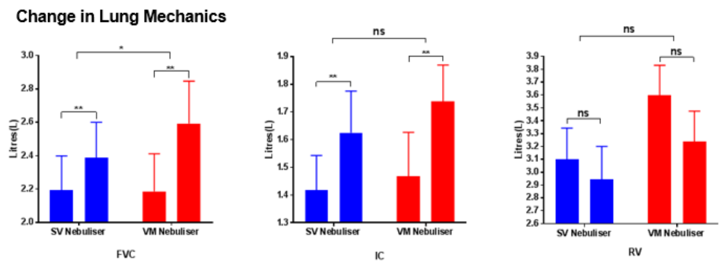


Vibrating Mesh	Jet neb	P value
34.1 ± 6	5.2 ± 1.1	<0.001

- Lung deposition was six times greater with Vibrating Mesh (Aerogen® Ultra) vs the Jet Neb

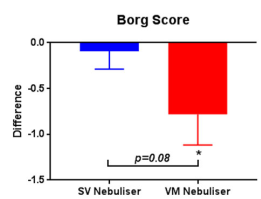
26 11. Dugernier *et al.*

COPD Clinical Outcome Data



Beaumont Hospital COPD Study (VM vs JN)

- VM (Aerogen Ultra) group achieved a significantly greater improvement in post-bronchodilator FVC compared to the Jet Neb group
- Only the VM group demonstrated significant reductions in post-bronchodilator BORG breathlessness score.

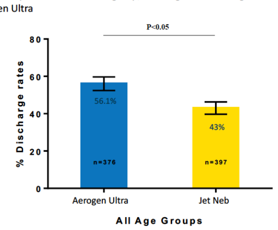


22. Cushen, V., et al.

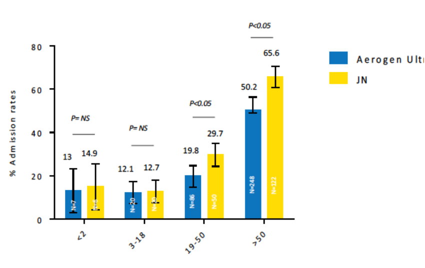
VMN with Adapter vs Jet Neb in the Emergency Department

Discharge rates

When compared to the Jet neb group, discharges are 30% higher with Aerogen Ultra

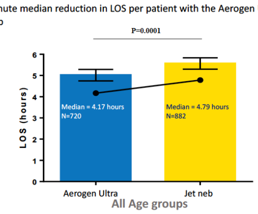


Admission Rates by Age with 95% Confidence Intervals



Length of Stay Reduced by 13%

37 minute median reduction in LOS per patient with the Aerogen Ultra v jet neb

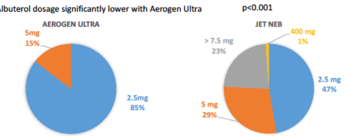


95% CI = 0.25 hours to 0.77 hours

Mann-Whitney test and CI: Significance at p=0.0001

Albuterol Dosage

Albuterol dosage significantly lower with Aerogen Ultra p<0.001



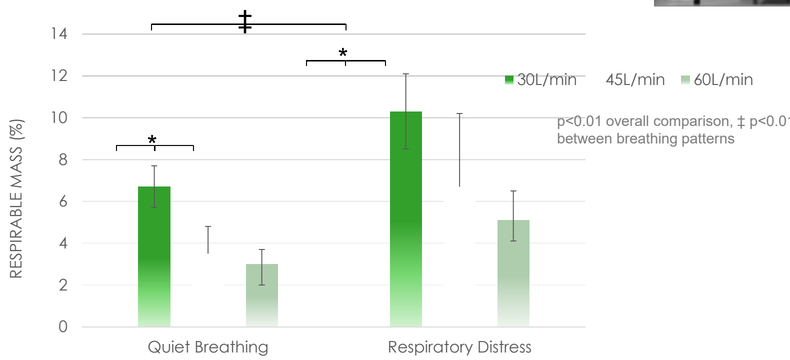
Albuterol concentration	Aerogen Ultra Albuterol Dosage	
	N	%
2.5 mg	548	85
5 mg	93	15
≥ 7.5 mg	0	0
400 mg	0	0

Albuterol concentration	Jet neb Albuterol Dosage	
	N	%
2.5 mg	416	47
5 mg	250	29
≥ 7.5 mg	203	23
400 mg	10	1

Dunne AARC 2016

Adult HFNC (In Vitro)

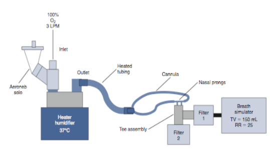
- In this bench model, aerosol delivery increased with respiratory distress compared to quiet breathing



- VM deposited significantly more drug in the lungs at the lower flow rate of 30 l/min than 45 l/min and 60 l/min.
- Adult model of respiratory distress (insp flow 55 L/min) compared to quiet breathing (15 l/min)
- VM demonstrated more aerosol particles with diameters of 0.4–4.4 µm, no added gas flow and a shorter nebulization duration compare to JN

17. Réminiac *et al. J Aerosol Med Pulm Drug Deliv* 2016

29



Resting Respiratory Pattern

	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	Inhaled Mass (n=5)	% Inhaled Dose (n=5)	P value
Gas/ Flow	10 L/min	10 L/min	30 L/min	30 L/min	50 L/min	50 L/min	
Oxygen 100%	.652±.16	13.2±3.6	1.644±.24	32.8±5.0	1.263±.08	25.4± 1.8	<.01*
Heliox (80/20)	.873±.15	17.4±3.1	1.757±.24	35.2± 4.7	1.501±.20	29.8±4.1	<.01*

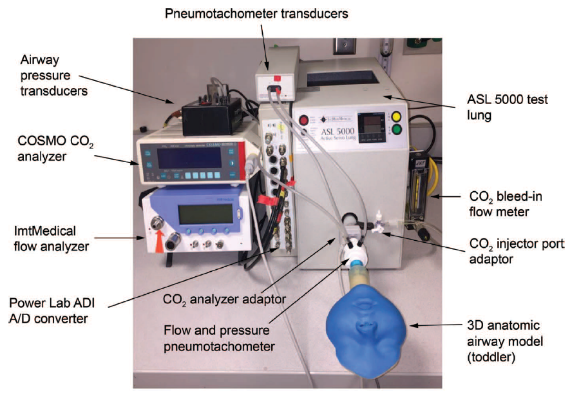
Distressed Respiratory Pattern

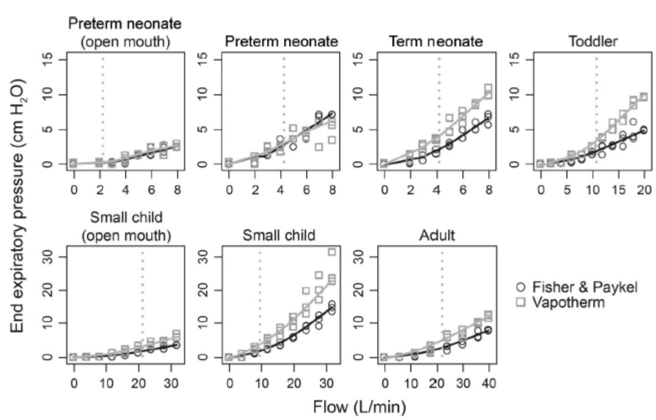
	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	Inhaled Mass (mg) (n=3)	% Inhaled Dose (n=3)	P value
Gas/ Flow	10 L/min	10 L/min	30 L/min	30 L/min	50 L/min	50 L/min	
Oxygen 100%	.667±.032	26.7±1.29	.289±.029	11.6±1.17	.088±.004	3.5±0.17	<.01*
Heliox (80/20)	.684±.059	27.4±2.37	.356±.022	14.2±0.89	.147±.43	5.88±1.73	<.01*

Dailey, Fink 2017

Effect of High-Flow Nasal Cannula on Expiratory Pressure and Ventilation in Infant, Pediatric, and Adult Models

Katie R Nielsen MD MPH, Laura E Ellington MD, Alan J Gray, Larissa I Stanberry PhD, Lincoln S Smith MD, and Robert M DiBlasi RRT-NPS FAARC



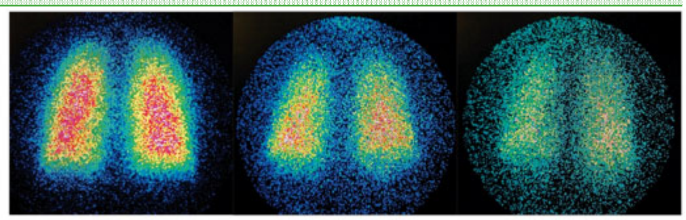


Nielson, DiBlasi
Resp Care 2017

HFNC Adult Imaging

23 healthy adults received aerosol therapy with vibrating mesh (VM) during HFNC (normal tidal breathing)

	10L/min	30L/min	50L/min
Heated	11.8 ± 4.9	3.76 ± 1.36*	2.23 ± 0.81*

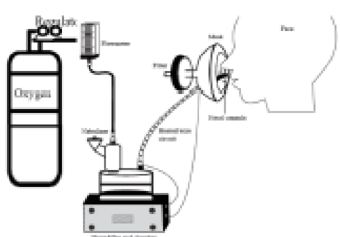


*p<0.05 compared to 10L/min o
Alcoforado et al. ISAM poster presentation 2016

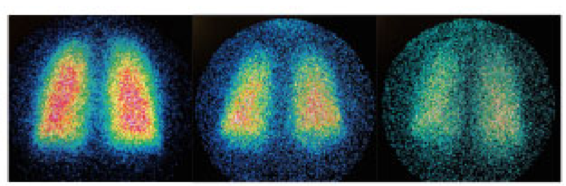
- Inverse relationship of lung deposition to flow rates

33 Alcoforado et al. ATS 2016

HFNC at 10, 30 and 50 L/min



	10L/min (n=08)	30L/min (n=07)	50L/min (n=08)	p-value
Lung (%)	11.81±4.90	3.76±1.36*	2.23±0.81**	0.000#
Upper airway(%)	36.46±10.49	42.46±14.43	46.72±8.58	0.213
Stomach(%)	0.25±0.10	0.69±0.75	0.23±0.32	0.118
Nebulizer(%)	10.29± 5.75	6.89± 4.37	7.63±5.63	0.437
Nasal Cannula(%)	6.51±2.46	9.76±2.47***	13.37±3.07**	0.000
Tubing(%)	16.93±4.78	19.08±8.98	16.92 ± 5.64	0.749
Chamber(%)	9.25 ± 4.33	13.08 ± 8.28	7.96 ± 1.74	0.277#
Filter (%)	8.69 ±3.09	4.23 ± 2.41*	4.90 ± 2.77**	0.011



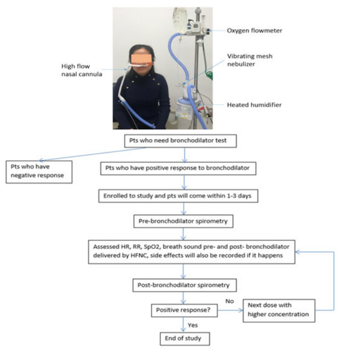
10L/min 30L/min 50L/min

Alcoforado 2016

Clinical Study of Dose for Bronchodilator with HFNC

Purpose

To determine whether a cumulative bronchodilator dose during HFNC achieve similar spirometry response as pre and post bronchodilator test in PFT Lab.



Jie Li[1], MS, RRT-ACCS-NPS; ERS 2018

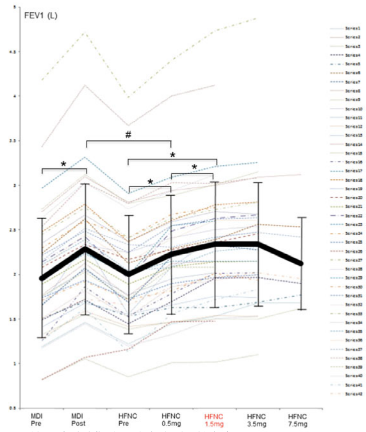
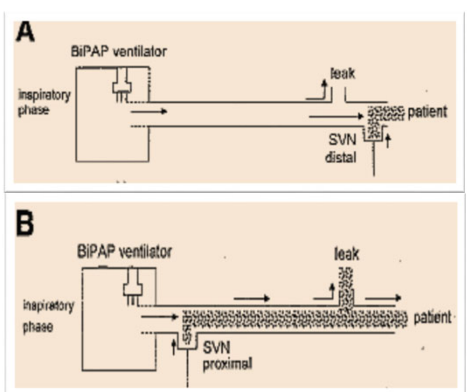


Fig 3. FEV1 Pre/ Post-bonchodilator via MDI+VHC and HFNC at each cumulative dose. *P< 0.001

- The Aerosolized bronchodilator via HFNC at 50 L/min produced a similar response as 4 Puffs MDI+VHC in these stable mild to moderate COPD ad asthma patients
- Despite reported low inhaled aerosol pulmonary efficiency with HFNC at 50 L/min, the standard label dosage of albuterol (2.5mg, US) would be sufficient starting dose while delivering albuterol via HFNC in this population

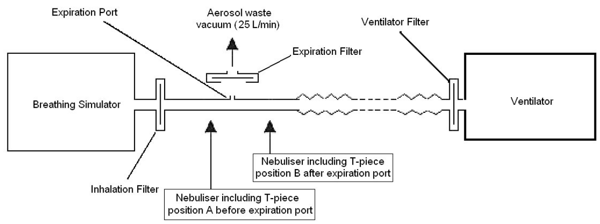
Aerosol Delivery Non Invasive Ventilation – Place neb between leak and patient



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

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

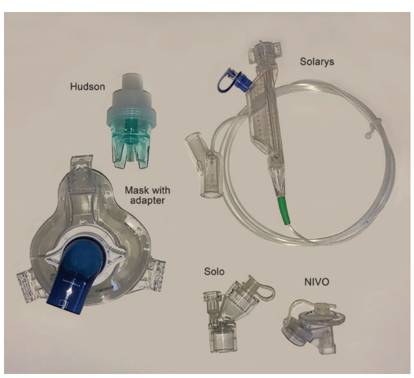
Position Neb Between Leak and Mask for best delivery

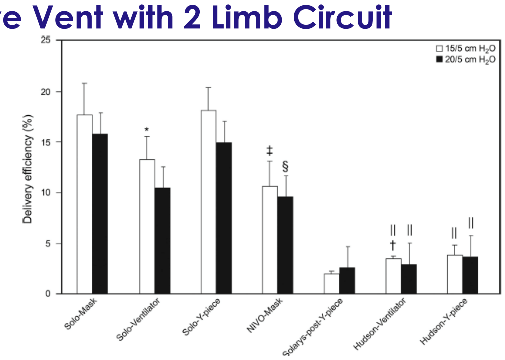


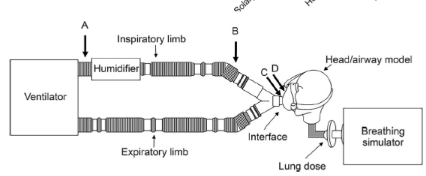
Nebulizer	Position closer to filter (A)		Position farther from filter (B)	
	Inhalation Filter (µg)	Nebulizer (µg)	Inhalation Filter (µg)	Nebulizer (µg)
Aeroneb	2573 ± 151	891 ±163	936 ± 273	1001 ± 263
Sidestream	1207 ± 161	2261 ± 795	341 ± 70	2420 ± 154

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

Pediatric Non Invasive Vent with 2 Limb Circuit





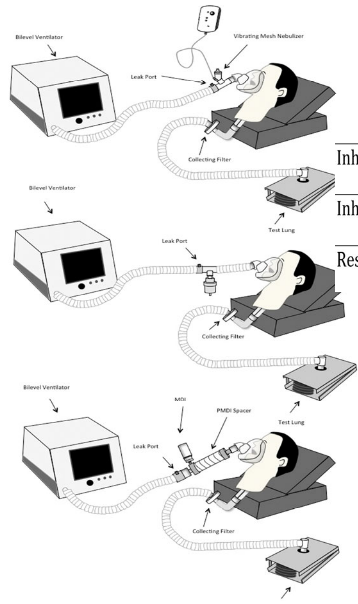


Velasco, Berlinski Resp Care 2017

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

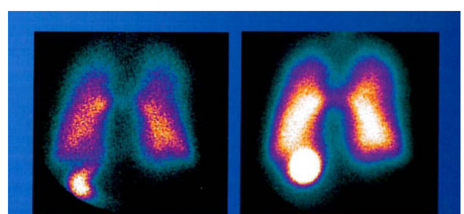
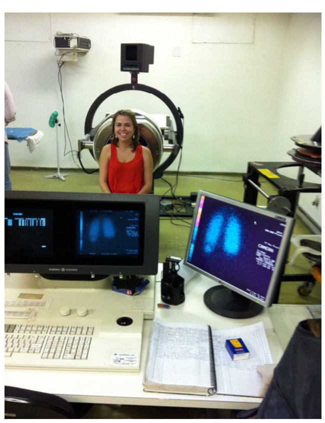


Figure 2: Typical distribution of aerosol deposited in lungs with JET(left) and MESH (right) with 3 mL dose volume.

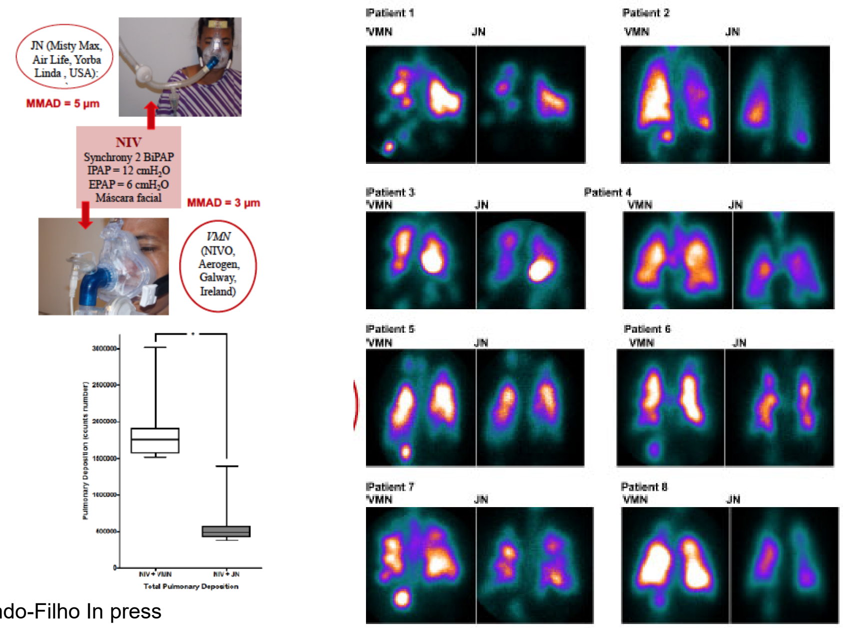


Lung deposition (corrected for absorption) with the Mesh was > 3 fold greater than JN, independent of dose volume used with the MESH.

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).

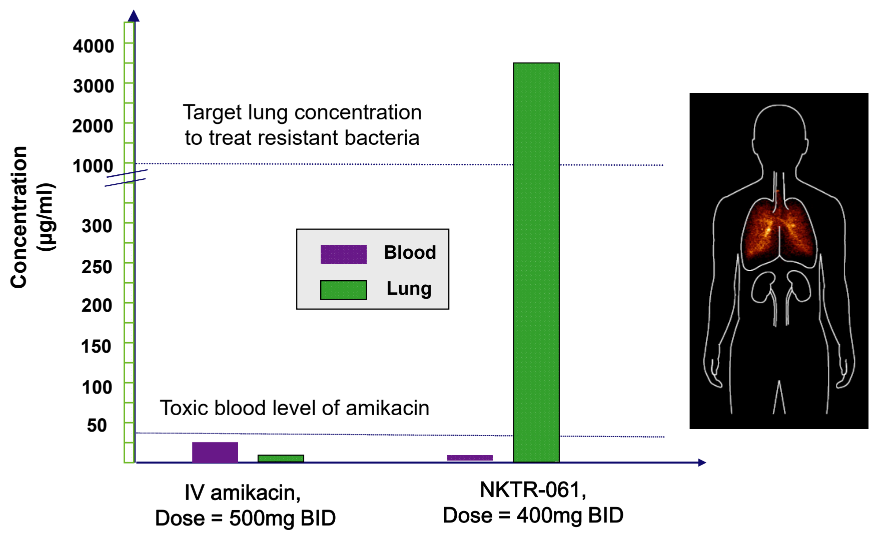
NIV – VMN vs JN – COPD Patients



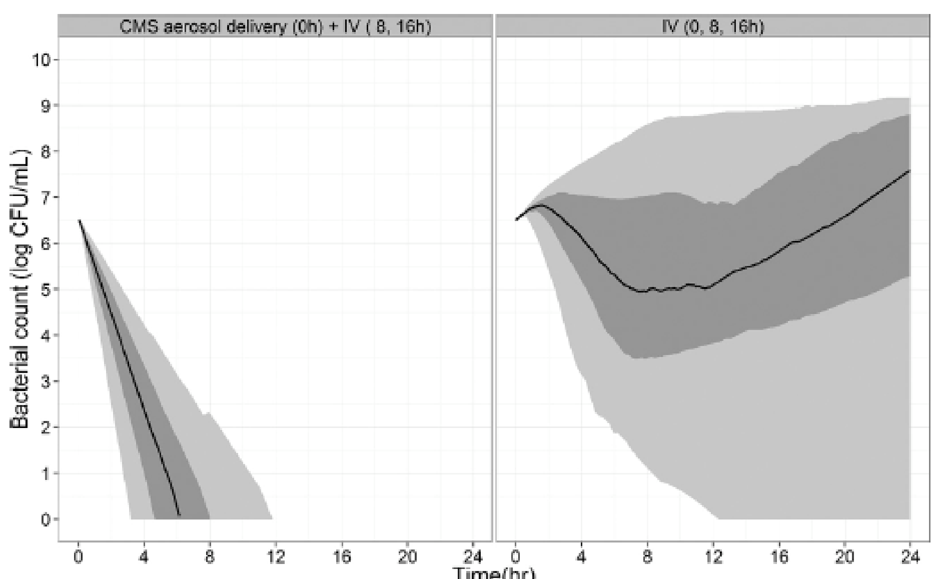
Galindo-Filho In press

Pulmonary Drug Delivery System – Amikacin Inhale®

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



Colistin by Aerosol + IV vs IV Alone



Boisson ACC 2014

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 and placement makes a difference in drug delivery to the lung
- Selection of Drug Dose for Specific Device can Achieve Effective Lung Doses

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