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Aerosol Delivery via Continuous High Frequency Oscillation During Mechanical Ventilation

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ABSTRACT

BACKGROUND: As the use of continuous high-frequency oscillation (CHFO) combined with nebulization during mechanical ventilation becomes more prevalent clinically, it is important to evaluate its aerosol delivery efficacy.

METHODS: A bench study was conducted simulating two adult and two pediatric conditions. The CHFO device (Metaneb) integrated into the inspiratory limb of a conventional critical care ventilator was attached to an endotracheal tube (ETT) with a collection filter and test lung. High frequency oscillation with high flow setting was used with jet nebulizers attached to the manifold, and a vibrating mesh nebulizer (VMN) placed between ETT and ventilator circuit versus at the inlet of the humidifier. Albuterol (2.5 mg in 3 mL) was nebulized for each condition (n=3). Drug was eluted from the collection filter and assayed with UV spectrophotometry (276 nm).

RESULTS: During CHFO, mean inhaled dose with jet nebulizers were very low (<2% with adult settings and <1% with pediatric settings). Across both adult and pediatric conditions, when VMN was placed between ETT and Y-piece during CHFO, inhaled dose was higher than that with VMN placed at the inlet of humidifier, median 11.1% (IQR 7.0% - 13.7%) vs median 6.0% (IQR 3.9% - 7.2%) $P = .002$, but still lower than the inhaled dose with VMN placed at inlet of humidifier with CHFO off, median 22.7% (IQR 19.5% - 25.4%) vs median 11.1% (IQR 7.0% - 13.7%) $P<.001$. Inhaled dose with the 10-year old scenario was higher than the 5-year old scenario in all settings except aerosol delivery via CHFO.

CONCLUSIONS: During invasive mechanical ventilation with CHFO, aerosol delivery with JN in the manifold resulted in marginal inhaled dose. VMN at the ETT during CHFO delivered 6

fold more aerosol than JN, while delivering only half of inhaled dose with VMN placed at the inlet of humidifier without CHFO.

Key words: Continuous high-frequency oscillation; aerosol delivery; mechanical ventilation; vibrating mesh nebulizer, jet nebulizer.

Introduction

The Metaneb (Hill-Rom, Batesville, IN) is a continuous high-frequency oscillation (CHFO) device that includes settings to support lung expansion, secretion clearance and aerosol medication delivery, and is widely used in the hospital setting for patients with and without mechanical ventilation among adult and pediatric populations.[1-3] CHFO mobilizes secretions by administering high-frequency mini bursts of air to the lungs promoting the upward (cephalad) movement of secretions.[4] Simultaneously, the device can deliver aerosolized medications through its integrated jet nebulizer (Salter labs, Salt Lake City, UT),[5] positioned in the manifold. Concurrent delivery of aerosolized medications with CHFO could be advantageous, however, aerosol deposition may be highly variable.[6]

We recently reported an in vitro study[7] during simulated spontaneous breathing in an adult model with CHFO, using the integrated jet nebulizer and another common jet nebulizer placed in the manifold per label, the inhaled dose was < 2%, while the inhaled dose increased to 3% when the jet nebulizers were moved between the manifold and manikin. This finding is similar to the results in the two in-vivo studies among healthy volunteers implemented by Reychler et al[8,9], who used a similar device called intrapulmonary percussive ventilation (IPV, Percussionaire; Percussionaire Corporation; Sandpoint, ID). CHFO and IPV are similar in their delivery of high flow air bursts to the lung and the increase in mean airway pressure, which create an upward movement of secretions and prevent early closure of lung areas.[10] Both devices are designed to be used either in combination with a conventional ventilator or as standalone devices.[10] Using this CHFO device placed in-line with a mechanical ventilator, Berlinski and Willis[11] conducted an in-vitro study with a pediatric model, they found that 1-4% of albuterol was delivered at the end of endotracheal tube (ETT). Recently, Karashima et al[10] compared

aerosol delivery with IPV placed in-line with a ventilator and stand-alone in an adult intubation model, regardless of the device set-ups or ventilator settings, aerosol deposition at the end of ETT ranged from 2-3%. Metaneb is also commonly utilized in both adult and pediatric patients,[5] but data on aerosol deposition with CHFO during invasive ventilation is still lacking.

Thus, we aimed to assess the performance of aerosol delivery via the CHFO device during adult and pediatric mechanical ventilation, to test our hypothesis that aerosol delivery efficiency would be similar to previous findings using mask with simulated spontaneous breathing.

Methods

A critical care ventilator (PB 840, Medtronic, Minneapolis, MN) with an active heated humidification system and a 22 mm ID heated wire circuit (Fisher & Paykel, Auckland, New Zealand) was attached to an endotracheal tube with a collection filter (Respirgard 303, CareFusion, San Diego, CA), which was placed at the distal tip of the endotracheal tube. The filter was attached to a test lung (TTL, Michigan Instruments, Grand Rapids, MI) with compliance and resistance set per test scenarios, with adult (COPD and normal) and pediatric (20 kg and 30 kg) settings[12-14] applied (Table 1). The sizes for endotracheal tubes (Medtronic, Minneapolis, MN) were 8.0mm ID for adults, 6.0mm for the 30 kg child, and 5.0mm for the 20 kg child. Metaneb circuit and manifold were connected between the inspiratory limb and the Y-piece, using a "T" adapter, per manufacturer recommendations.[4] Metaneb settings were set to deliver high frequency oscillation with high flow (Figure 1).

Albuterol powder (1.0 g, Sigma-Aldrich, St Louis, Missouri) was mixed with 1200mL of sterile water to form a concentration of 0.83mg/mL. For each of the nebulization treatments (n=3), 3mL (2.5 mg) of albuterol solution was administered. After nebulization ended the

collection filter was removed and rinsed with 10 mL solution (20% ethanol with 0.1M HCl). The filter was capped at both ends after adding the elution solution, then the liquid was allowed to pass through the filter medium several times. The circuit was cleared of condensate between treatments, and the collection filter was placed superior to the endotracheal tube to avoid risk of non-aerosols reaching it. The sample was then analyzed with UV spectrophotometry (276nm).

The Metaneb device was designed to use a Salter Lab jet nebulizer (JN) positioned in the device manifold (per manufacturer label). Inhaled dose was compared with that delivered with another disposable jet nebulizer (AirLife 002446, CareFusion, Yorba Linda, CA) operated at the same manifold position. Both JNs were gently tapped at onset of sputter until no aerosol was generated for at least 1 min. A vibrating mesh nebulizer (VMN, Aerogen Solo, Aerogen Ltd., Ireland) was placed between the ETT and Y-piece of the ventilator circuit using a 15 mm T-piece, and at the inlet of the humidifier using a 22 mm adapter, where aerosol was administered with and without CHFO. VMN was run until aerosol was not visible.

Statistical analysis

In this study, the inhaled dose was calculated as percentage of albuterol captured by the collection filter to the nominal dose, and expressed as mean ± standard deviation (SD) or median (Inter-Quartile Range [IQR]) for each experiment (n=3), depending on the distribution of variables. The Kolmogorov- Smirnov test was used to test the normality of distribution for considered variables. Independent t test or Mann Whitney test was used to compare the inhaled dose between devices under each scenario and overall comparison. A *P* value of <.05 was considered to be statistically significant. Data analysis was conducted with SPSS 23.0 (SPSS, Chicago, IL).

Results

With CHFO mode on, using the integrated JN provided by the manufacturer, mean inhaled dose was < 2% for both adult scenarios and < 1% in both pediatric scenarios. When the VMN was placed at the inlet of the humidifier, the inhaled dose was higher than that with JN, median 6.0% (IQR 3.9% - 7.2%) vs median 1.0% (IQR 0.8%, 1.7%) $P < .001$, while was still lower than the inhaled dose with VMN placed between the ETT and Y-piece, median 6.0% (IQR 3.9% - 7.2%) vs median 11.1% (IQR 7.0% - 13.7%) $P = .002$ (Table 2).

In contrast, with CHFO off, the VMN placed at the inlet of humidifier delivered three folds more aerosol than the same position with CHFO on, median 22.7% (IQR 19.5% - 25.4%) vs median 6.0% (IQR 3.9% - 7.2%) $P < .001$ (Figure 2), and had an inhaled dose increase of two times more than VMN placed between the ETT and Y-piece with CHFO on, median 22.7% (IQR 19.5% - 25.4%) vs median 11.1% (IQR 7.0% - 13.7%) $P < .001$.

With adult mechanical ventilation settings, no significant difference of inhaled dose were found between COPD and normal adult scenarios, while with pediatric settings, the inhaled dose with the 10 year old child scenario was higher than the 5-year old child scenario, except with the integrated JN with CHFO mode on (Table 2).

Discussion

To our knowledge, this is the first study to characterize medical aerosol delivery with the Metaneb CHFO during mechanical ventilation in simulated adult and pediatric conditions. In our study, we found JNs in the manifold delivered marginal doses of < 2% for both simulated adult and pediatric models, which are likely not clinically efficacious.

These findings are consistent with our previous report of marginal inhaled dose achieved in an adult model of spontaneous breathing, with the same CHFO device and JNs. In that study, inhaled dose with JNs placed in the manifold during quiet breathing was approximately 2%.[7]

This supports the hypothesis that manifold design generates sufficient turbulence causing the majority of aerosol emitted by the JNs to be impacted prior to reaching the patient airway. In the earlier study, when the integrated JN (Salter lab) was placed between the manifold and the manikin airway, inhaled dose marginally increased to 2.3% during CHFO, conversely, the JN with aerosol mask and without CHFO delivered 8.0%. These results of lower inhaled dose with CHFO than JN alone align with the findings using IPV, that aerosol delivery with IPV was only ¼ to ½ of that with JN alone.[8-11]

In contrast, placement of the VMN between ETT and Y-piece delivered seven times more inhaled dose than both JNs with CHFO. However, when the VMN was placed at the inlet of the humidifier without CHFO, inhaled dose was similar to prior reports of inhaled dose during CMV[15] and three times greater than when CHFO was applied, across both adult and pediatric scenarios. Berlinski and Willis[11] found that when IPV was placed between ETT and Y-piece, the inhaled dose was comparable to that with JN alone placed at the same position. Although we did not study aerosol delivery with JN alone placed at the ETT and Y-piece considering VMN is more efficient in aerosol delivery than JN, and aerosol deposition is higher with VMN placed at the inlet of humidifier than placed at the ETT and Y-piece,[11] we speculate that the turbulence created at the circuit/ETT interface during CHFO increased impactive losses for aerosol passing through the ventilator circuit. The reduction of inhaled dose with the addition of CHFO provides insights to its negative impact on aerosol delivery. Thus placing nebulizers close to the patient airway rather than at the manifold position might help improve aerosol delivery. This agrees with

Fang et al's[16] in-vitro reports during high frequency oscillation ventilation, which demonstrated that both JN and VMN delivered higher inhaled dose with the nebulizer placed between the ETT and Y-piece compared to negligible inhaled dose with the nebulizer placed at the inlet of humidifier.

In our study, the presence of mechanical ventilation did not seem to further reduce the inhaled dose of aerosol during CHFO compared to administration during spontaneous breathing. Turbulent breathing patterns, when added to the effect of Metaneb CHFO, may also alter aerosol delivery by producing impaction in different parts of the ventilator circuit, in the endotracheal tube, and potentially the trachea.[17] We expected that the combination of the turbulent flow of the Metaneb CHFO mini bursts with the inspiratory gas patterns during mechanical ventilation may contribute to low deposition. The placement of the Metaneb device into the ventilator circuit using a 90 degree angle T-piece adapter was expected to increase losses of aerosol medication during the expiratory phase of ventilation between each mechanically ventilated breath.[11] However, it appears that the placement of the JN in the manifold of the Metaneb circuit was the primary factor reducing inhaled dose during mechanical ventilation.

Additionally, changes in airway resistance and lung compliance as used to differentiate normal adult and COPD conditions did not significantly impact aerosol deposition during CHFO. This is likely because with continuous nebulization, the cumulative inspiratory time per minutes is a better predictor of inhaled dose than moderate changes in compliance and resistance of the test lung.

Consequently, our findings suggest that the most efficient method to deliver inhaled medications during mechanical ventilation with CHFO was with the VMN placed between ETT and Y-piece. Other options for aerosol delivery during mechanical ventilation alongside CHFO

may include inline drug delivery via pressurized meter dose inhaler with an appropriate connecter.[17] Further confirmatory studies are needed to evaluate these options.

Clinical Implication

Our findings suggest that the CHFO device integrated with a mechanical ventilator to deliver aerosolized medication did not generate a clinically relevant inhaled dose. The Metaneb CHFO device may be effective in providing secretion clearance or lung expansion therapy during mechanical ventilation, however, aerosol delivery with the device as marketed is a fraction of that reported with JN or VMN during mechanical ventilation without CHFO, thus it should be used to nebulize medications before or after CHFO therapy if clinically indicated. If there is a need to provide aerosolized medication during secretion clearance, such as hypertonic saline or other mucoactive agents, placement of a VMN between the ETT and Y-piece during CHFO might be a satisfactory alternative. Further studies are warranted to confirm the clinical benefits of such concomitant therapy.

Limitations of the Study

Our study utilized an in-vitro model of mechanical ventilation using endotracheal tube sizes specific for adult and pediatric scenarios. Aerosol delivery efficiency would likely vary with the use of different breathing parameters or modes of ventilation. We collected aerosol on the collection filters at the end of the ETT, which is a well-established model, but known to overestimate drug delivery efficiency compared to in vivo studies where some portion of inhaled aerosol is exhaled. We also limited the setting for CHFO with the primary one used at our institution during mechanical ventilation, the impact of other settings were beyond the scope of this study, but might merit future investigation.

Conclusion

Aerosol deposition via the Metaneb CHFO with its integrated nebulizer during mechanical ventilation was less than 2% for both adult and pediatric simulated scenarios; in-line placement of vibrating mesh nebulizer between endotracheal tube and Y-piece improved aerosol delivery during CHFO to a clinically relevant dose. Further in vivo studies are recommended to confirm our findings and evaluate aerosol deposition with CHFO.

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Conflict of interest

Dr. Fink is Chief Science Officer for Aerogen Pharma. Dr. Li declares receiving research funding from Fisher & Paykel Healthcare Ltd, Aerogen Ltd and Rice Foundation and lecture honorarium from AARC, Fisher & Paykel Healthcare Ltd and Aerogen Ltd outside the submitted work. Mr. Elshafei has no conflict to disclose.

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QUICK LOOK

Current Knowledge

Continuous high-frequency oscillation (CHFO) has become widely utilized in inpatient clinical settings due to its reported benefits in mobilizations of secretions and lung expansion. In the intensive care unit, CHFO device (Metaneb, Hill-Rom) is commonly used during mechanical ventilation for secretion clearance and when indicated, for aerosol delivery via its integrated jet nebulizer.

What this paper contributes to our knowledge

This bench study revealed that the Metaneb CHFO device with its integrated jet nebulizer resulted in very low aerosol deposition during adult and pediatric simulated mechanical ventilation. Placement of a vibrating mesh nebulizer between the ETT and Y-piece improved aerosol deposition during CHFO.

Figure legends

Figure 1. Experimental setup illustrating the delivery of CHFO through mechanical ventilation. A collection filter was placed between the model lung and ETT. The CHFO device circuit and manifold was connected between the ventilator inspiratory limb and the Y-piece using a "T" piece adapter. CHFO was set at high frequency oscillation with high flow. VMN was placed between ETT and ventilator circuit and then at inlet of the humidifier (not shown).
ETT = endotracheal tube; CHFO = continuous high-frequency oscillation; VMN = vibrating mesh nebulizer.

Figure 2. Inhaled doses (mean ± SD) for the adult (COPD, normal) and pediatric (10 yrs old, 5 yrs old) settings with VMN placed at the inlet of humidifier during mechanical ventilation with CHFO off and on. Inhaled dose was higher in all scenarios with CHFO off compared to CHFO on, and inhaled dose was higher with adult than pediatric settings.

SD = standard deviation; COPD = chronic obstructive pulmonary disease; VMN = vibrating mesh nebulizer; CHFO = continuous high-frequency oscillation.

Table 1. Adult and Pediatric Scenarios Mechanical Ventilation Settings

	Adult Normal (70 Kg)	**Adult COPD (70 Kg)**	**Pediatric 10 year old (30 Kg)**	**Pediatric 5 year old (20 Kg)**
Rrs (cmH_2O/L/sec)	5	20	20	20
Cst (ml/cmH_2O)	60	100	40	25
Mechanical Ventilation Mode	PRVC	PRVC	PRVC	PRVC
Vt (ml)	420	420	180	120
RR	16	16	15	20
Ti (Sec)	1.0	1.0	1.0	0.75
PEEP (cmH_2O)	8	8	5	5
Metaneb CHFO Settings	High Frequency/High Flow	High Frequency/High flow	High Frequency/High flow	High Frequency/High flow
ETT (mmID)	8.0	8.0	6.0	5.0

Rrs= respiratory resistance, Cst=respiratory compliance, PRVC=pressure regulated volume control, Vt=tidal volume, RR=respiratory rate, Ti=inspiratory time, PEEP=positive end expiratory pressure, CHFO=continuous high frequency oscillation, ETT=endotracheal tube, ID= endotracheal tube inner diameter size in mm.

Table 2. Inhaled dose (mean±SD), median (IQR) with vibrating mesh nebulizer placed at inlet of humidifier and between ETT and y-piece, and two jet nebulizers operated at the manifold with CHFO on versus off during invasive ventilation.

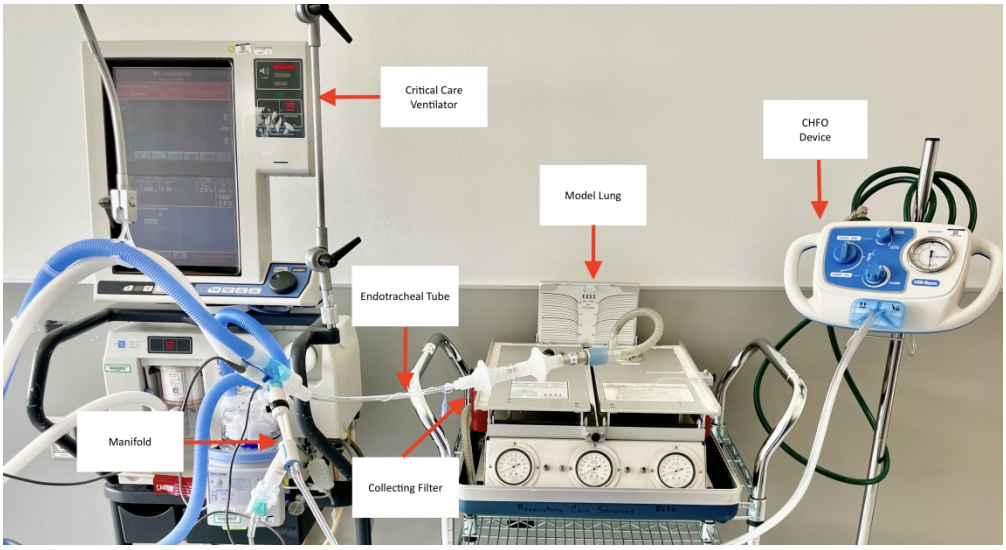
	Adult COPD %	Adult Normal %	*P*	10 Year Old (30 Kg), %	5 Year Old (20 Kg), %	*P*	Overall
VMN placed at the inlet of humidifier:							
CHFO Off	25.5±.53	24.7±1.19	*.359*	21.1±.71	18.6±.47	.007	22.7 (19.5 - 25.4)
CHFO On	7.0±.20	7.3±.20	*. 179*	4.8±.22	3.5±.10	.001	6.0 (3.9 - 7.2)
P	<.001	.001		<.001	<.001		<.001
VMN placed between ETT and Y-piece: CHFO On	14.0±.47	12.6±.93	*.080*	10.0±.26	5.5±.44	<.001	11.1 (7.0 - 13.7)
***P*[a]**	<.001	.008		<.001	.013		.002
***P*[b]**	<.001	<.001		<.001	<.001		<.001
JN Manifold: CHFO On							
Salter lab	1.8±.21	1.2±.46	*.133*	.8±.06	.8±.05	.539	1.0 (.8 - 1.7)
AirLife	1.4±.20	1.6±.30	*.481*	N/A	N/A	N/A	N/A
***P*[c]**	<.001	<.001		<.001	.003		<.001

[a] comparison between VMN placed at the inlet of humidifier vs placed at the ETT and Y-piece with CHFO on

[b] comparison between VMN placed at the inlet of humidifier with CHFO off vs placed at the ETT and Y-piece with CHFO on

[c] comparison between VMN placed at the ETT and Y-piece with CHFO on and Salter lab JN at manifold with CHFO on

VMN=Vibrating mesh nebulizer, CHFO=Continuous high frequency oscillation, JN=Jet nebulizer, ETT=Endotracheal tube.



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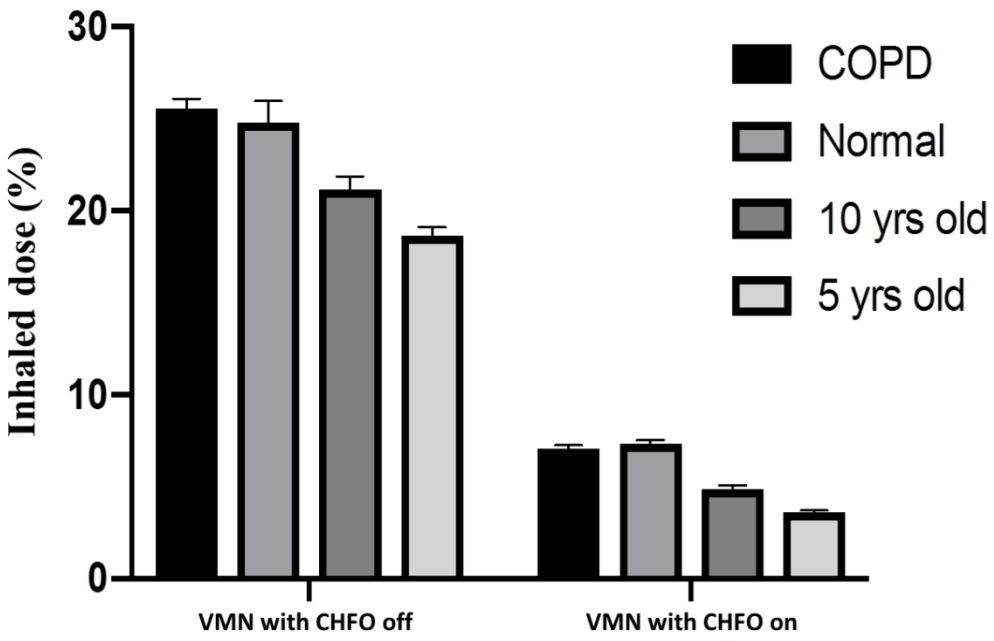

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