Update in aerosolized drug delivery through mechanical ventilation

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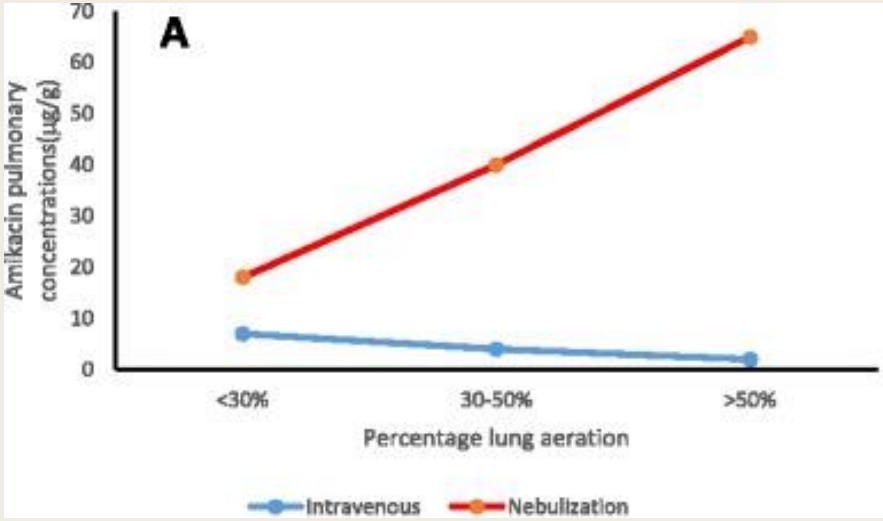
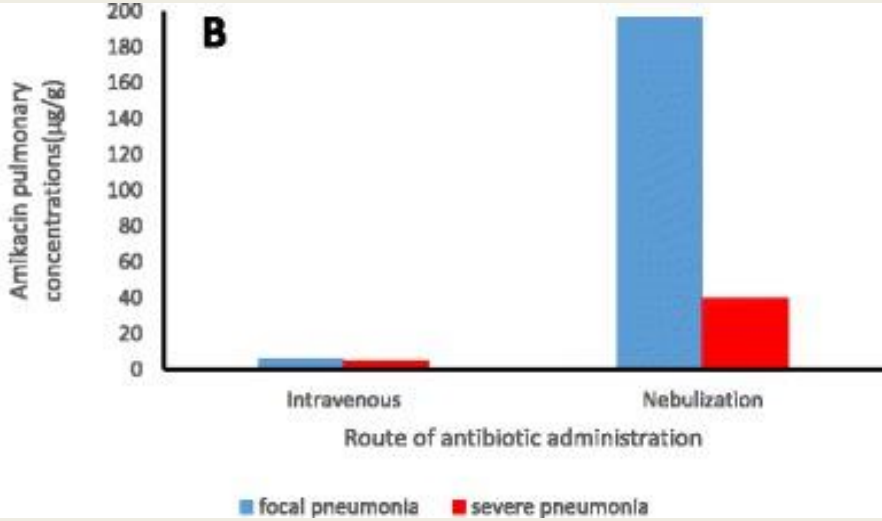
Why aerosolized medication?

- A very large surface area of ~75 m^2 for drug absorption
- Good vascularization
- Immense capacity for solute exchange
- The very thin alveolar epithelium (~0.1 – 0.5 μm thick) permits rapid drug absorption.
- Low systemic side effects





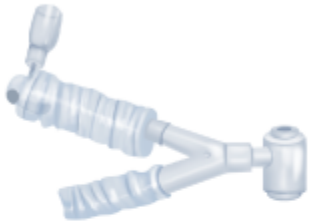
Elman M, Anesthesiology. 2002;97:199–206

Influencing factors on drug delusion during mechanical venation

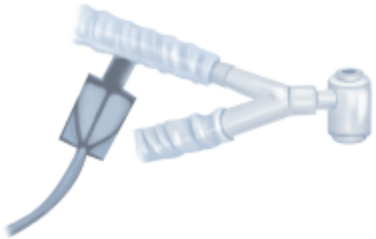
Ventilator-related
- Ventilation mode
- Tidal volume
- Respiratory rate
- Duty cycle
- Inspiratory waveform
- Breath-triggering mechanism

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

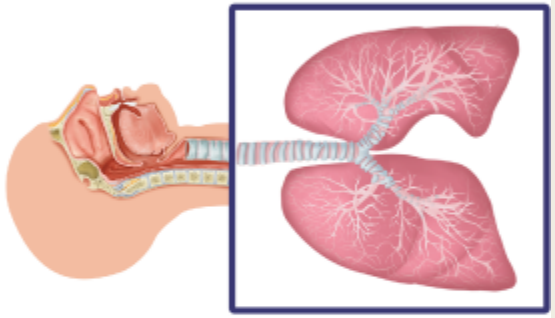
Device-related—MDI
- Type of spacer or adapter
- Position of spacer in circuit
- Timing of MDI actuation
- Type of MDI



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



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



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

Dhand R. *J Aerosol Med Pulm Drug Deliv 2015*

Ventilator-related factors

Ventilator-Related

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

Enhancing factors

- CPAP > CMV

  Dhand AJCCM 1998

- Greater V_T than dead space
- With > without PEEP

  Mouliudi ICM 2000

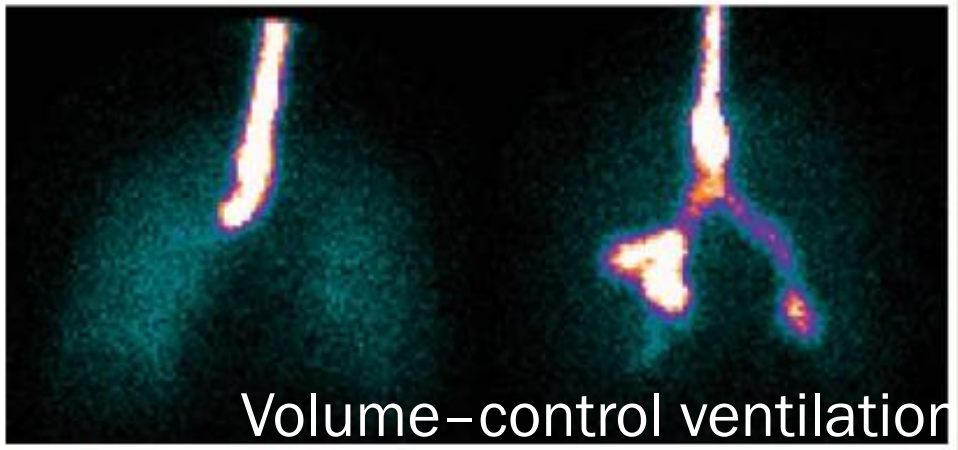
Ventilator-related factors

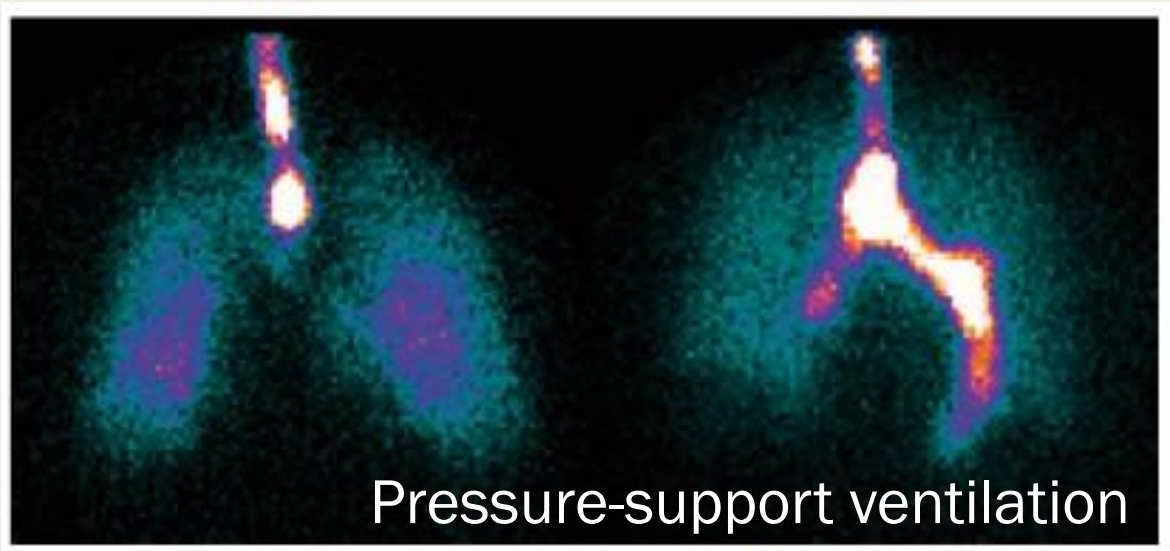
Dugernier, J., et al. (2016). *Ann Intensive Care* **6**: 73.

- Compare lung deposition of a radiolabeled (^{99m}TC) aerosol generated with a VMN with VCV vs. PSV modes

	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

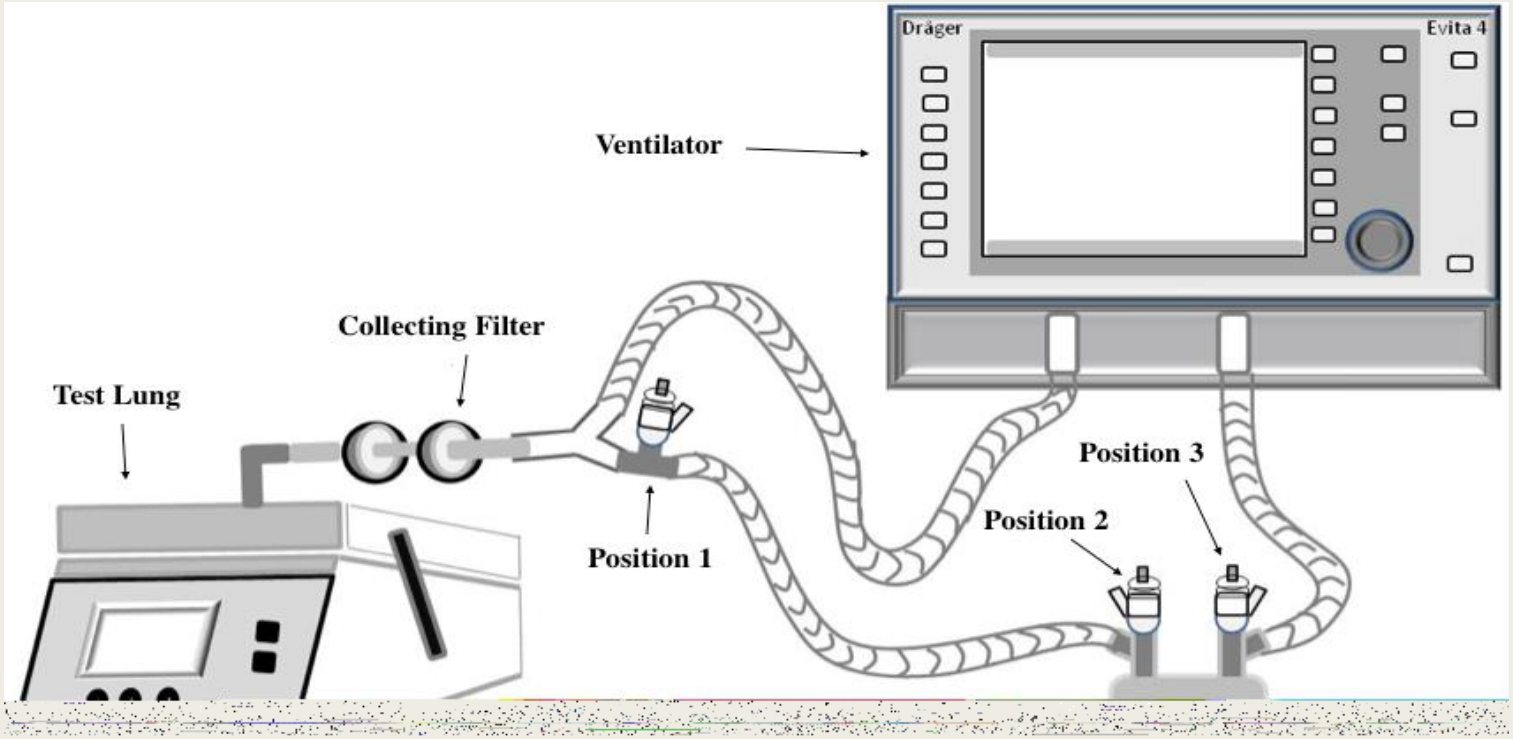
Ventilator-related factors





Conclusions: VCV was associated with higher lung deposition of nebulized particles as compared to PSV. The clinical benefit of this effect warrants further studies.

Ventilator-related factors -APRV mode



Ge HG, *JAMPPD* 2018

Ventilator-related factors -APRV mode

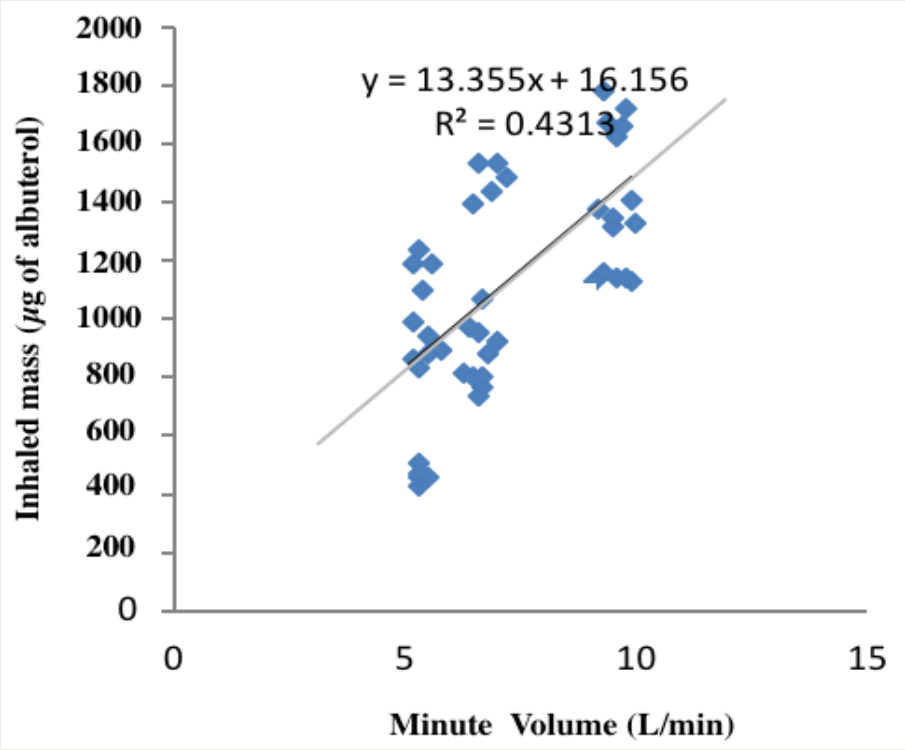
	Position 1 Insp limb at Y	Position 2 Humidifier outlet	Position 3 Humidifier inlet
PCV	796.9±13.9 (15.9%)	971.9 ± 69.4 (19.4%)	1490.6 ± 61.1 (29.8%)
PCV_{BF6}	1046.88±27.1 (20.8%)	1057.3 ± 52.9 (21.1%)	1182.3 ± 61.4 (23.6%)
APRV	475.0±28.4 (9.5%)	893.8± 40.4 (17.9%)	1153.1± 99.7 (23.1%)
APRVs	1153.1±13.1 (23.1%)	1368.8±37.6 (27.4%)	1706.2±60.9 (34.1%)

Ge HG, *JAMPPD* 2018

Ventilator-related factors -APRV mode

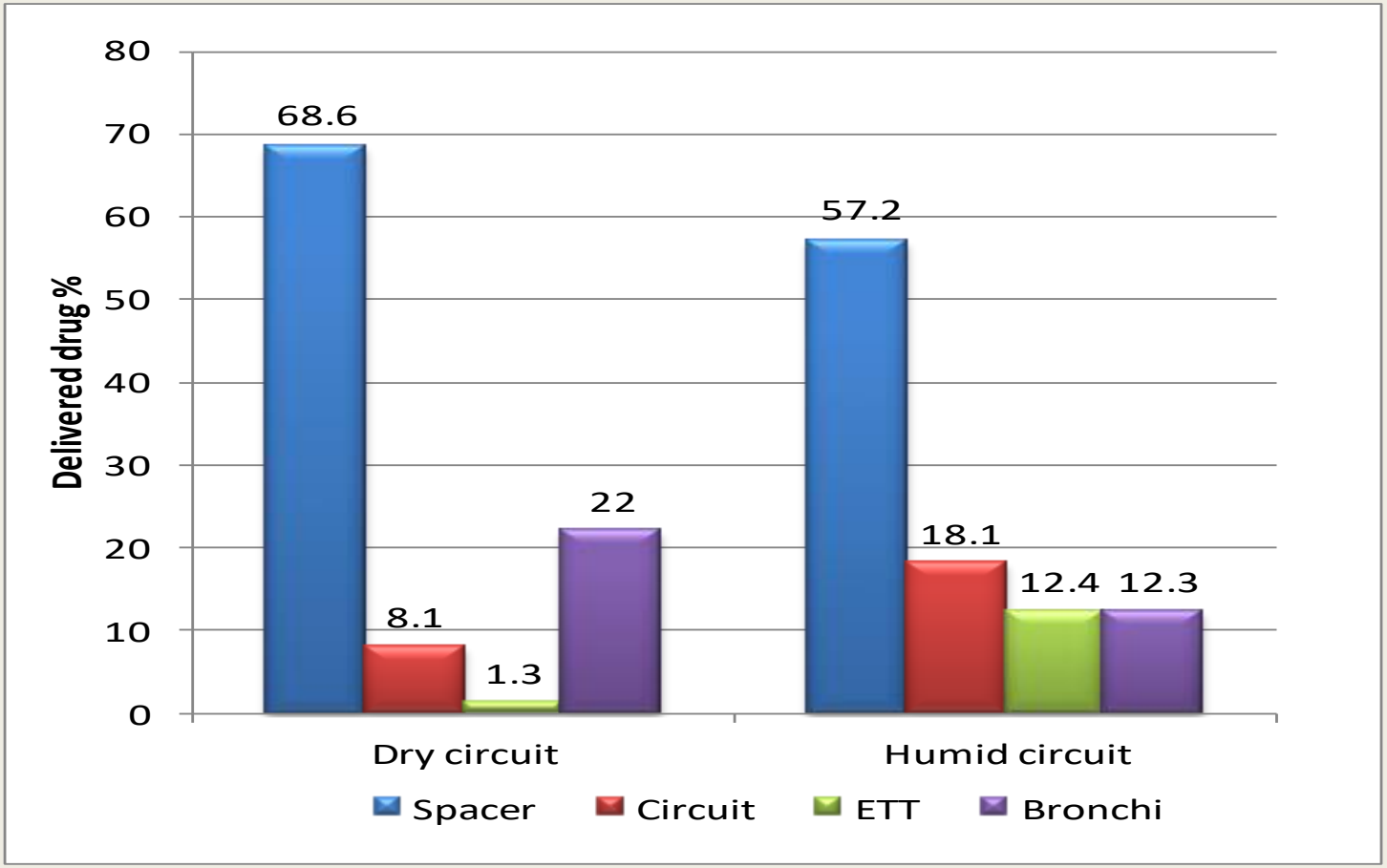
Conclusions:

Spontaneous breathing increased the albuterol delivery during APRV, compared with APRV alone and PCV modes. Placing the nebulizer proximal to the ventilator was more efficient for all modes tested.



Circuit-related factors

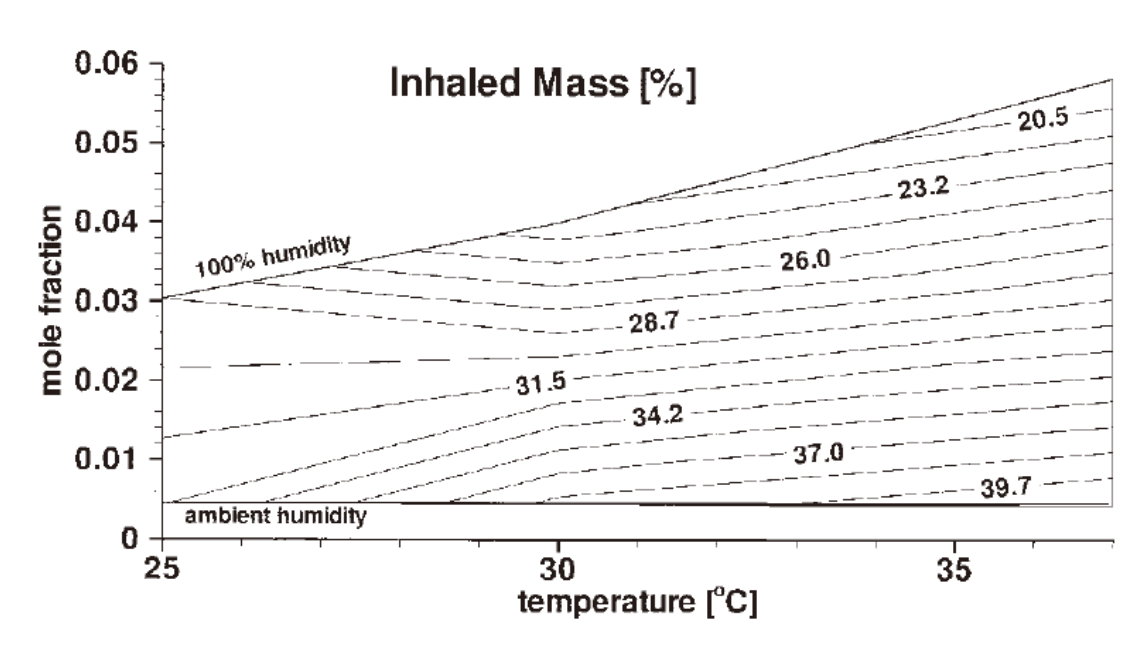
- Heated vs non-heated circuit



Fink, AJRCCM 1999

Circuit-related factors

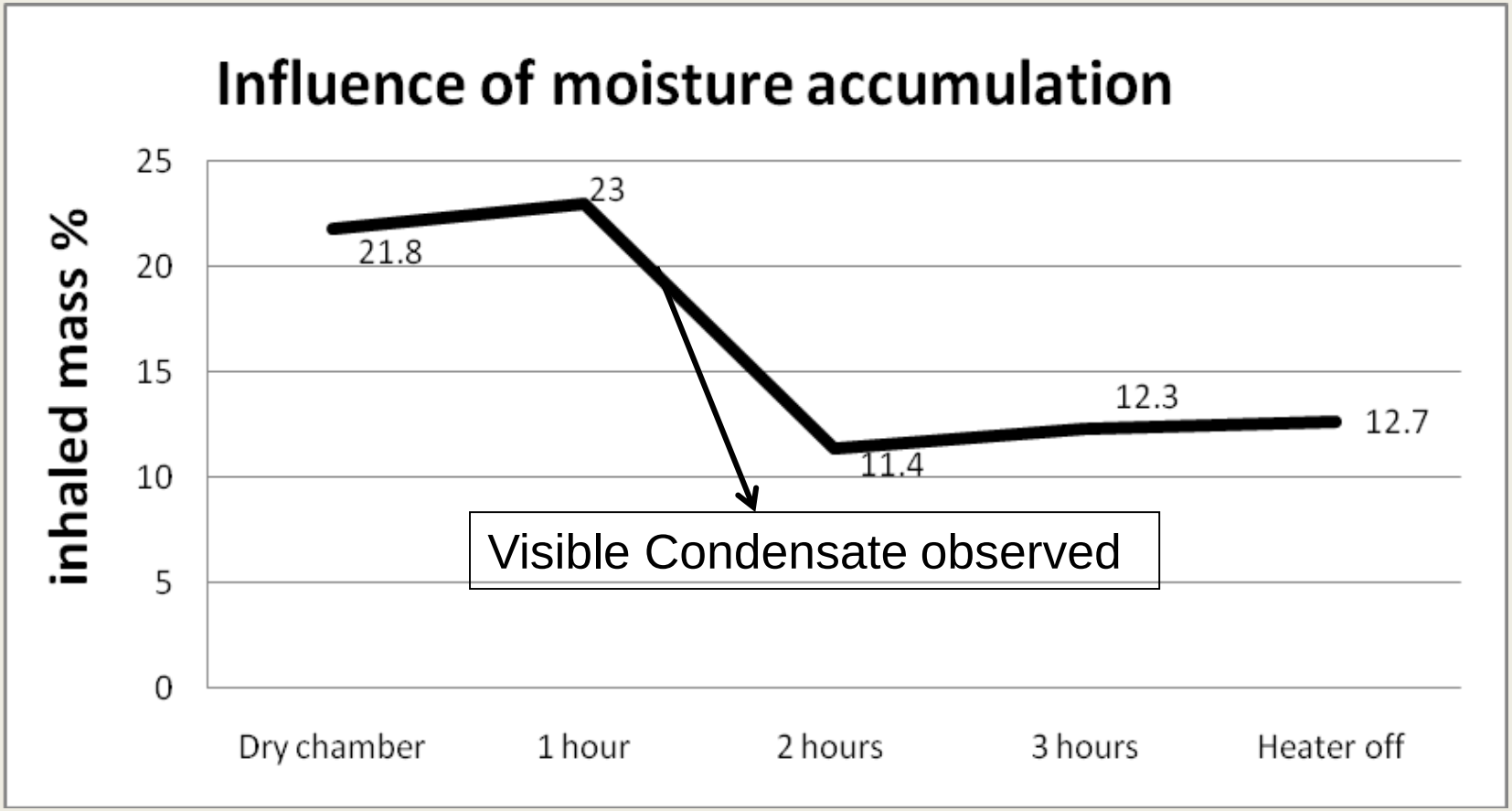
- The mole fraction of water vapor in the ventilation air (and not the temperature) is the major factor behind the sharp drop in the amount of drug delivered to the lung.
- The presence of water vapor does not affect performance because of hygroscopic growth. Instead, it influences the initial atomization process and the early stages of aerosol generation.



Lange AJRCCM 2000

Circuit-related factors

- Do not turn off the heater to delivery aerosol



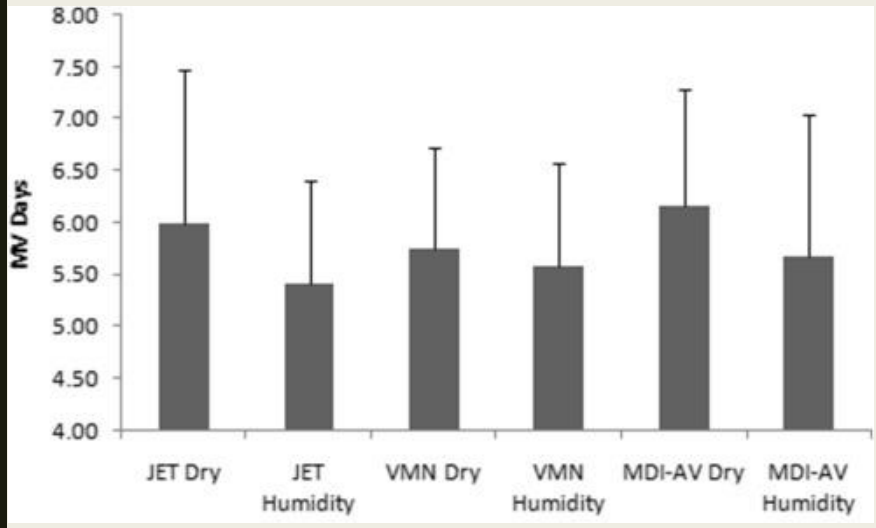
Lin HL, Fink JB Resp Care 2010

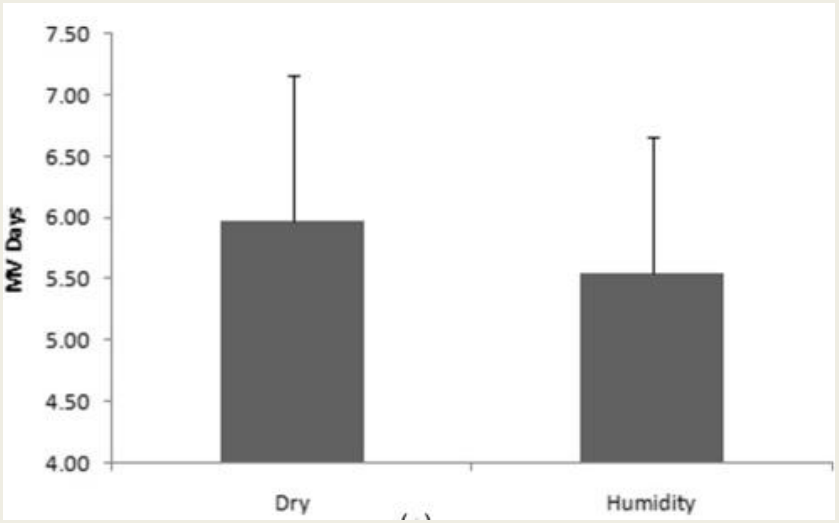
Circuit-related factors

- Aerosol-delivery with or without humidification did not have any significant effect on lung deposition, MV days, and ICU days

Salbutamol urine levels, as percent [mean (SD)] of dose, achieved after aerosol administration during mechanical ventilation with (Humidity) and without (Dry) heated humidification.

Condition results	Dry delivery	Humid delivery
URSAL0.5%	1.5 (1.0)	1.7 (1.2)
URSAL24%	8.0 (4.8)	8.4 (4.1)

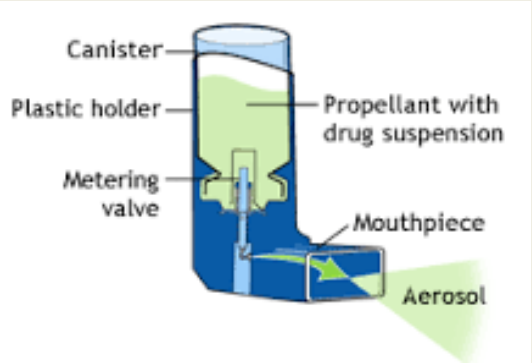


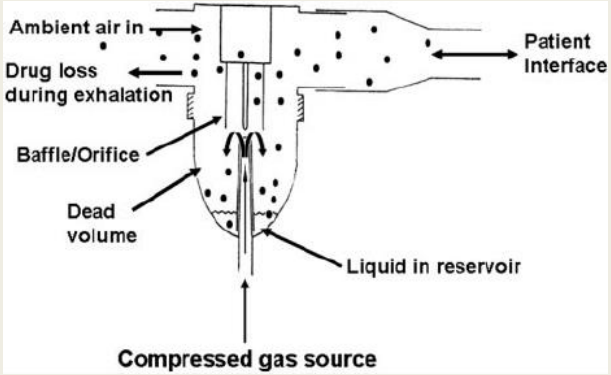


Moustafa Pulm Pharmacol Ther. 2017 Aug;45:40-46; Heart Lung. 2017 Nov - Dec;46(6):464-467

Device-related factors

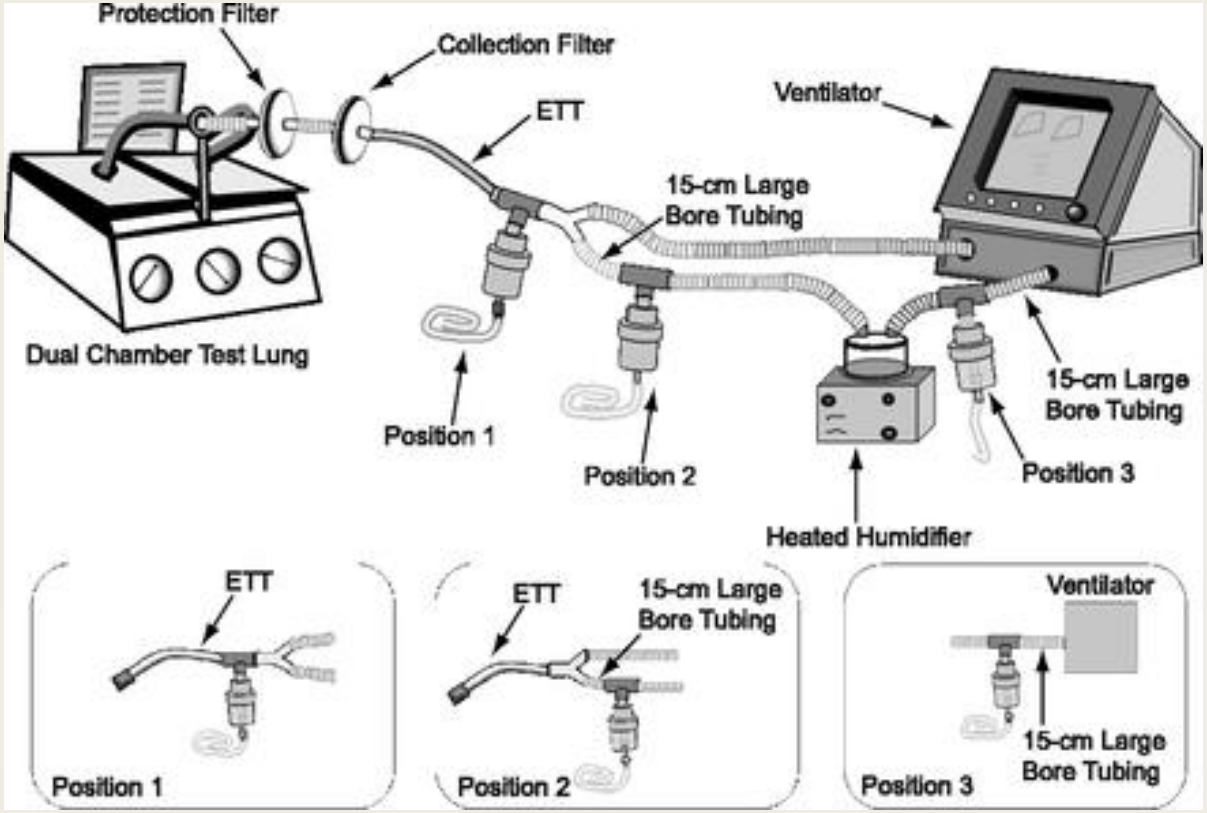
- Aerosol generators:
  - *Pressurized metered dose inhaler: 10-15%*
  - *Small volume nebulizer: 5~10%*
  - *Vibrating mesh nebulizer: 30-40%*
  - *Ultrasonic nebulizer: 10~25%*





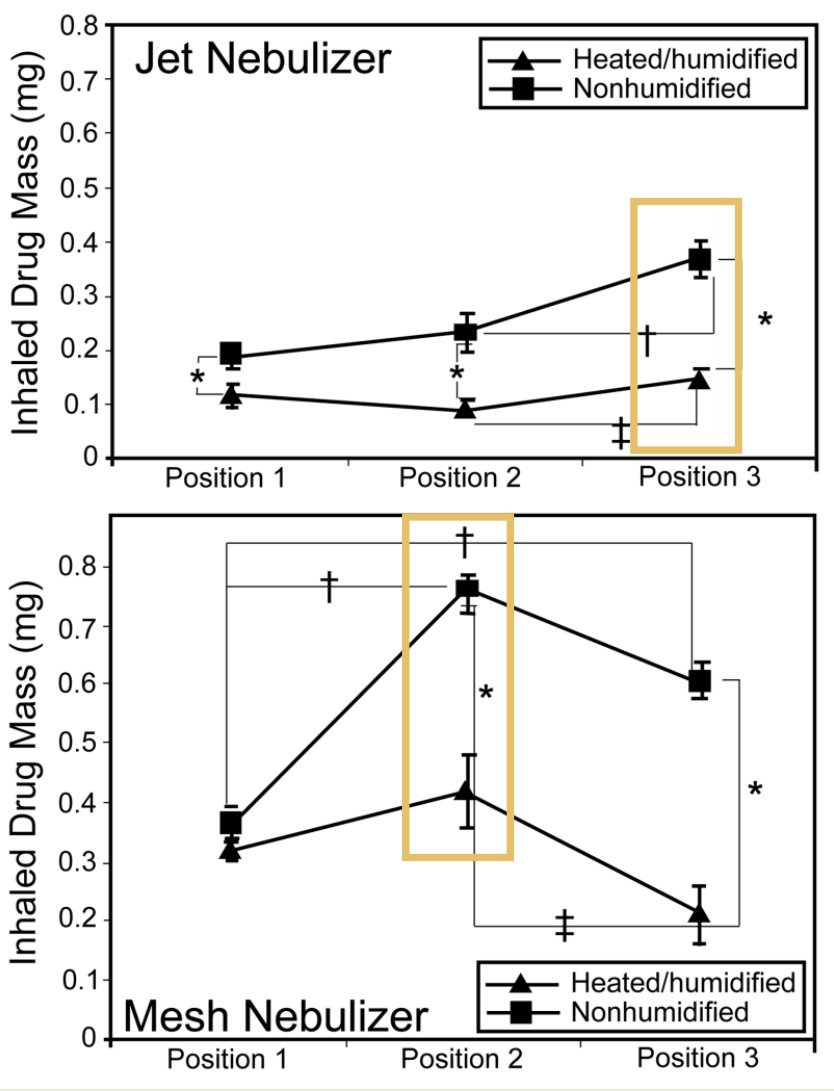
Device-related factors

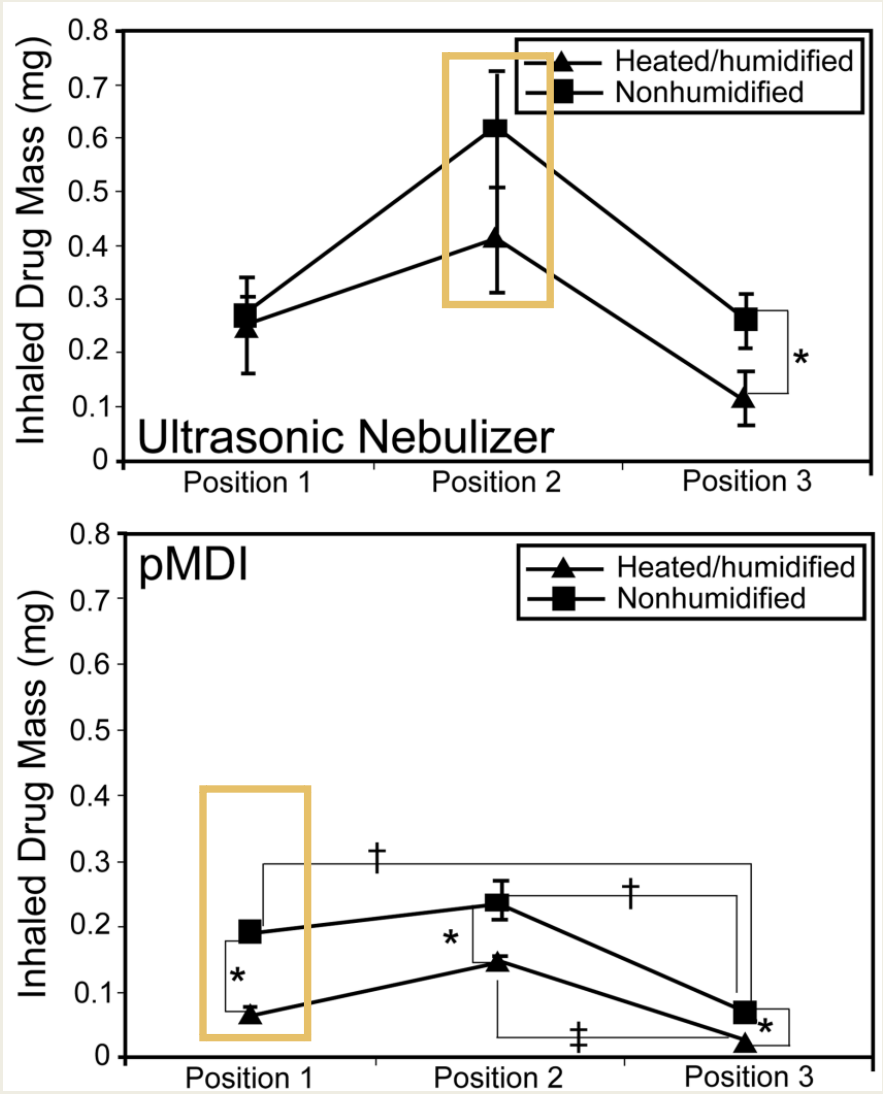
- Ari et al
  - *Compared jet nebulizer, vibrating mesh nebulizer, and ultrasonic nebulizer*



Ari Respir Care. 2010 Jul;55(7):837-44.

Device-related factors

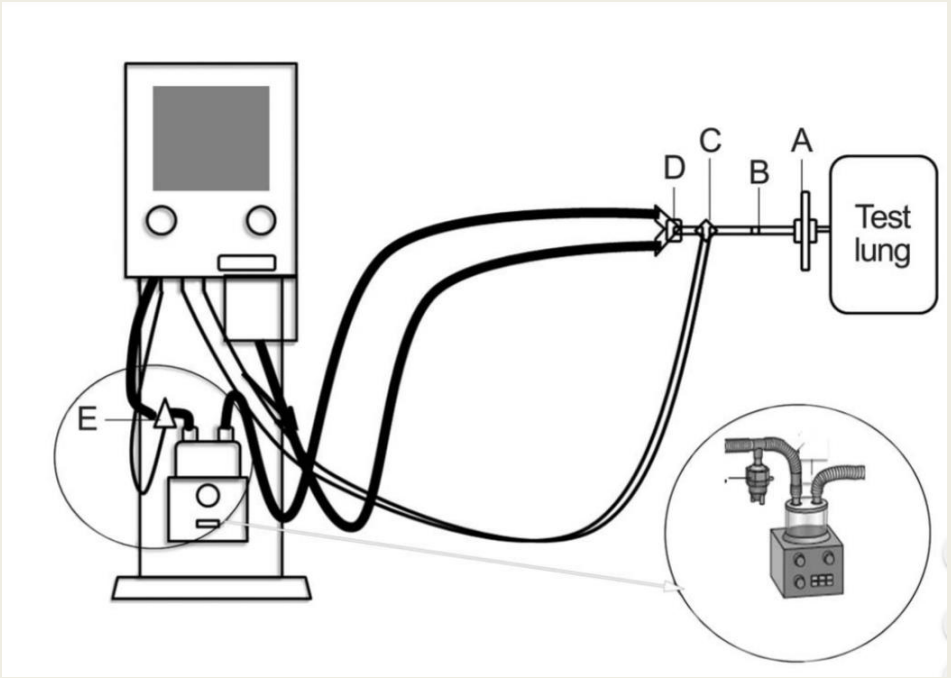




Ari Respir Care. 2010 Jul;55(7):837-44.

Device-related factor

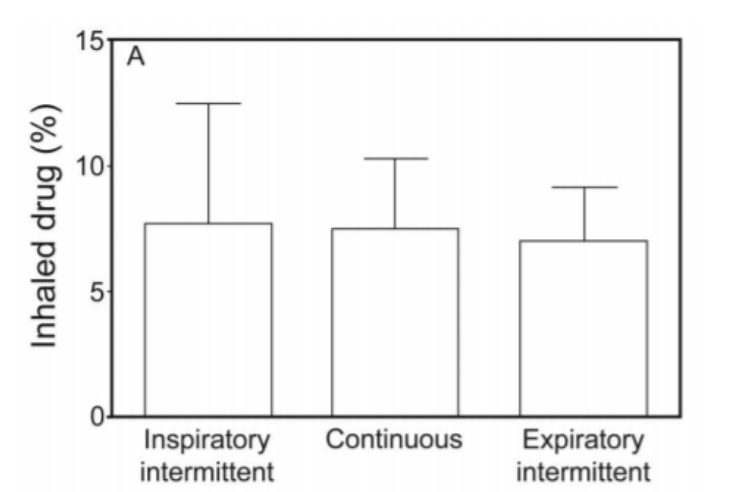
- Aerosol delivery by different nebulization modes in pediatric and adult mechanical ventilators.
- Three pneumatic nebulization modes by the Galileo Gold ventilator
  - inspiratory intermittent
  - continuous
  - expiratory intermittent

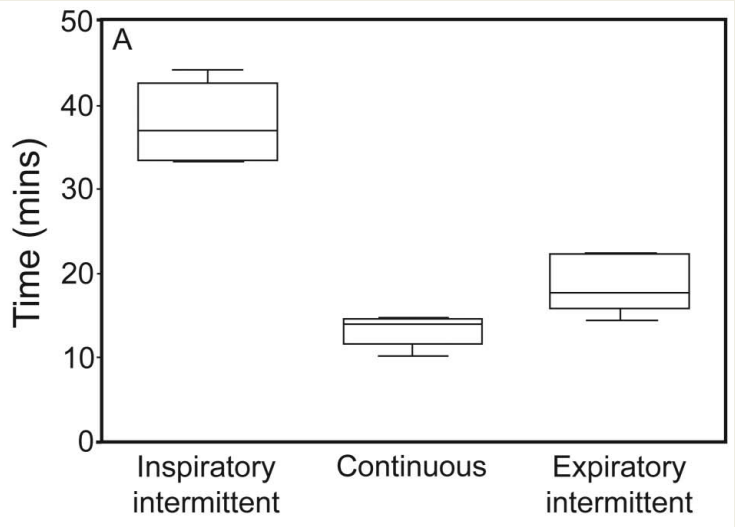


Wan Respir Care. 2014 Oct;

Device-related factors

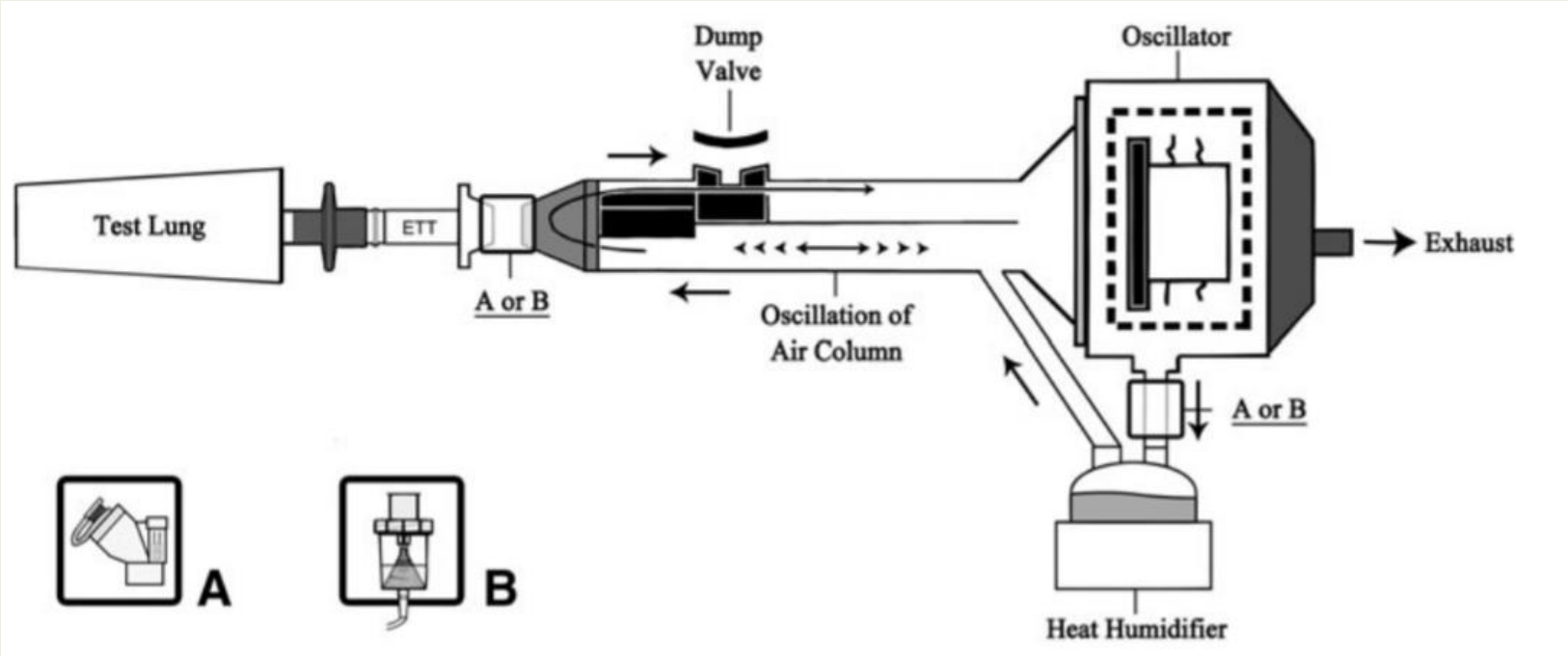
- The inhaled drug, as a percentage of total dose in both lung models, was 5.1-7.5%, without statistical significance among the 3 modes.
- Median nebulization times for IIM, CM, and EIM were 38.9, 14.3, and 17.7 min
- Use of expiratory intermittent mode and continuous nebulization should be considered to reduce treatment time.





Aerosol delivery during HFOV

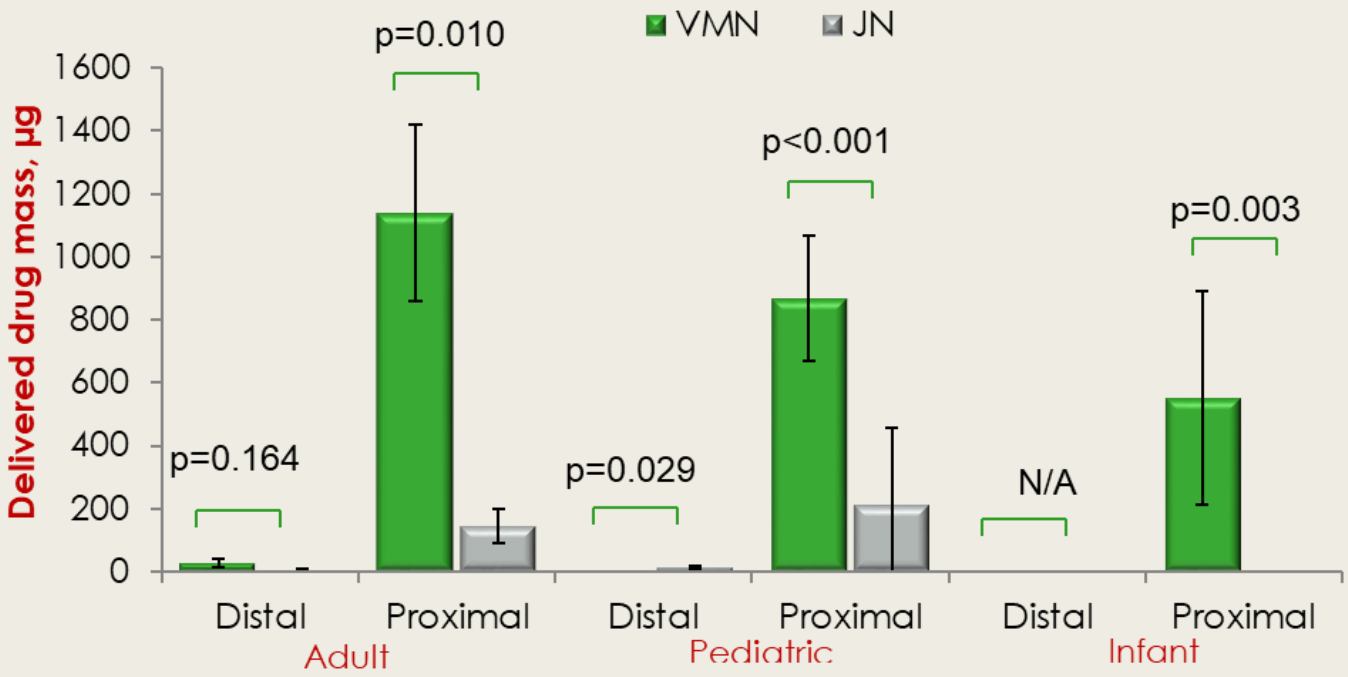
- Sensormedics 3100A/B ventilators were used to deliver infant, pediatric, and adult HFOV.
- placed 1) between the ventilator circuit and the endotracheal tube (ETT) (proximal position); and 2) at the inlet of the heated humidifier (distal position)



Fang J Aerosol Med Pulm Drug Deliv. 2016

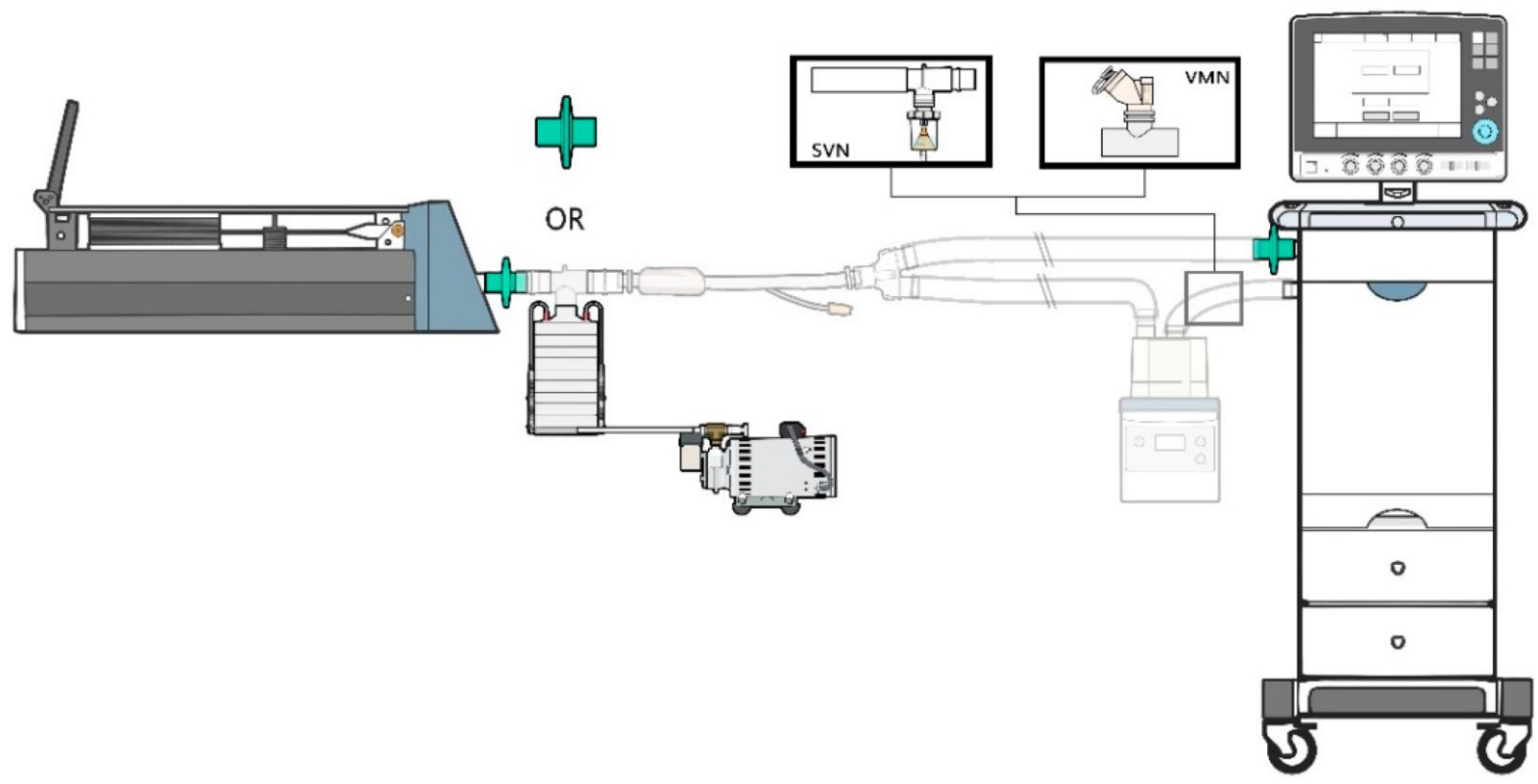
Aerosol delivery during HFOV

- When placed proximal to the patient, drug delivery **was significantly greater** from vibrating mesh *vs* the JN in pediatric and infant lung models.
- Any nebulizer placed distal provides poor aerosol delivery.



Aerolized antibiotic through mechanical ventilation

Size Distribution of Colistin Delivery by Different Type Nebulizers and Concentrations During Mechanical Ventilation



Liu Pharmaceutics 2019 Sep

- VMN-L: 1 vial colistin (200 MIU) dilute to 6 mL via VMN
- JN-L: 1 vial colistin (200 MIU) dilute to 6 mL via JN
- JN-H: 2 vial colistin (400 MIU) dilute to 6 mL via JN

Table 1. Nebulizer performance on the delivery of colistin.

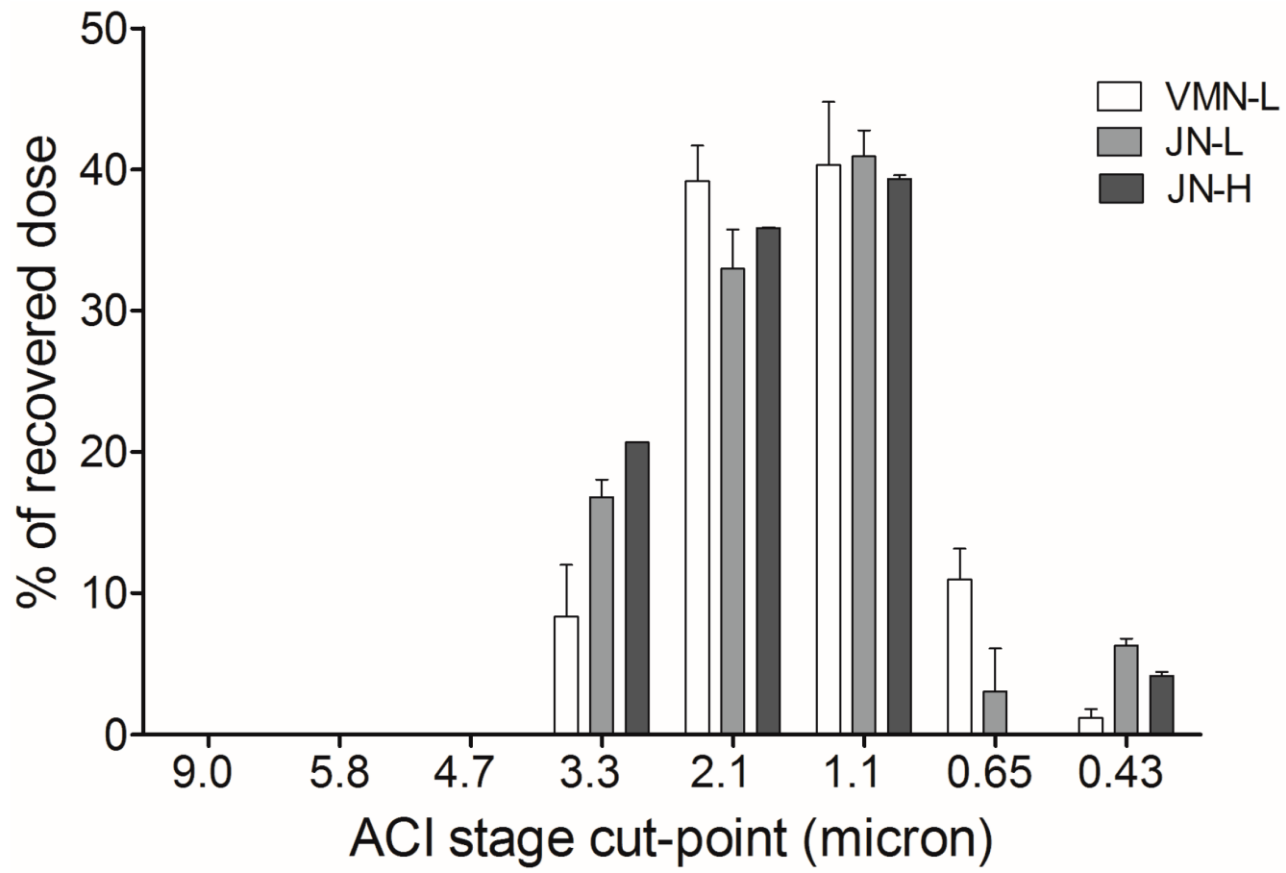
Variables	VMN-L	JN-L	JN-H	*P*-Value
Inhaled mass (mg)	53.80 ± 14.79	19.82 ± 3.34 *	31.72 ± 4.48 *	<0.001
Inhaled mass (%)	34.44 ± 9.47	12.69 ± 2.14 †	10.15 ± 1.43 †	<0.001
Nebulization time (min)	42.35 ± 2.30	21.12 ± 0.86 ‡	21.65 ± 0.42 ‡	<0.001
Delivery efficiency (mg/min)	1.27 ± 0.32	0.94 ± 0.17	1.46 ± 0.20 §	0.023
Delivery efficiency (%/min)	0.81 ± 0.20	0.60 ± 0.1	0.47 ± 0.06 ‖	0.014

- VMN- delivers greater inhaled mass, longer nebulization time

Liu Pharmaceutics 2019 Sep

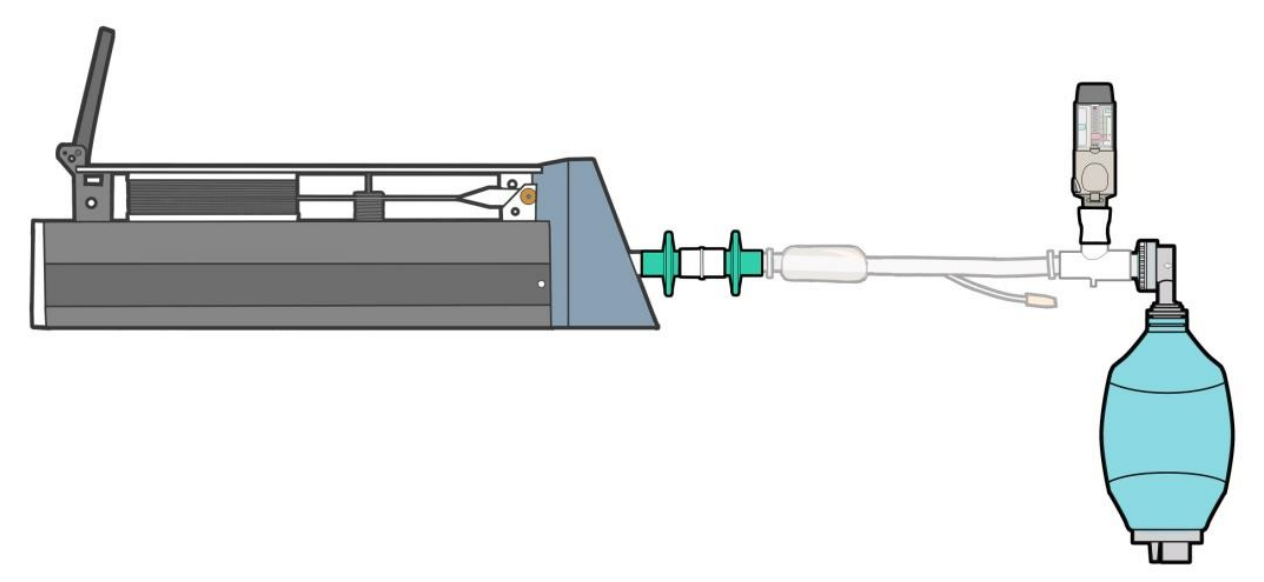
- Similar particle size distal to the ETT, regardless drug concentration

Variables	VMN-L	JN-L	JN-H	*P*-Value
MMAD (μm)	2.03 ± 0.24	2.09 ± 0.17	2.26 ± 0.05	0.434



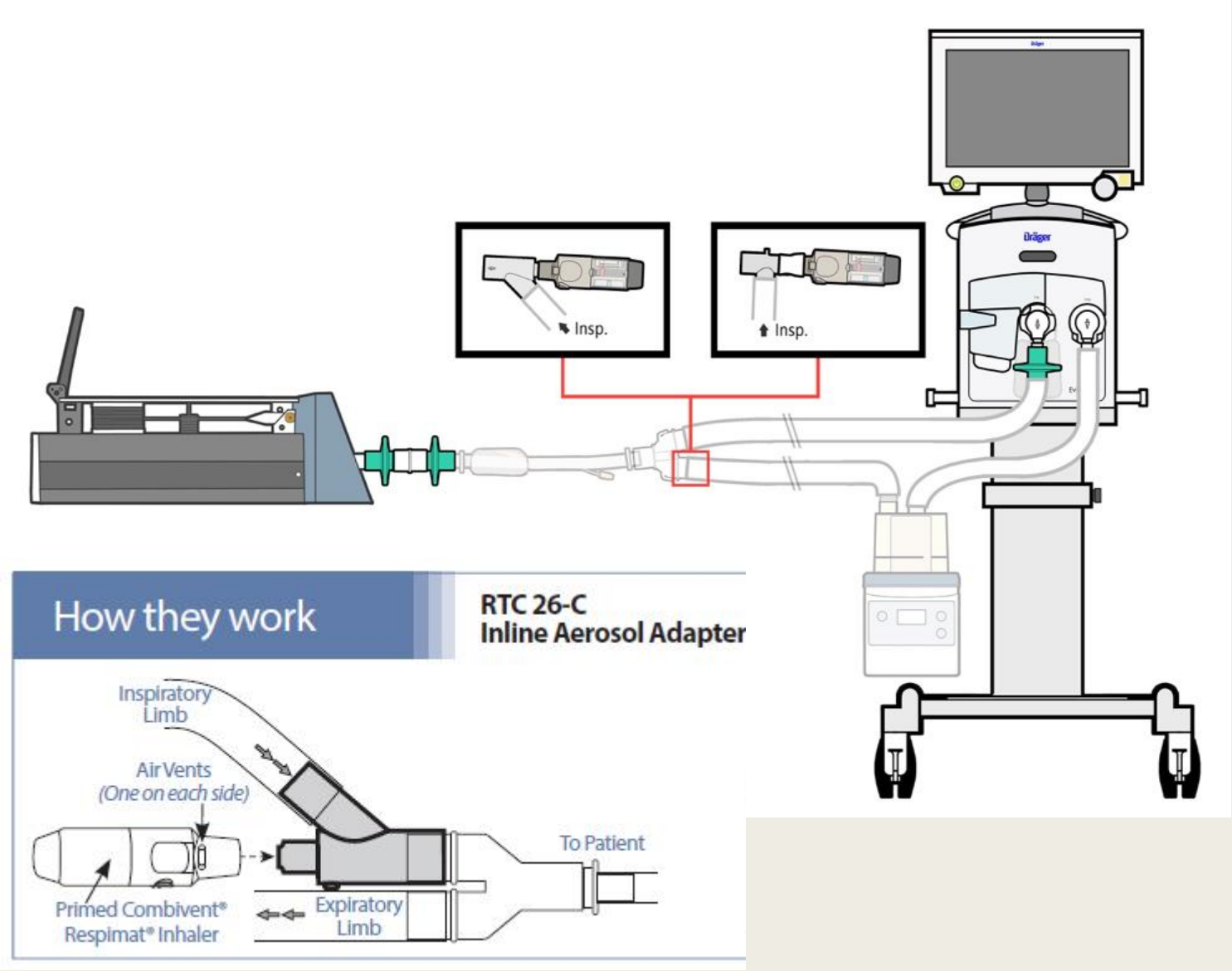
Resmipat through mechanical ventilation

- The optimal inhaled drug dose and method of connecting to a ventilator system is unknown. We aimed to evaluate SMI delivery with different adaptors via endotracheal tube with different actuation timing during mechanical ventilation.



Fang 2019 AARC open forum

Resmipat through mechanical ventilation



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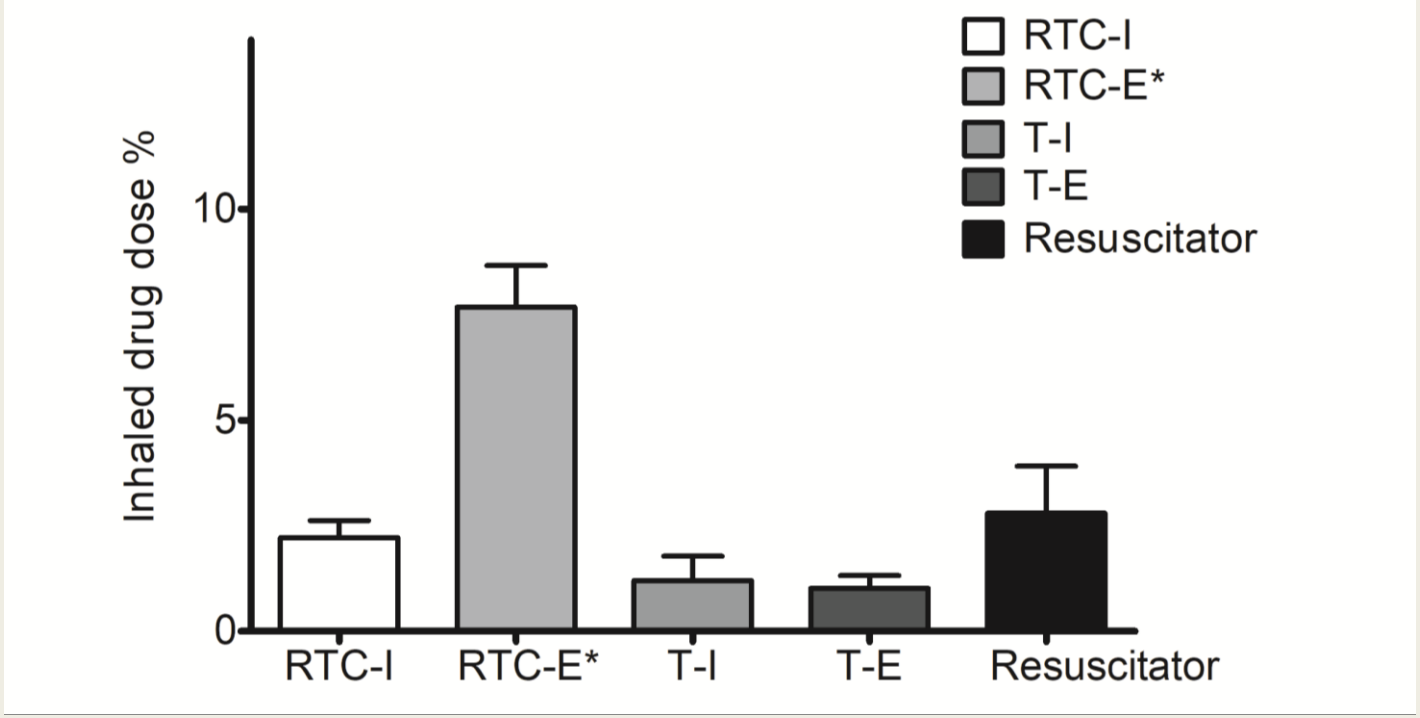
Resmipat through mechanical ventilation

- Spontaneous vs vas MV: 22.08 ± 4.8% vs 7.68 ± 0.98%
- Respimat delivery via RCT adaptor synchronized with expiration yields greatest inhaled dose.

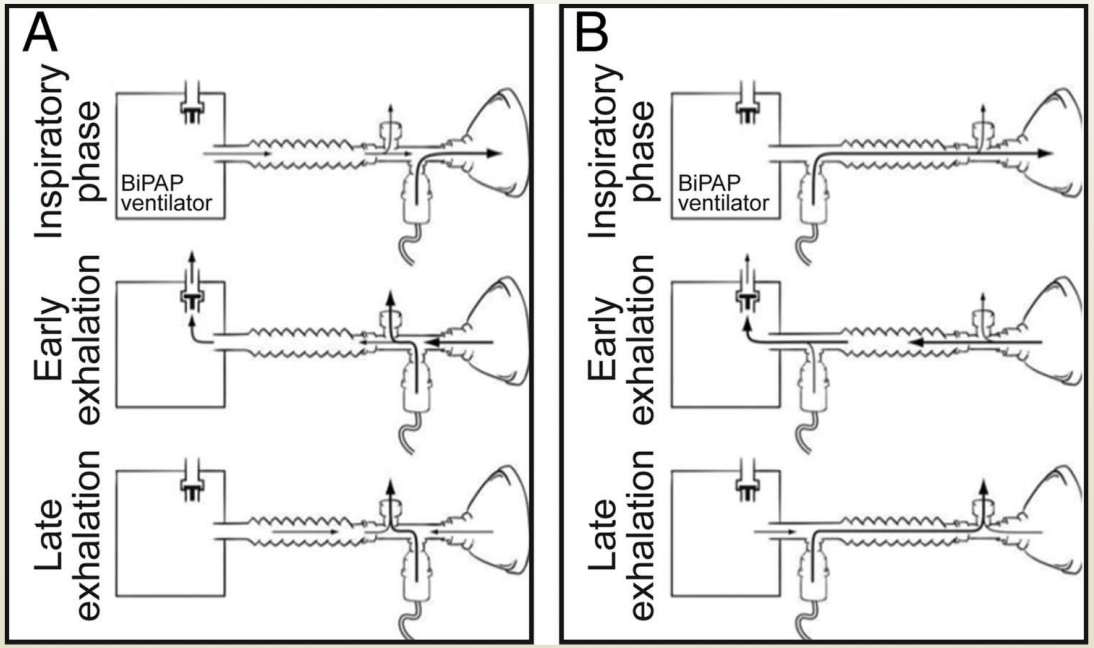


Aerosol therapy through MV

- Summary
  - Technology and techniques has increased lung dose from 2% to > 40% during CMV
  - Placement of the device is the key element.
  - Humidity is no longer a influencing factor… Don’t turn off the heated humidifier.
  - Lower the inspiratory flow (mode) temporary if possible.

Aerosol therapy through non-invasive mechanical ventilation

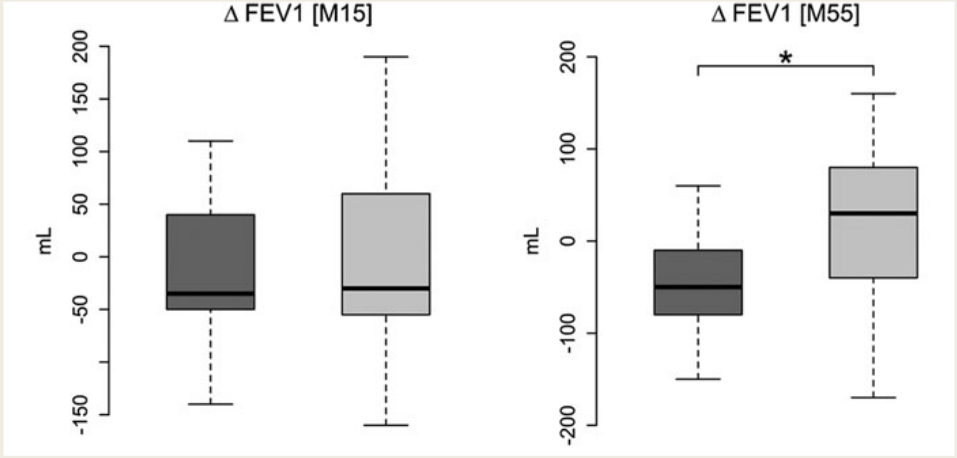
- The best position for the aerosol generator is between the leak port and the mask.
- The pMDI might be more efficient than a nebulizer when the leak port is in the mask.



Hess, D.R Respir Care, 2015. **60**(6): p. 880-91

Aerosol therapy through NIV

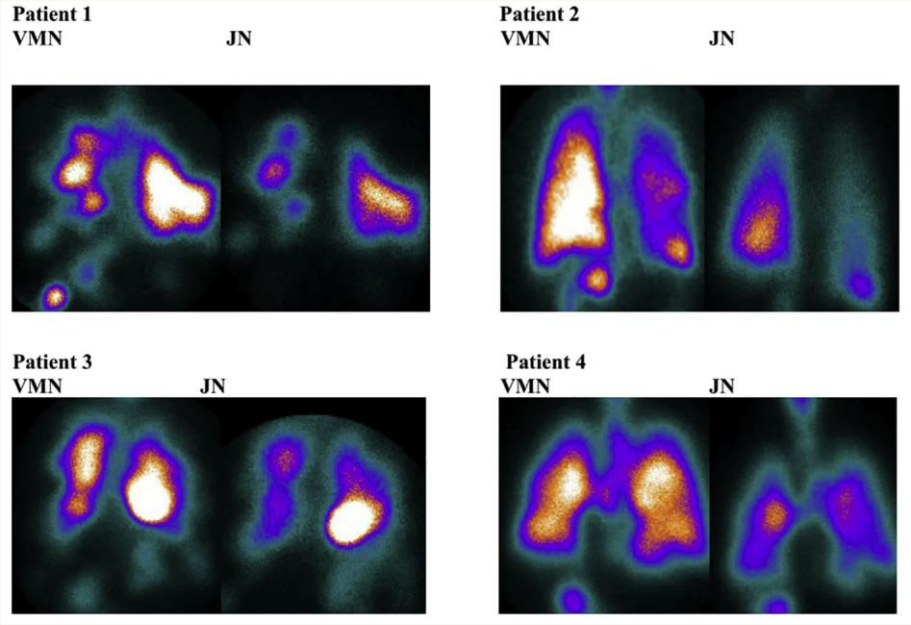
- Bodet-Contentin 2019
  - Salbutamol could be nebulized through an NIV circuit in COPD exacerbation and improve
  - Aerosols were generated by a vibrating mesh nebulizer positioned just after the Y-piece.
  - FEV_1 increased significantly from baseline to 40 minutes after the end of salbutamol nebulization.



Bodet-Contentin et al J Aerosol Med Pulm Drug Deliv. 2019 Jun;32(3):149-155

Aerosol therapy through non-invasive mechanical ventilation

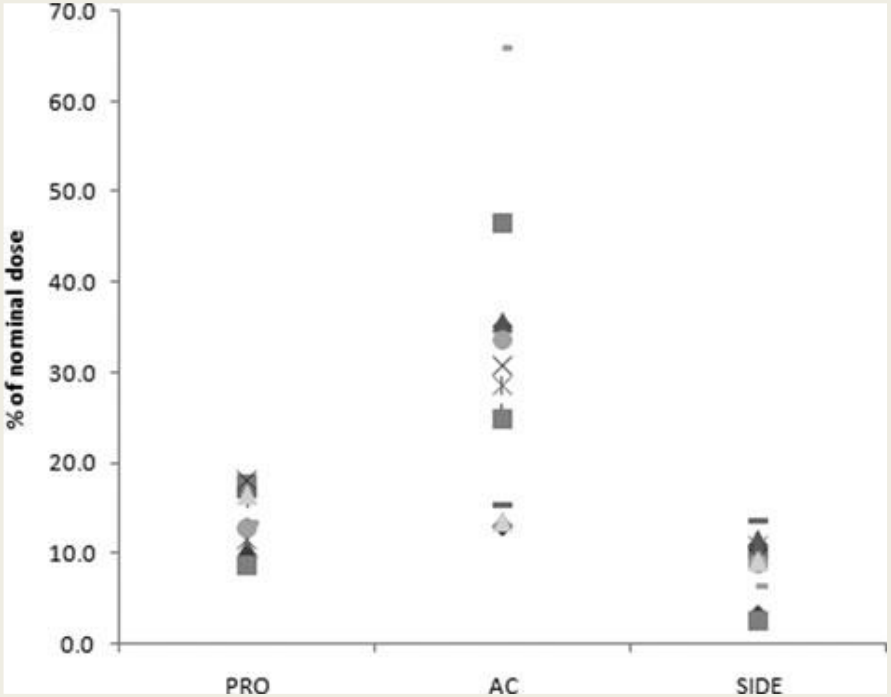
- Galindo-Filho et al 2019
  - A crossover single dose study with moderate to severe COPD randomly allocated to receive aerosol administration by the VMN and a jet nebulizer
  - VMN deposited > 3 fold more radioaerosol into the lungs



Galindo-Filho et al Respir Med. 2019 Jul;153:60-67

Aerosol therapy through non-invasive mechanical ventilation

- Hassan et al 2017
  - Compared aerosol delivery during NIV with 3 types of aerosol generators: MDI with aerochamber (AC), vibrating mesh nebulizer (PRO), and sidestream jet nebulizer (SIDE)
  - MDI with spacer had higher ID%, USAL0.5% and lower MMAD, and the PRO had a higher FPD, USAL0.5%, USAL24%, compared to SIDE.



Hassan et al Exp Lung Res. 2017 Feb;43(1):19-28

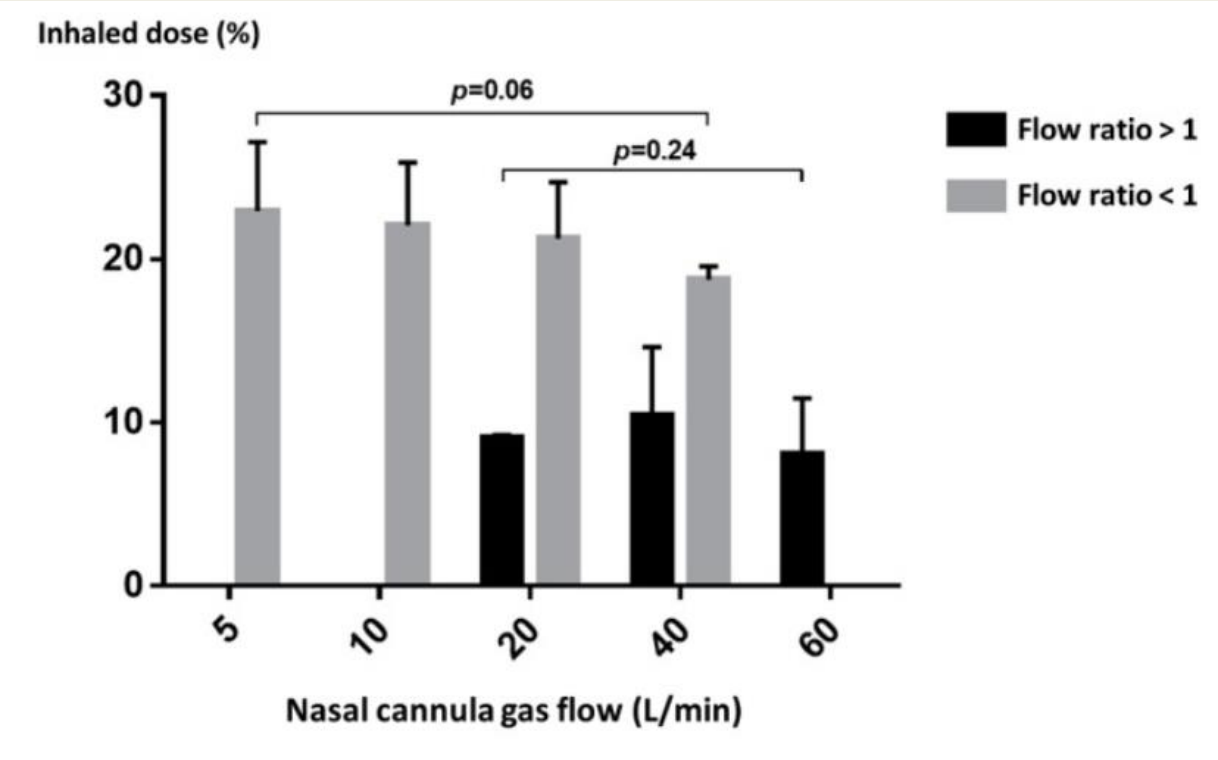
Aerosol delivery through NHC

- Barriers:
  - Nose filtration effects (impact further on infants)
  - Particle velocity: greater impaction (25% ↓'d)
  - Humidification: facilitates particle growing
  - Continuous delivery of aerosolized particles

- Intrathorcic deposition: 14% by nasal vs. 57% by oral inhalation

Aerosol delivery through NHC - In vitro

- Li et al 2019
  - Inhaled dose is related to the ratio of gas flow to patient inspiratory flow



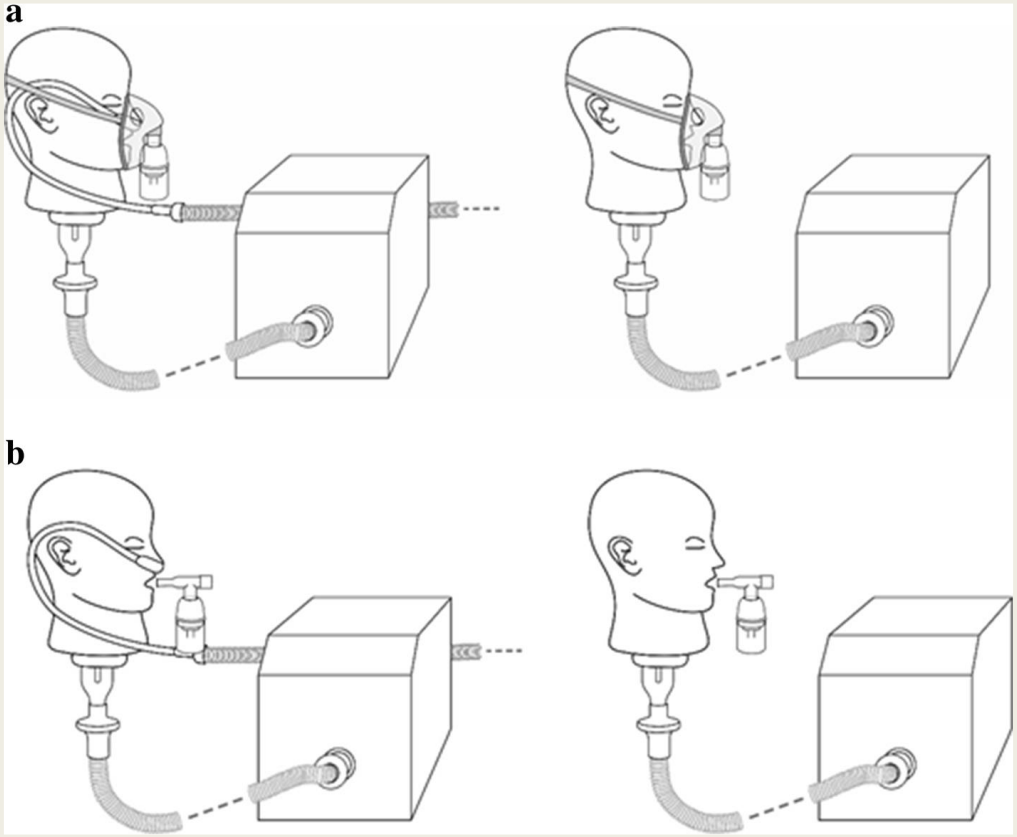
Li et al *Pharmaceutics.* 2019 May 10;11(5)

Aerosol delivery through NHC

- Evaluate aerosol delivery using two nebulizer types across different drug delivery interfaces, nasal cannula, facemask, and mouthpiece, during simulated adult HFNT.

Healthy: TV: 500 mL, RR 15, I/E= 1:1

Distressed: TV: 750 mL, RR 30, I/E= 1:1



Bennett, G., et al., *Intensive Care Med Exp,* 2019.

Aerosol delivery through NHC

- Aerosol dose was observed when the VMN was integrated with HFNT
- Greater during simulated distressed breathing

	Supplemental gas flow rate (LPM)	Aerosol dose (%) Healthy adult breathing	Aerosol dose (%) Distressed adult breathing
VMN + HFNT at 50LPM	N/A	2.88 ± 0.15	6.81 ± 0.45
Mask + VMN/Ultra	0LPM	3.43 ± 0.62	28.76 ± 1.72
	2LPM	29.93 ± 0.46	35.47 ± 1.81
	6LPM	22.44 ± 0.63	36.21 ± 0.78
Mask + VMN/Ultra + HFNT at 50LPM	0LPM	0.33 ± 0.07	0.86 ± 0.04
	2LPM	1.62 ± 0.46	2.96 ± 0.26
	6LPM	1.07 ± 0.25	4.23 ± 0.93
Mouthpiece + VMN/Ultra	0LPM	0.63 ± 0.07	1.92 ± 1.12
	2LPM	28.72 ± 1.24	21.37 ± 0.78
	6LPM	31.52 ± 0.35	28.46 ± 0.38
Mouthpiece + VMN/Ultra + HFNT at 50LPM	0LPM	0.56 ± 0.13	0.73 ± 0.37
	2LPM	2.16 ± 0.06	0.97 ± 0.20
	6LPM	1.82 ± 0.41	3.11 ± 0.53
Mask + JN	8LPM	6.13 ± 0.09	9.07 ± 0.26
Mask + JN + HFNT at 50LPM	8LPM	0.82 ± 0.16	5.72 ± 0.71
Mouthpiece + JN	8LPM	12.68 ± 1.16	12.90 ± 2.52
Mouthpiece + JN + HFNT at 50LPM	8LPM	0.86 ± 0.11	0.69 ± 0.53

Bennett, G., et al., Intensive Care Med Exp, 2019.

Aerosol delivery through NHC -Clinical trial

- Maney et al 2019
  - Compare the delivery of salbutamol, with 2 different nebulizers, in patients with COPD receiving low-flow oxygen therapy through an HFNC

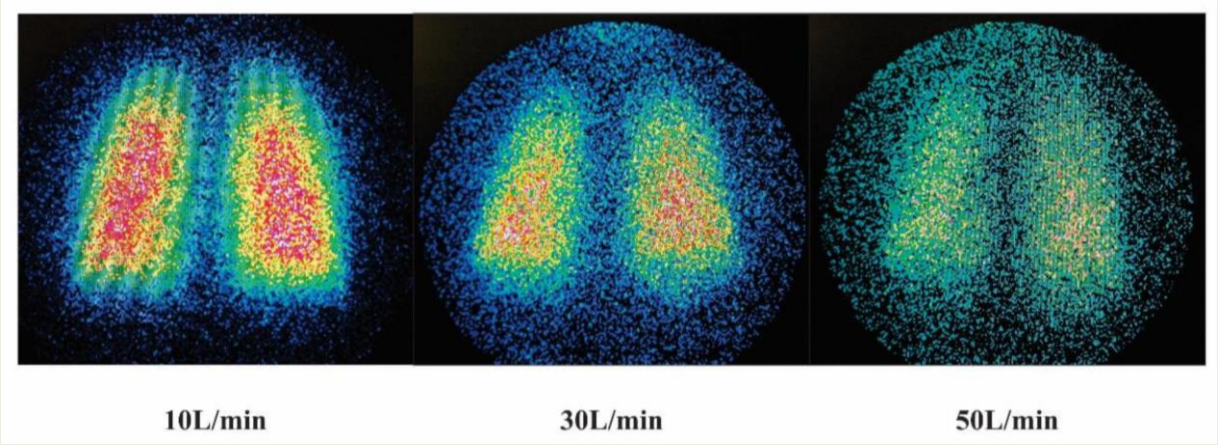
	Vibrating Mesh Nebulizer with T-Piece	pMDI and Vibrating Mesh Nebulizer with Spacer	Jet Nebulizer with T-Piece
In vivo			
Urinary salbutamol excretion 30 min post-inhalation, μg	50.6 ± 19.7	45.7 ± 16.1	26.4 ± 10.8
Urinary salbutamol excretion 30 min post-inhalation, %	1.0 ± 0.4*†	0.9 ± 0.3*‡	0.5 ± 0.2*†‡
Urinary salbutamol excretion 24 h post-inhalation, μg	611.1 ± 218.6	707.5 ± 270.4	393.6 ± 155.7
Urinary salbutamol excretion 24 h post-inhalation, %	12.2 ± 4.4*†	13.6 ± 5.2*‡	7.9 ± 3.1*†‡
Ex vivo			
Emitted dose, μg	1,277.2 ± 143.7	1,657.2 ± 308.9	602 ± 196.3
Emitted dose, %	25.5 ± 2.9*†	31.9 ± 5.9*‡	12 ± 3.9*†‡

Madney et al Respir Care. 2019 Apr;64(4):453-461.

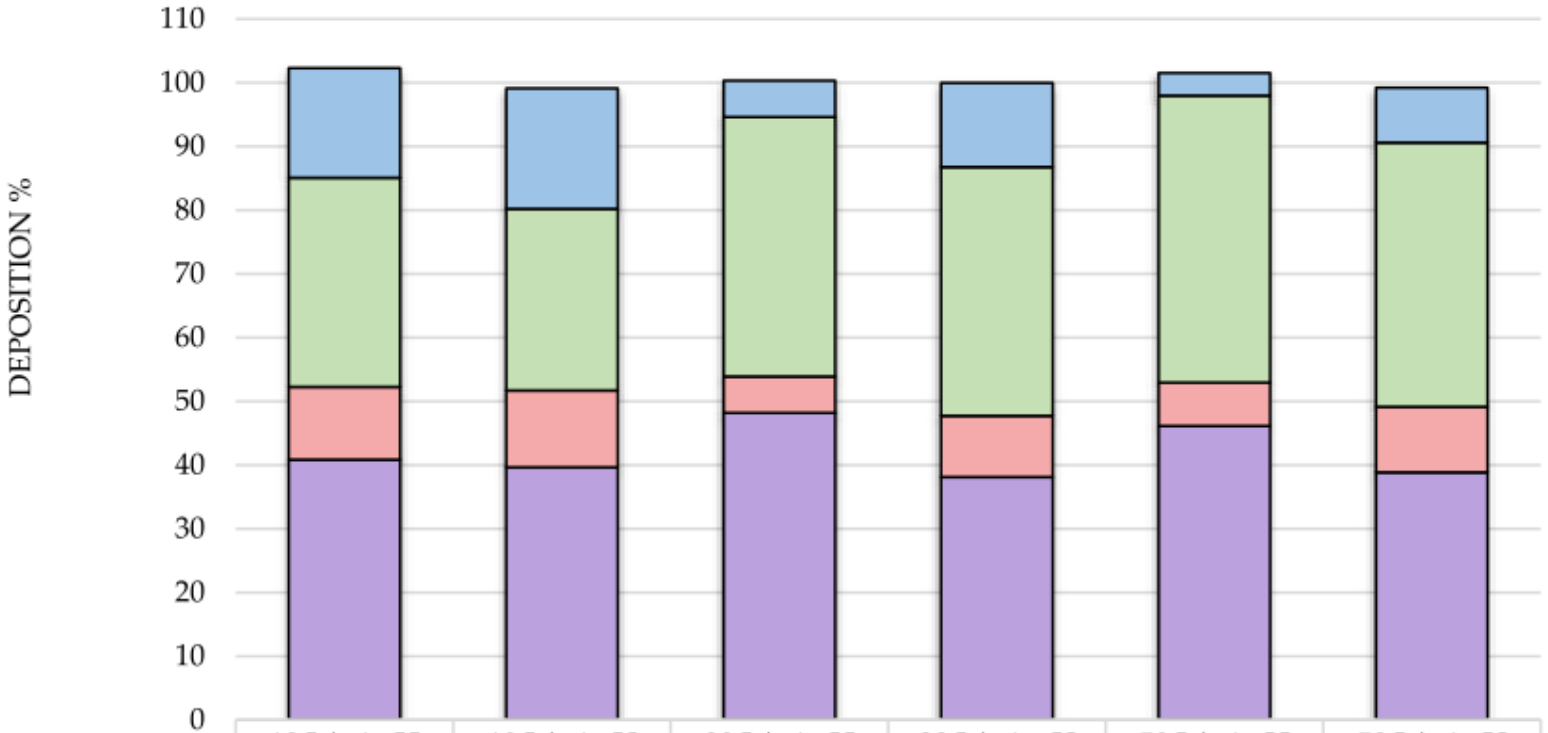
Aerosol delivery through NHC -Clinical trial

- Alcoforado et al 2019 on healthy adults

Compartment	10 L/min (n = 8)	30 L/min (n = 7)	50 L/min (n = 8)	p-Value
Lung (%)	17.23 ± 6.78	5.71 ± 2.04 *	3.46 ± 1.24 **	<0.001 #
Upper airway (%)	34.48 ± 10.25	42.10 ± 13.92	46.07 ± 8.45	0.213
Stomach (%)	0.37 ± 0.15	1.05 ± 1.12	0.35 ± 0.49	0.116
Nebulizer (%)	13.57 ± 7.42	9.43 ± 6.30	10.30 ± 7.12	0.437
Cannula (%)	8.78 ± 3.63	13.18 ± 3.32 ***	18.40 ± 3.48 **	<0.001



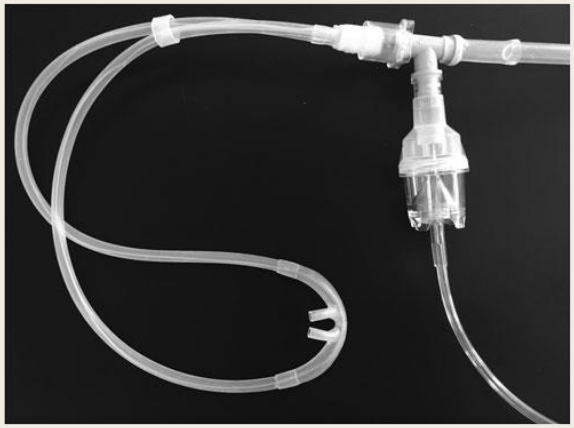
Alcoforado et al Pharmaceutics. 2019 Jul 7;11(7)

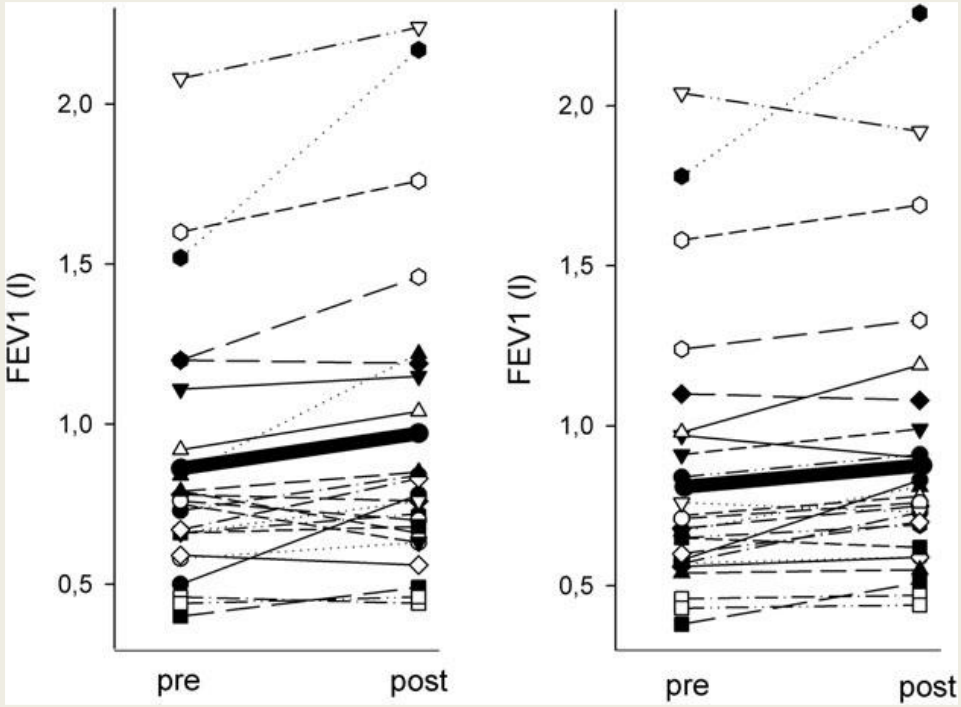


	10 L/min H	10 L/min U	30 L/min H	30 L/min U	50 L/min H	50 L/min U
LUNG	17.2	18.9	5.7	13.2	3.5	8.6
UPPER AIRWAY	32.8	28.5	40.7	39.1	45.0	41.5
FILTER	11.4	12.1	5.7	9.6	6.8	10.3
DEVICE	40.9	39.6	48.2	38.1	46.1	38.9

Aerosol delivery through NHC

- Bräunlich et al 2018 on COPD patients
  - No significant differences in the effects on lung function of either oral aerosol or high-flow adapted nasal in-halation.

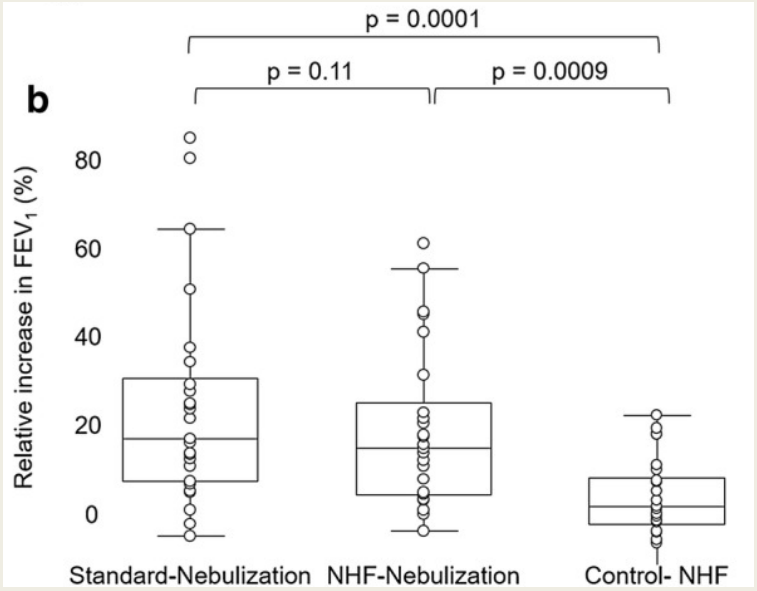




Braunlich et al J Aerosol Med Pulm Drug Deliv. 2018 Aug;31(4):248-254.

Aerosol delivery through NHC

- Reminiac et al 2018
  - 25 patients with reversible airflow obstruction received 3 treatments
  - Albuterol vibrating mesh nebulization within a nasal high-flow circuit induces similar bronchodilation to standard facial mask jet nebulization.



Reminiac et al Ann Intensive Care. 2018 Dec 20;8(1):128

Wallin *et al. BMC Pulmonary Medicine* (2019) 19:42
https://doi.org/10.1186/s12890-019-0807-9

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Aerosol drug delivery to the lungs during nasal high flow therapy: an in vitro study

Martin Wallin[1,2], Patricia Tang[1], Rachel Yoon Kyung Chang[1], Mingshi Yang[2], Warren H. Finlay[3] and Hak-Kim Chan[1*]

FPF = 32% (of loadd dose)

Abstract

Background: Aerosol delivery through a nasal high flow (NHF) system is attractive for clinicians as it allows for simultaneous administration of oxygen and inhalable drugs. However, delivering a fine particle fraction (FPF, particle wt. fraction < 5.0 μm) of drugs into the lungs has been very challenging, with highest value of only 8%. Here, we aim to develop an efficient nose-to-lung delivery system capable of delivering improved quantities (FPF > 16%) of dry powder aerosols to the lungs via an NHF system.

Methods: We evaluated the FPF of spray-dried mannitol with leucine with a next generation impactor connected to a nasopharyngeal outlet of an adult nasal airway replica. In addition, we investigated the influence of different dispersion (20–30 L/min) and inspiratory (20–40 L/min) flow rates, on FPF.

Results: We found an FPF of 32% with dispersion flow rate at 25 L/min and inspiratory flow rate at 40 L/min. The lowest FPF (21%) obtained was at the dispersion flow rate at 30 L/min and inspiratory flow rate at 30 L/min. A higher inspiratory flow rate was generally associated with a higher FPF. The nasal cannula accounted for most loss of aerosols.

Conclusions: In conclusion, delivering a third of inhalable powder to the lungs is possible in vitro through an NHF system using a low dispersion airflow and a highly dispersible powder. Our results may lay the foundation for clinical evaluation of powder aerosol delivery to the lungs during NHF therapy in humans.

Keywords: Aerosol, Powders, Inhalable drugs, Nasal cannula, Pulmonary disease, chronic obstructive, Lungs, Nasal high flow

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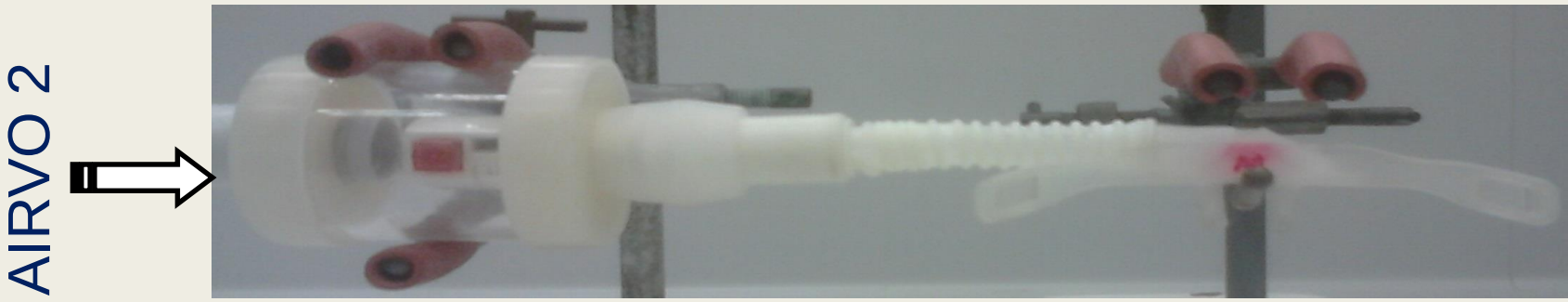


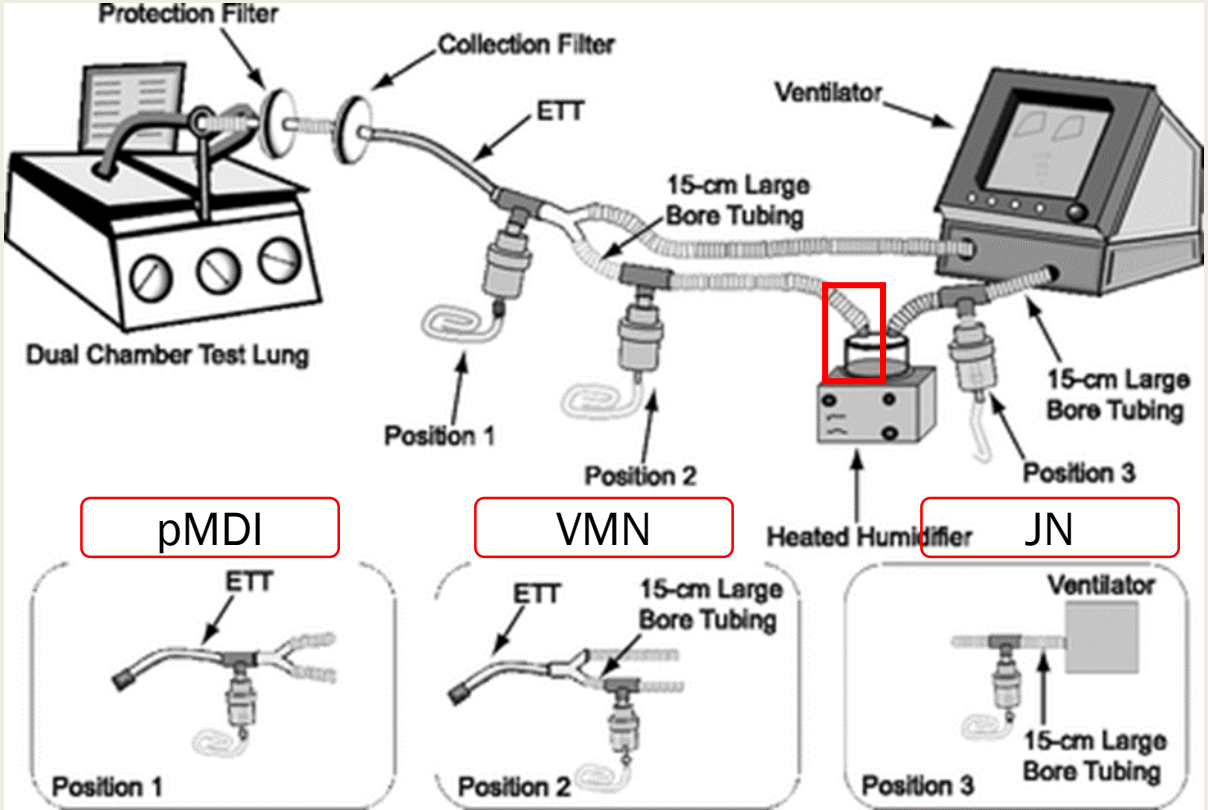
Table 4 Aerosol performance of Man+Leu at different dispersion and inspiratory flow rates

Dispersion flow rate (L/min)	Inspiratory flow rate (L/min)	Replica deposition (% of loaded dose)	NGI deposition (% of loaded dose)	FPF (% of loaded dose)
20	20	13.28 ± 2.08	24.05 ± 0.17	23.04 ± 0.21
	30	19.09 ± 0.59	26.51 ± 0.90	25.64 ± 0.91
	40	14.59 ± 1.30	24.14 ± 1.02	23.68 ± 0.99
25	25	17.40 ± 0.78	27.76 ± 1.08	27.45 ± 0.99
	40	18.76 ± 1.91	32.32 ± 0.47	32.15 ± 0.47
30	30	15.06 ± 0.74	21.72 ± 0.74	21.03 ± 0.85
	40	20.11 ± 2.14	27.16 ± 0.79	26.60 ± 0.71

The loaded dose in all experiments was 40 ± 4 mg powder. Data are represented as the mean ± SEM ($n = 3$)

Summary

- Intubated patients
  - *Appropriate placement for different devices*
  - *Heated humidifier should be remained on..*



Summary

- Non-invasive ventilation
  - *Vibrating mesh nebulizer yield greater inhaled dose.*
  - *The best position for the aerosol generator is between the leak port and the mask.*
- High flow oxygen therapy
  - *Reduced gas flow ratio < 1.0*

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