Aerosol Delivery via Continuous High-Frequency Oscillation During Mechanical Ventilation

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BACKGROUND: As the use of continuous high-frequency oscillation 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 that simulated 2 adult and 2 pediatric conditions. A continuous high-frequency oscillation device 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 placed between the ETT and the ventilator circuit versus at the inlet of the humidifier. Albuterol (2.5 mg in 3 mL) was nebulized for each condition (no. = 3). The drug was eluted from the collection filter and assayed with ultraviolet spectrophotometry (276 nm). RESULTS: During continuous high-frequency oscillation, the mean inhaled dose with jet nebulizers was low (<2% with the adult settings and <1% with the pediatric settings). Across both adult and pediatric conditions, when the vibrating mesh nebulizer was placed between the ETT and the Y-piece during continuous high-frequency oscillation, the inhaled dose was higher than with the placement of the vibrating mesh nebulizer at the inlet of the humidifier, median 11.1% (IQR 7.0%–13.7%) median 6.0% (IQR 3.9%–7.2%) (*P* = .002) respectively, but still lower than the inhaled dose with the vibrating mesh nebulizer placed at the inlet of the humidifier with continuous high-frequency oscillation off, median 22.7% (IQR 19.5%–25.4%) versus median 11.1% (IQR 7.0%–13.7%) (*P* < .001). The inhaled dose with the 10-year-old scenario was higher than with the 5-year-old scenario in all settings except aerosol delivery via continuous high-frequency oscillation. CONCLUSIONS: During invasive mechanical ventilation with continuous high-frequency oscillation, aerosol delivery with jet nebulizers in the manifold resulted in a marginal inhaled dose. The vibrating mesh nebulizer at the ETT during continuous high-frequency oscillation delivered 6-fold more aerosol than did the jet nebulizer, while delivering only half of the inhaled dose with the vibrating mesh nebulizer placed at the inlet of the humidifier without continuous high-frequency oscillation. *Key words: Continuous high-frequency oscillation; aerosol delivery; mechanical ventilation; vibrating mesh nebulizer; jet nebulizer.* [Respir Care 2022;67(4):415–420. © 2022 Daedalus Enterprises]

Introduction

The MetaNeb (Hillrom, Batesville, Indiana) is a continuous high-frequency oscillation 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] Continuous high-frequency oscillation mobilizes secretions by administering high-frequency mini bursts of air to the lungs, which promotes the upward (cephalad) movement of secretions.[4] Simultaneously, the device can deliver aerosolized medications through its integrated jet nebulizer (Salter Labs, Salt Lake City, Utah),[5] positioned in the manifold. Concurrent delivery of aerosolized medications with continuous high-frequency oscillation could be advantageous; however, aerosol deposition may be highly variable.[6]

We recently reported an in vitro study during simulated spontaneous breathing in an adult model with continuous high-frequency oscillation when using the integrated jet nebulizer and another common jet nebulizer placed in the manifold per label, the inhaled dose was < 2%, whereas the inhaled dose increased to 3% when the jet nebulizers were moved between the manifold and the manikin.[7] This finding is similar to the results in the 2 in vivo studies among healthy volunteers implemented by Reychler et al,[8,9] who used a similar device, called intrapulmonary percussive ventilation (IPV) (Percussionaire, Sandpoint, Idaho). Continuous high-frequency oscillation 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]

With this continuous high-frequency oscillation 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 an endotracheal tube (ETT). Recently, Karashima et al[10] compared aerosol delivery with IPV placed in line with a ventilator and standalone in an adult intubation model; regardless of the device setups or ventilator settings, aerosol deposition at the end of ETT ranged from 2% to 3%. The MetaNeb device is also commonly used in both adult and pediatric patients,[5] but data on aerosol deposition with continuous high-frequency oscillation during invasive ventilation are still lacking. Thus, we aimed to assess the performance of aerosol delivery via the continuous high-frequency oscillation device during adult and pediatric mechanical ventilation to test our hypothesis that aerosol delivery efficiency would be similar to previous findings when using a mask with simulated spontaneous breathing.

QUICK LOOK

Current knowledge

Continuous high-frequency oscillation has been used in in-patient clinical settings due to its reported benefits in mobilization of secretions and lung expansion. In the ICU, continuous high-frequency oscillation device are 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 continuous high-frequency oscillation device with its integrated jet nebulizer resulted in low aerosol deposition during adult and pediatric simulated mechanical ventilation. Placement of a vibrating mesh nebulizer between the endotracheal tube and the Y-piece improved aerosol deposition during continuous high-frequency oscillation.

Methods

A critical care ventilator (PB 840, Medtronic, Minneapolis, Minnesota) with an active heated humidification system and a 22-mm inner diameter heated wire circuit (Fisher & Paykel, Auckland, New Zealand) was attached to an ETT with a collection filter (Respirgard 303, CareFusion, San Diego, California), which was placed at the distal tip of the ETT. The filter was attached to a test lung (TTL, Michigan Instruments, Grand Rapids, Michigan) with compliance and resistance set per test scenarios, with adult (COPD and normal) and pediatric (20 kg and 30 kg) settings[2,12,13] applied (Table 1). The sizes for the Shiley ETTs (Medtronic) were 8.0 mm inner diameter for adults, 6.0 mm for the 30-kg child, and 5.0 mm for the 20-kg child. The MetaNeb circuit and manifold were connected between the inspiratory limb and the Y-piece by using a "T" adapter per manufacturer recommendations.[4] MetaNeb device settings were set to deliver high-frequency oscillation with high flow (Fig. 1).

Albuterol powder (1.0 g) (Sigma-Aldrich, St Louis, Missouri) was mixed with 1,200 mL of sterile water to form a concentration of 0.83 mg/mL. For each of the nebulization treatments (no. = 3), 3 mL (2.5 mg) of albuterol solution was administered. After nebulization ended, the collection filter was removed and rinsed with 10 mL of solution (20% ethanol with 0.1 M 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 ETT to avoid the risk of non-aerosols reaching it. The sample was then analyzed with ultraviolet spectrophotometry (276 nm).

The MetaNeb device was designed to use a Salter Lab jet nebulizer positioned in the device manifold (per manufacturer label). Inhaled dose was compared with that delivered with another disposable jet nebulizer (AirLife 002446, CareFusion) operated at the same manifold position. Both jet nebulizers were gently tapped at the onset of sputter until no aerosol was generated for at least 1 min. A vibrating mesh nebulizer (Aerogen Solo, Aerogen, Galway, Ireland) was placed between the ETT and the Y-piece of

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Table 1. Adult and Pediatric Scenarios Mechanical Ventilation Settings

Setting	Normal Adult (70 kg)	Adult With COPD (70 kg)	Pediatric, Age 10 y (30 kg)	Pediatric, Age 5 y (20 kg)
Respiratory resistance, cm H_2O/L/s	5	20	20	20
Respiratory compliance, mL/cm H_2O	60	100	40	25
Mechanical ventilation mode	PRVC	PRVC	PRVC	PRVC
Tidal volume, mL	420	420	180	120
Breathing frequency, breaths/min	16	16	15	20
Inspiratory time, s	1.0	1.0	1.0	0.75
PEEP, cm H_2O	8	8	5	5
MetaNeb continuous high-frequency oscillation device settings	High frequency/high flow	High frequency/high flow	High frequency/high flow	High frequency/high flow
ETT inner diameter, mm	8.0	8.0	6.0	5.0

PRVC = pressure regulated volume control,
ETT = endotracheal tube.

the ventilator circuit when using a 15-mm T-piece, and at the inlet of the humidifier when using a 22-mm adapter, when aerosol was administered with and without continuous high-frequency oscillation. Vibrating mesh nebulizer was run until the aerosol was not visible.

Statistical Analysis

In this study, the inhaled dose was calculated as the percentage of albuterol captured by the collection filter to the nominal dose and expressed as mean ± SD or median (interquartile range [IQR]) for each experiment (no. = 3), depending on the distribution of the variables. The Kolmogorov-Smirnov test was used to test the normality of distribution for the considered variables. The independent *t* test or the Mann Whitney test was used to compare the inhaled dose between devices under each scenario and overall comparison. $P < .05$ was considered to be statistically significant. Data analysis was conducted with SPSS 23.0 (SPSS, Chicago, Illinois).

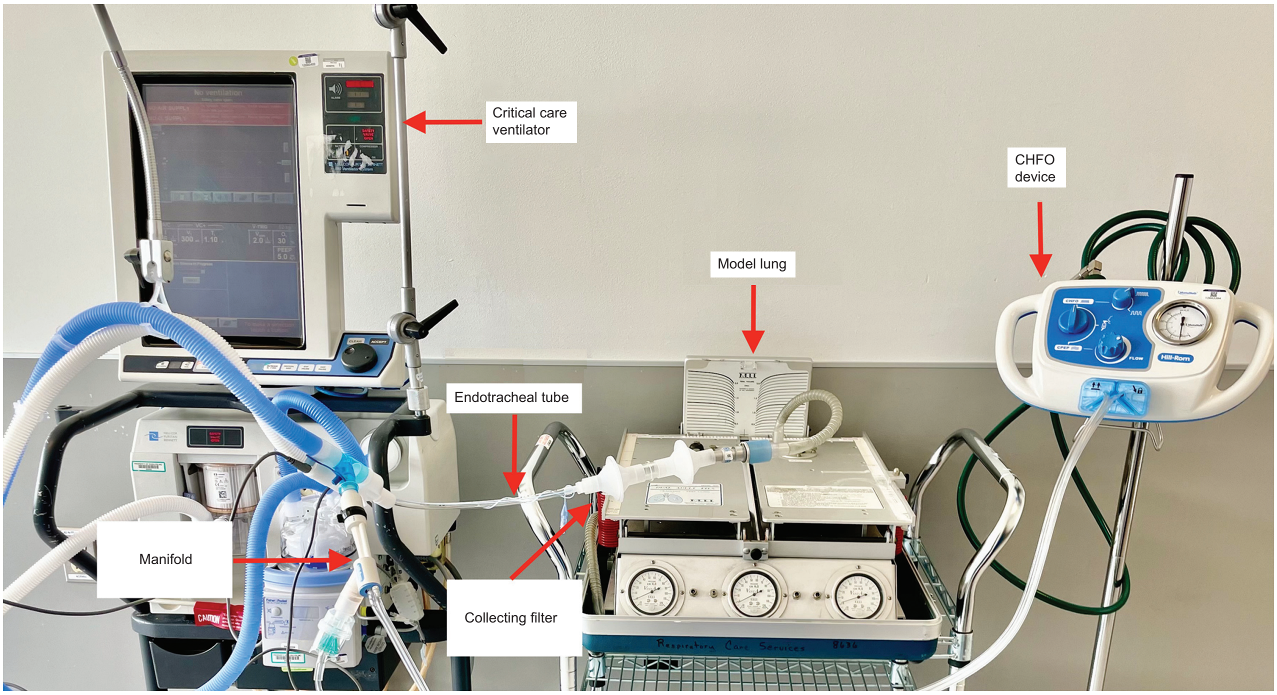

Fig. 1. Experimental setup illustrating the delivery of continuous high-frequency oscillation (CHFO) through mechanical ventilation. A collection filter was placed between the model lung and the endotracheal tube (ETT). The CHFO device circuit and manifold was connected between the ventilator inspiratory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

Table 2. Inhaled Dose, VMN Placed at the Inlet of the Humidifier and Between the ETT and the Y-Piece, and 2 Jet Nebulizers Operated at the Manifold with CHFO on vs CHFO off During Invasive Ventilation

Parameter	Adult COPD, %	Adult Normal %	*P*	Age 10 y (30 kg), %	Age 5 y (20 kg), %	*P*	Overall
VMN placed at the inlet of the humidifier:							
CHFO off	25.5 ± 0.53	24.7 ± 1.19	.36	21.1 ± 0.71	18.6 ± 0.47	.007	22.7 (19.5–25.4)
CHFO on	7.0 ± 0.20	7.3 ± 0.20	.18	4.8 ± 0.22	3.5 ± 0.10	.001	6.0 (3.9–7.2)
P	<.001	.001		<.001	<.001		<.001
VMN placed between the ETT and the Y-piece							
CHFO on	14.0 ± 0.47	12.6 ± 0.93	.08	10.0 ± 0.26	5.5 ± 0.44	<.001	11.1 (7.0–13.7)
*P**	<.001	.008		<.001	.01		.002
P†	<.001	<.001		<.001	<.001		<.001
Jet nebulizer manifold: CHFO on							
Salter Lab	1.8 ± 0.21	1.2 ± 0.46	.13	0.8 ± 0.06	0.8 ± 0.05	.54	1.0 (0.8–1.7)
AirLife	1.4 ± 0.20	1.6 ± 0.30	.48	NA	NA	NA	NA
P‡	<.001	<.001		<.001	.003		<.001

Data are presented as mean ± SD and median (IQR).
*Comparison between the VMN placed at the inlet of the humidifier vs placed at the ETT and the Y-piece with CHFO on.
†Comparison between the VMN placed at the inlet of the humidifier with CHFO off vs placed at the ETT and Y-piece with CHFO on.
‡Comparison between the VMN placed at the ETT and Y-piece with CHFO on and Salter Lab the jet nebulizer at manifold with CHFO on.
ETT = endotracheal tube
CHFO = continuous high-frequency oscillation
VMN = vibrating mesh nebulizer
NA = not applicable
IQR = interquartile range

Results

With the continuous high-frequency oscillation mode on, by using the integrated jet nebulizer provided by the manufacturer, the mean inhaled dose was < 2% for both adult scenarios and < 1% in both pediatric scenarios. When the vibrating mesh nebulizer was placed at the inlet of the humidifier, the inhaled dose was higher versus that with the jet nebulizer, median 6.0% (IQR 3.9%–7.2%) versus median 1.0% (IQR 0.8%–1.7%) $P < .001$; whereas it was still lower versus the inhaled dose with a vibrating mesh nebulizer placed between the ETT and the Y-piece, median 6.0% (IQR 3.9%–7.2%) versus median 11.1% (IQR 7.0%–13.7%); $P = .002$ (Table 2).

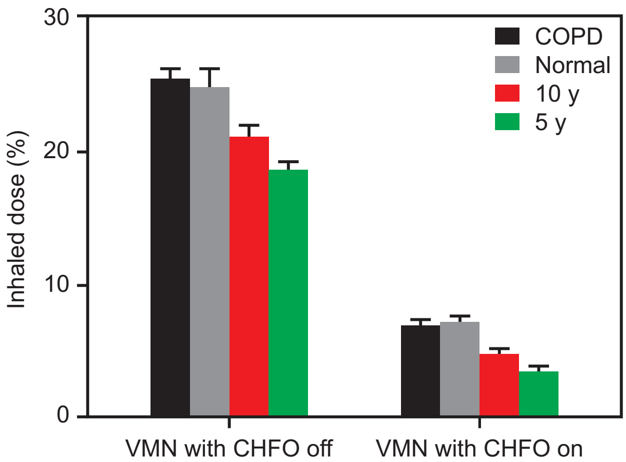

Fig. 2. Inhaled doses (mean ± SD) for the adult (COPD and normal) and pediatric (ages 10 y and 5 y) settings with the vibrating mesh nebulizer (VMN) placed at the inlet of the humidifier during mechanical ventilation with the continuous high-frequency oscillation (CHFO) off and on. The inhaled dose was higher in all the scenarios with the CHFO off compared with the CHFO on, and inhaled dose was higher with the adult than pediatric settings.

In contrast, with the continuous high-frequency oscillation off, the vibrating mesh nebulizer placed at the inlet of the humidifier delivered 3-fold more aerosol versus the same position with the continuous high-frequency oscillation on, median 22.7% (IQR 19.5%–25.4%) versus median 6.0% (IQR 3.9%–7.2%) ($P < .001$) (Fig. 2), and had an inhaled dose increase of 2 times more versus the vibrating mesh nebulizer placed between the ETT and Y-piece with continuous high-frequency oscillation on, median 22.7% (IQR 19.5%–25.4%) versus median 11.1% (IQR 7.0%–13.7%); $P < .001$. With the adult mechanical ventilation settings, no significant differences of the inhaled dose were found between the COPD and normal adult scenarios, whereas, with pediatric settings, the inhaled dose with the 10-year-old child scenario was higher than that with the 5-year-old child scenario, except with the integrated jet nebulizer with the continuous high-frequency oscillation mode on (Table 2).

Discussion

In our study, we found that jet nebulizers in the manifold delivered marginal doses of <2% for both simulated adult and pediatric models, which are likely not clinically efficacious. These findings were consistent with our previous report of marginal inhaled dose achieved in an adult model of spontaneous breathing with the same continuous high-frequency oscillation device and jet nebulizers.[7] In that study, the inhaled dose with jet nebulizers placed in the manifold during quiet breathing was ~2%.[7] This supports the hypothesis that the manifold design generates sufficient turbulence that causes the majority of the aerosol emitted by the jet nebulizers to be impacted before reaching the patient's airway. In the earlier study, when the integrated jet nebulizer (Salter Lab) was placed between the manifold and the manikin airway, the inhaled dose marginally increased, to 2.3%, during continuous high-frequency oscillation; conversely, the jet nebulizer with an aerosol mask and without continuous high-frequency oscillation delivered 8.0%.[7] These results of a lower inhaled dose with continuous high-frequency oscillation than with a jet nebulizer alone aligned with the findings when using IPV, that aerosol delivery with IPV was only one fourth to one half of that with a jet nebulizer alone.[8-11]

In contrast, placement of the vibrating mesh nebulizer between the ETT and the Y-piece delivered 7 times more inhaled dose than both jet nebulizers with continuous high-frequency oscillation. However, when the vibrating mesh nebulizer was placed at the inlet of the humidifier without continuous high-frequency oscillation, the inhaled dose was similar to previous reports of inhaled dose during continuous mechanical ventilation[14] and 3 times greater than when continuous high-frequency oscillation was applied across both adult and pediatric scenarios. Berlinski and Willis[11] found that, when IPV was placed between the ETT and the Y-piece, the inhaled dose was comparable with that with the jet nebulizer alone placed at the same position. Although we did not study aerosol delivery with the jet nebulizer alone placed at the ETT and Y-piece, when considering that the vibrating mesh nebulizer is more efficient in aerosol delivery than a jet nebulizer and aerosol deposition is higher with vibrating mesh nebulizer placed at the inlet of humidifier than when placed at the ETT and Y-piece,[11] we speculate that the turbulence created at the circuit-ETT interface during continuous high-frequency oscillation increased impactive losses for the aerosol passing through the ventilator circuit. The reduction of the inhaled dose with the addition of continuous high-frequency oscillation provides insights into 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 an in vitro report by Fang et al[15] during high-frequency oscillation ventilation, which demonstrated that both the jet nebulizer and the vibrating mesh nebulizer delivered a higher inhaled dose with the nebulizer placed between the ETT and the Y-piece compared with a negligible inhaled dose with the nebulizer placed at the inlet of the humidifier.

In our study, the presence of mechanical ventilation did not seem to further reduce the inhaled dose of aerosol during continuous high-frequency oscillation compared with administration during spontaneous breathing. Turbulent breathing patterns, when added to the effect of the MetaNeb continuous high-frequency oscillation device, may also alter aerosol delivery by producing impaction in different parts of the ventilator circuit, in the ETT, and, potentially, in the trachea.[16] We expected that the combination of the turbulent flow of the MetaNeb continuous high-frequency oscillation device 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 by using a 90° 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 seems that the placement of the jet nebulizer in the manifold of the MetaNeb circuit was the primary factor that reduced the inhaled dose during mechanical ventilation.

In addition, changes in airway resistance and lung compliance as used to differentiate normal adult and COPD conditions did not significantly impact aerosol deposition during continuous high-frequency oscillation. This is likely because, with continuous nebulization, the cumulative inspiratory time per minutes is a better predictor of the inhaled dose than moderate changes in compliance and resistance of the test lung. Consequently, analysis of our findings suggests that the most efficient method to deliver inhaled medications during mechanical ventilation with continuous high-frequency oscillation was with the vibrating mesh nebulizer placed between the ETT and the Y-piece. Other options for aerosol delivery during mechanical ventilation alongside continuous high-frequency oscillation may include in-line drug delivery via pressurized metered-dose inhaler with an appropriate connecter.[16] Further confirmatory studies are needed to evaluate these options.

Clinical Implication

Analysis of our findings suggests that the continuous high-frequency oscillation device integrated with a mechanical ventilator to deliver aerosolized medication did not generate a clinically relevant inhaled dose. The MetaNeb continuous high-frequency oscillation 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 the jet nebulizer or the vibrating mesh nebulizer during mechanical ventilation without continuous high-frequency oscillation, thus, it should be used to nebulize medications before or after continuous high-frequency oscillation therapy if clinically indicated. If there is a need to provide aerosolized medication during secretion clearance, such as hypertonic saline solution or other mucoactive agents, placement of a vibrating mesh nebulizer between the ETT and the Y-piece during continuous high-frequency oscillation might be a satisfactory alternative. Further studies are warranted to confirm the clinical benefits of such concomitant therapy.

Limitations of the Study

Our study used an in vitro model of mechanical ventilation by using ETT 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 the 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 with in vivo studies in which some portion of inhaled aerosol is exhaled. We also limited the setting for continuous high-frequency oscillation 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.

Conclusions

Aerosol deposition via the MetaNeb continuous high-frequency oscillation device with its integrated nebulizer during mechanical ventilation was $< 2\%$ for both adult and pediatric simulated scenarios; in-line placement of a vibrating mesh nebulizer between the ETT and the Y-piece improved aerosol delivery during continuous high-frequency oscillation to a clinically relevant dose. Further in vivo studies are recommended to confirm our findings and to evaluate aerosol deposition with continuous high-frequency oscillation.

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REFERENCES

1. Ortiz-Pujols S, Boschini LA, Klatt-Cromwell C, Short KA, Hwang J, Cairns BA, Jones SW. Chest high-frequency oscillatory treatment for severe atelectasis in a patient with toxic epidermal necrolysis. J Burn Care Res 2013;34(2):e112-e115.
2. Morgan S, Hornik CP, Patel N, Williford WL, Turner DA, Cheifetz IM. Continuous high-frequency oscillation therapy in invasively ventilated pediatric subjects in the critical care setting. Respir Care 2016;61(11):1451-1455.
3. Ferguson A, Wright S. Innovative chest physiotherapy techniques (the MetaNeb® System) in the intubated child with extensive burns. Respir Med Case Rep 2017;22:232-234.
4. Hillrom. MetaNeb system brochure (2021). https://www.hillrom.com/content/dam/hillrom-aem/us/en/marketing/products/metaneb-system/documents/209300-EN-r3_MetaNeb-Vest-205_Brochure-LR.pdf. *Accessed April 20, 2021.*
5. Food and Drug Administration (FDA). MetaNeb 510(k) summary (K151689) (2016). Silver Spring, Maryland: FDA. https://www.accessdata.fda.gov/cdrh_docs/pdf15/K151689.pdf. *Accessed June 20, 2019.*
6. Kallet RH. Adjunct therapies during mechanical ventilation: airway clearance techniques, therapeutic aerosols, and gases. Respir Care 2013;58(6):1053-1073.
7. Li J, Elshafei AA, Gong L, Fink JB. Aerosol delivery during continuous high frequency oscillation for simulated adults during quiet and distressed spontaneous breathing. Respir Care 2020;65(2):227-232.
8. Reychler G, Keyeux A, Cremers C, Veriter C, Rodenstein DO, Liistro G. Comparison of lung deposition in two types of nebulization: intrapulmonary percussive ventilation vs jet nebulization. Chest 2004;125(2):502-508.
9. Reychler G, Wallemacq P, Rodenstein DO, Cumps J, Leal T, Liistro G. Comparison of lung deposition of amikacin by intrapulmonary percussive ventilation and jet nebulization by urinary monitoring. J Aerosol Med 2006;19(2):199-207.
10. Karashima T, Mimura-Kimura Y, Miyakawa K, Nakamura A, Shimahara F, Kamei H, Mimura Y. Variations in the efficiency of albuterol delivery and intrapulmonary effects with differential parameter settings on intrapulmonary percussive ventilation. Respir Care 2019;64(5):502-508.
11. Berlinski A, Willis JR. Albuterol delivery via intrapulmonary percussive ventilator and jet nebulizer in a pediatric ventilator model. Respir Care 2010;55(12):1699-1704.
12. Arnal J-M, Garnero A, Saoli M, Chatburn RL. Parameters for simulation of adult subjects during mechanical ventilation. Respir Care 2018;63(2):158-168.
13. Hess D. Respiratory mechanics in mechanically ventilated patients. Respir Care 2014;59(11):1773-1794.
14. Ari A, Areabi H, Fink JB. Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. Respir Care 2010;55(7):837-844.
15. Fang T-P, Chen Y-J, Yang T-M, Wang S-H, Hung M-S, Chiu S-H, et al. Optimal connection for tiotropium SMI delivery through mechanical ventilation: an in vitro study. Pharmaceutics 2020;12(3):291-299.
16. Dugernier J, Ehrmann S, Sottiaux T, Roeseler J, Wittebole X, Dugernier T, et al. Aerosol delivery during invasive mechanical ventilation: a systematic review. Crit Care 2017;21(1):264-274.