# Aerosol Delivery During Continuous High Frequency Oscillation for Simulated Adults During Quiet and Distressed Spontaneous Breathing

Jie Li, Ahmad A Elshafei, Lingyue Gong, and James B Fink

**BACKGROUND: Continuous high-frequency oscillation (CHFO) is a therapeutic mode for the mobilization of secretions. The Metaneb CHFO device also incorporates aerosol administration using an integrated jet nebulizer. However, the effectiveness of aerosol delivery and influential factors remain largely unreported. METHODS: A collecting filter was placed between an adult manikin with a representative upper airway and a breath simulator, set to simulate quiet and distressed patterns of spontaneous adult breathing. The Metaneb CHFO device was attached to the manikin via a mask. Two jet nebulizers were tested in 2 different positions: placement in the manifold and placement between manifold and mask. A vibrating mesh nebulizer was placed between the manifold and mask with and without extension tubing. Aerosol administration was compared during CHFO and during nebulization mode alone. Albuterol (2.5 mg in 3 mL) was nebulized for each condition. The drug was eluted from the filter and assayed with ultraviolet spectrophotometry (276 nm). RESULTS: During CHFO, inhaled doses with jet nebulizers were low (~ 2%), regardless of nebulizer placement. Inhaled dose was improved with the vibrating mesh nebulizer placed between the manifold and mask (12.48 ± 2.24% vs 2.58 ± 0.48%, $P = .004$). Inhaled doses with the jet nebulizer in the manifold with nebulization mode alone was lower than with the jet nebulizer with an aerosol mask (4.03 ± 1.82% vs 10.39 ± 2.79%, $P = .004$). Inhaled dose was greater with distressed breathing than quiet breathing. The use of a vibrating mesh nebulizer ($P < .001$) and distressed breathing ($P = .001$) were identified as predictors of increased inhaled dose. CONCLUSIONS: Inhaled dose with a jet nebulizer via the Metaneb CHFO device was lower than with a jet nebulizer alone. Placement of a vibrating mesh nebulizer at the airway and distressed breathing increased inhaled dose.** *Key words: Continuous high-frequency oscillation; inhaled dose; inhalation therapy; vibrating mesh nebulizer.* [Respir Care 2020;65(2):227–232. © 2020 Daedalus Enterprises]

## Introduction

Continuous high-frequency oscillation (CHFO) of the airway is a pneumatically generated mode of positive airway pressure, purported to deliver small bursts of subphysiologic volumes to the airway.[1] CHFO has been reported to improve secretion clearance and lung expansion.[2-4] The Metaneb (Hill-Rom, Batesville, Indiana) is a CHFO device that also delivers continuous positive expiratory pressure[5] and continuous aerosol using a jet nebulizer (Salter Labs, Salt Lake City, Utah), which is integrated into the device manifold. Aerosol can be administered alone (ie, nebulization mode), or in CHFO or continuous positive expiratory pressure mode. This combination of simultaneous medical aerosol administration and secretion clearance treatment is intended to create synergy with the two treatments and to reduce the time re-

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quired to administer serial therapies. As such, it is a common clinical practice to provide aerosolized medication via CHFO. However, the delivery efficiency of aerosol with CHFO has not been well reported, with early reports suggesting that the efficiency may be far less than administration with standard nebulizers alone. Because little is known about the influential factors on the effectiveness of aerosol delivery using the Metaneb device with CHFO, we aimed to quantify inhaled aerosol delivery and to investigate the influential factors that might improve the aerosol delivery with CHFO administration in spontaneously breathing adults.

## Methods

### Experimental Setup

An adult manikin (Laerdal adult airway management trainer, Stavanger, Norway), with size-appropriate airway anatomy including tongue, pharynx, larynx, chordae vocals, and trachea, was attached to one of the 2 chambers of a test lung (TTL, Michigan Instruments, Grand Rapids, Michigan), and the other chamber was connected to a critical care ventilator (Dräger Evita XL, Dräger, Germany). The 2 chambers were connected via a rigid metal piece that made both chambers move together. As such, the ventilator directly inflated one chamber, functioning as respiratory muscle to simulate spontaneous breathing in the other chamber, which was attached to the manikin (Fig. 1). A monitor (NICO2, Respironics, Murrysville, Pennsylvania) was placed between the manikin's trachea and the chamber to verify tidal volume ($V_T$). Based on the feedback from the NICO2 monitor, ventilator settings were adjusted to achieve the target breathing profiles. A collecting filter (Respirgard 303, CareFusion, Yorba Linda, California) was placed between the manikin's trachea and the chamber, with an additional filter placed behind the collecting filter to protect the model lung. Instead of using a mouthpiece, the Metaneb device was connected to the manikin using a resuscitation mask (CareFusion) with and without 6 inches of corrugated tubing (22-mm inner diameter). The resuscitation mask was firmly sealed to the manikin face using a rubber strap system (King Systems, Noblesville, Indiana) (Fig. 1). The Metaneb device was set at high-frequency oscillation with low flow.

Albuterol powder (1.0 g, Sigma-Aldrich, St Louis, Missouri) was reconstituted with 1,200 mL sterile water for a concentration of 0.83 mg/mL; 3 mL of 2.5 mg albuterol was nebulized for each condition. The nebulizer cup was gently tapped for both jet nebulizers until no aerosol was generated for at least 1 min. After nebulization, the filter was removed and eluted with 10 mL solution (20% ethanol with 0.1 M HCl), which was assayed with ultraviolet spectrophotometry (276 nm).

**QUICK LOOK**

**Current knowledge**

Continuous high-frequency oscillation (CHFO) has been reported to possibly improve secretion clearance and lung expansion. The CHFO device also incorporates aerosol administration using an integrated jet nebulizer. It is a common clinical practice to provide aerosolized medication via CHFO.

**What this paper contributes to our knowledge**

Little inhaled dose (~ 2%) was delivered using the jet nebulizer marketed with the CHFO device, which was lower than the inhaled dose (~ 10%) with a standard jet nebulizer and aerosol mask. In-line placement of a vibrating mesh nebulizer at the airway and distressed breathing were predictors of increased inhaled dose during CHFO.

### Comparison Among Groups

**Breathing Pattern.** The ventilator was adjusted to produce parameters representing quiet breathing ($V_T$ = 500 mL, breathing frequency = 15 breaths/min, inspiratory-expiratory ratio = 1:3) and distressed breathing ($V_T$ = 700 mL, breathing frequency = 30, inspiratory-expiratory ratio = 1:1.5), as used in previous published studies.[6,7]

**Nebulizers Utilized During CHFO.** The manufacturer-supplied nebulizer on the Metaneb device was a Salter Labs jet nebulizer positioned in the manifold (per manufacturer label) of the device. Inhaled dose was compared with that delivered with another disposable jet nebulizer (AirLife 002446, CareFusion, Yorba Linda, California) at the manifold position (Fig. 2A). A vibrating mesh nebulizer (Aerogen Solo, Aerogen, Galway, Ireland) was utilized to deliver aerosol with placement between the mask and manifold.

**Nebulizer Placement Outside the Manifold During CHFO.** The manufacturer-supplied Salter Labs jet nebulizer was placed between mask and manifold, with the nebulizer port capped (Fig. 2B), and aerosol delivery at this position was compared with the manifold position. The vibrating mesh nebulizer was placed directly at the mask (Fig. 2C) and connected by a 6-inch section of corrugated tubing (22-mm inner diameter) (Fig. 2D).

**Nebulization Without CHFO.** The Metaneb device was set at the nebulization-only mode to deliver aerosol with the Salter Labs jet nebulizer placed in manifold, and inhaled dose was compared to aerosol delivery by the disposable AirLife jet nebulizer with an aerosol mask.

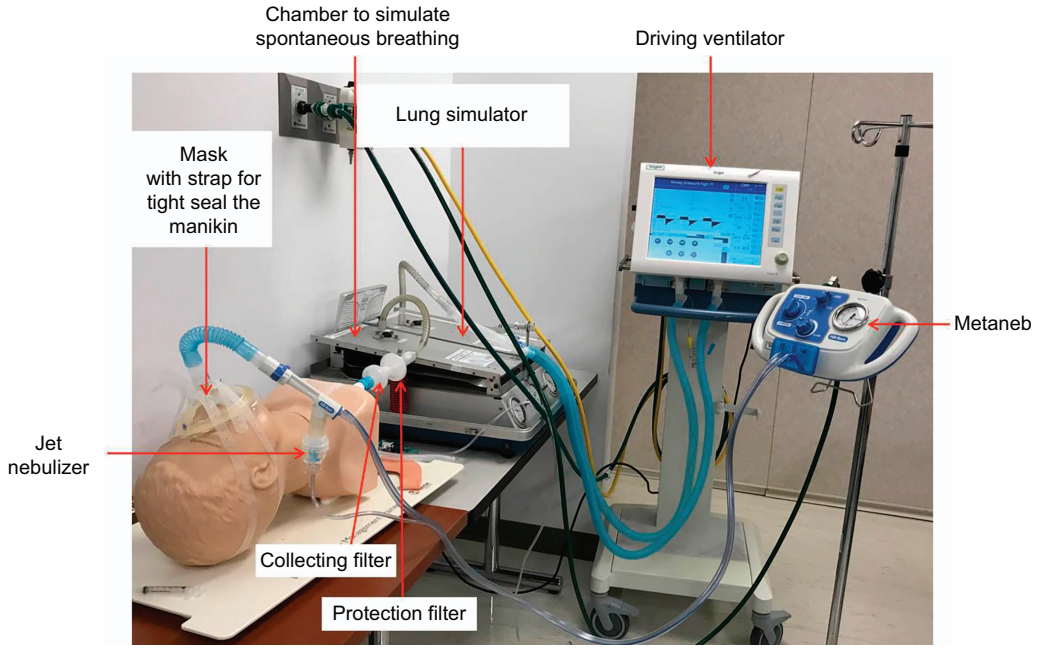


Fig. 1. Experimental setup.

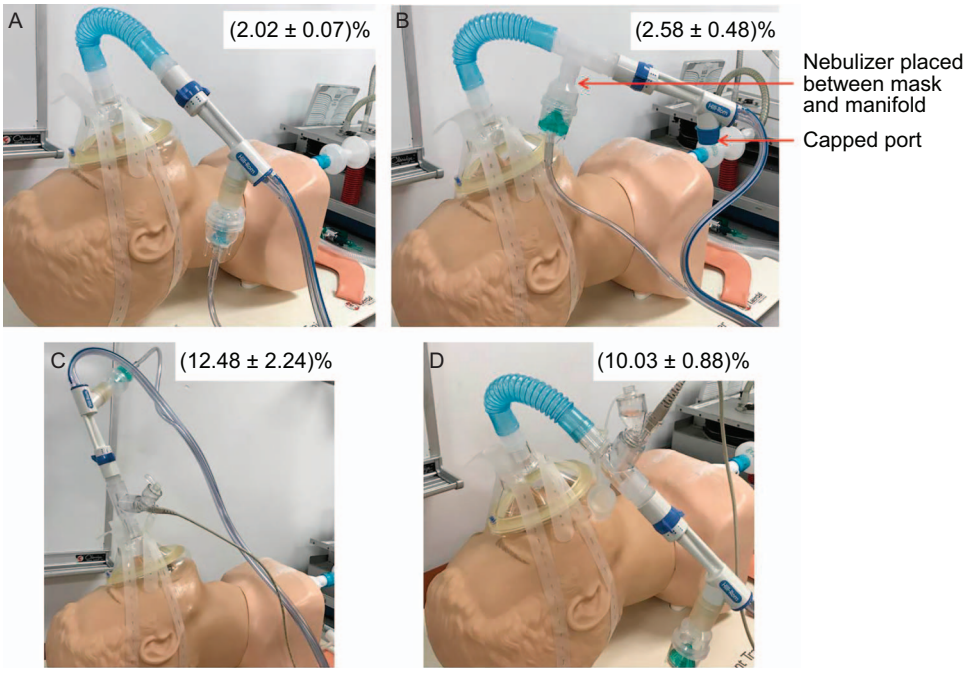


Fig. 2. Nebulizer placement. A: AirLife jet nebulizer placed at the manifold position. B: Salter Labs jet nebulizer placed between the mask and manifold with a capped port. C: Vibrating mesh nebulizer directly attached to the mask. D: Vibrating mask nebulizer placed between the mask and manifold using extension tubing.

### Statistical Analysis

In this study, the inhaled dose was calculated as percentage of the nominal dose and expressed as mean ± SD or median (interquartile range) for each experiment setting, with quiet and distressed breathing using different nebulizers and placement. The Mann-Whitney test was used to compare the inhaled dose with quiet and distressed breathing in each scenario and overall comparison. The Mann-Whitney test was also used to identify the differ-

Table 1. Inhaled Dose in Quiet and Distressed Breathing With Different Nebulizers and Different Placement

| Nebulizer | Placement | Inhaled Dose, % | | | *P* |
|---|---|---|---|---|---|
| | | Overall | Quiet Breathing | Distressed Breathing | |
| Continuous high-frequency oscillation: | | | | | |
| with integrated jet nebulizer (Salter Labs) | Manifold | 2.15 ± .72 | 1.53 ± 0.16 | 2.77 ± 0.36 | .050 |
| with disposable jet nebulizer (AirLife) | Manifold | 2.02 ± .07 | 1.84 ± 0.22 | 2.20 ± 0.12 | .08 |
| with integrated jet nebulizer (Salter Labs) | Between manifold and mask | 2.58 ± .48 | 2.26 ± 0.06 | 2.89 ± 0.53 | .08 |
| with vibrating mesh nebulizer | Between manifold and mask with extension tubing | 10.03 ± .88 | 9.39 ± 0.84 | 10.67 ± 0.12 | .050 |
| with vibrating mesh nebulizer | Directly connected to mask | 12.48 ± 2.24 | 10.45 ± 0.09 | 14.51 ± 0.37 | .050 |
| Nebulization alone with jet nebulizer (Salter Labs) | Manifold | 4.03 ± 1.82 | 2.87 ± 0.28 | 5.19 ± 0.66 | .050 |
| Jet nebulizer (AirLife) with aerosol mask | NA | 10.39 ± 2.79 | 7.95 ± 0.59 | 12.83 ± 1.16 | .050 |
| | | | 2.81 (1.93–8.94) | 5.01 (2.57–12.26) | .030 |

Data are presented as mean ± SD.

ence between vibrating mesh nebulizer and jet nebulizer during CHFO as well as different placement of each nebulizer. Multiple linear regression was used to explore how these factors predict inhaled dose. The bivariate relationship between the inhaled dose and the influential factors was investigated using the Pearson correlation analysis. Based on results from exploratory data analysis using a $P$ value of $< .20$, the variables were entered into a stepwise regression model. A $P$ value of $< .05$ was considered to be statistically significant for all predictor variables. Data analysis was conducted with SPSS 23.0 (SPSS, Chicago, Illinois).

## Results

### Inhaled Dose With Quiet Versus Distressed Breathing

Inhaled doses of albuterol expressed as percentage of the nominal dose (mean ± SD) for all experiments are shown in Table 1. The median (interquartile range) overall inhaled dose with distressed breathing was higher than with quiet breathing at 5.01% (2.57–12.26%) vs 2.81% (1.93–8.94%) ($P = .030$).

### Inhaled Dose With Different Nebulizer and Placement During CHFO

Combining quiet and distressed breathing, inhaled dose (mean ± SD) was similar with the 2 jet nebulizers (AirLife vs Salter Labs) at the manifold position (2.02 ± 0.07% vs 2.15 ± 0.72%, respectively, $P = .94$). When the nebulizer port was capped and the Salter Labs jet nebulizer was connected between the mask and manifold using extension tubing (Fig. 2B), the inhaled dose was slightly improved but not significantly greater than with placement in the manifold (2.58 ± 0.48% vs 2.15 ± 0.72%, respectively, $P = .42$). Placing the vibrating mesh nebulizer at the same position (between manifold and mask with an extension tubing) to deliver aerosol during CHFO (Fig. 2D) resulted in a higher inhaled dose than with the Salter Labs jet nebulizer (10.03 ± 0.88% vs 2.58 ± 0.48%, respectively, $P = .004$). The vibrating mesh nebulizer directly attached to the mask without extension tubing (Fig. 2C) generated a 20% higher inhaled dose (12.48 ± 2.24% vs 10.03 ± 0.88%, $P = .13$).

### Predictors of Inhaled Dose During CHFO

The 3 variables (breathing pattern, nebulizer placement, and nebulizer type) were marginally associated with the inhaled dose ($P < .20$). All of the 3 variables that were entered into the stepwise regression model were significant predictors of inhaled dose. Nebulizer type ($P < .001$) and breathing pattern ($P = .001$) were the independent predictors of increased aerosol delivery. The regression model explained 94.5% of total variance in inhaled dose delivered via CHFO. The regression model for inhaled dose (%) is $Y = (9.01 \times \text{nebulizer type}) + (1.516 \times \text{breathing pattern}) - 0.025$, where for "nebulizer type" the vibrating mesh nebulizer = 1 and the jet nebulizer = 0, and for "breathing pattern" distressed breathing = 1 and quiet breathing = 0. There was no significant collinearity observed (tolerance $> 0.20$, variance inflation factor $< 0.50$).

### Inhaled Dose With Metaneb in Nebulization Mode Alone and Jet Nebulizer With Aerosol Mask

The inhaled dose with the AirLife jet nebulizer with an aerosol mask was greater than that with Metaneb device in nebulization mode alone (10.39 ± 2.79% vs 4.03 ± 1.82%, respectively, $P = .004$).

## Discussion

### Inhaled Dose Through CHFO

The major finding in our study was the suboptimal delivery of aerosol using the nebulizer marketed with the CHFO device, which is integrated in the manifold per manufacturer instruction, raising concerns for the effectiveness of inhaled aerosol with this device.

The most comparable device to the Metaneb may be intrapulmonary percussive ventilation (IPV, Percussionaire, Sandpoint, Idaho),[8] which has a similar functional mechanism. Because there is little data available for Metaneb, the reports characterizing aerosol delivery during IPV might help explain the low deposition we found with the Metaneb device. An in vitro study of aerosol delivery via IPV for invasively ventilated adults found that ~ 2% could be delivered to the end of the endotracheal tube.[9] Similarly, 2 in vivo studies among spontaneously breathing adult subjects reported that only 0.8–2.5% of the nominal dose was delivered into the lung during IPV.[10,11]

The low aerosol delivery efficiency of both IPV and the Metaneb device might be explained by the manifold design, the nebulizer's position in the circuit, and the characteristics of the delivery gas. The reported mass median aerodynamic diameter and the fine-particle fraction for IPV was only 0.2 $\mu$m and 16.2%, respectively, which was in contrast to the 1.89 $\mu$m and 67.5% aerosol generated by the standard Salter Labs jet nebulizer.[10] Similarly, we found that the inhaled dose with the standard jet nebulizer and aerosol mask alone was as high as 10%, but when the same nebulizer was placed at the Metaneb manifold during CHFO, the inhaled dose was reduced to 2%. This result confirms that the mechanics of the CHFO manifold increases the impact-related loss of larger aerosol particles. One of the potential causes might be the manifold design in which aerosol is introduced from the nebulizer into the gas stream through a small orifice, which may be a significant barrier of aerosol delivery. However, when we moved the jet nebulizer from the manifold to between the mask and manifold, the increment in the inhaled dose was not significant. This might be explained by the turbulent flow created by the high frequency and small burst volume ventilation pattern distal the manifold. As for the impact of turbulence in aerosol deposition, the closer of nebulizer to the airway, the higher the inhaled dose that might be achieved. Berlinski and Willis[12] reported that the inhaled dose was higher when IPV was placed closer to endotracheal tube than when placed at the inlet of the humidifier during invasive ventilation. Similarly, we observed that both the jet nebulizer and the vibrating mesh nebulizer tended to generate higher deposition when the nebulizer was placed closer to the airway. In addition to the turbulence in the delivery gas, the additional operating gas flow to the jet nebulizer may also affect aerosol delivery during CHFO due to its continuous flushing effects. This might explain the significant improvement of inhaled dose when the vibrating mesh nebulizer was placed in-line with the CHFO device because the vibrating mesh nebulizer adds no gas flow. The inhaled dose of 10–12% with the vibrating mesh nebulizer is clinically relevant and comparable to the inhaled dose using the standard jet nebulizer administered with aerosol mask. This finding agrees with the in vitro report on high-frequency oscillation ventilation by Fang et al[13] that the vibrating mesh nebulizer delivered higher inhaled dose than the jet nebulizer when the nebulizers were placed between the ventilator circuit and endotracheal tube.

Karashima et al[9] reported that larger $V_T$ increased aerosol delivery during IPV. As expected, distressed breathing increased the inhaled dose, secondary to a longer aerosol inhalation time. This finding also agrees with studies by Réminiac et al[6] and Dailey et al[7] on aerosol delivery via high-flow nasal cannula.

### Clinical Implication

Our findings suggest that use of the CHFO device to deliver aerosolized medication with CHFO or nebulization mode alone could not generate a clinically relevant inhaled dose. CHFO might be beneficial to provide secretion clearance or lung expansion treatment, but the potential benefit of concomitant aerosol therapy is severely limited. If aerosolized medication is clinically indicated, the medication should likely be nebulized before or after CHFO using other free-standing aerosol generators, such as a jet nebulizer, or a vibrating mesh nebulizer. If there is a need to provide combined treatments of aerosolized medication during secretion clearance, such as hypertonic saline or other mucoactive agents,[14] placing a vibrating mesh nebulizer between the mask and the manifold during CHFO might be an acceptable delivery alternative. Further study is needed to confirm the clinical benefits of such a treatment.

In addition to low inhaled dose, the nebulizer carries a risk of contamination from the Metaneb circuit because patient secretions entering the mouthpiece could contaminate the manifold and the nebulizer.[15,16] Moreover, if the device is contaminated, the aerosol will carry the microorganism to the patients. Per the manufacturer's recommendation, the entire circuit only needs to be changed every 7 days, but there is no strict requirement on the cleaning or sterilization of the circuit, except for washing and air-drying the nebulizer after each aerosol dose, which has been reported to be ineffective, especially for cystic fibrosis patients.[17] Currently no data are available on the contamination rates of the Metaneb circuit and how often it requires changing, but it might be reasonable to change

the circuit more frequently for some high-risk patients, such as those with cystic fibrosis or those who are immunocompromised.[14] Considering the high cost of changing the entire circuit, our findings supporting the placement of the vibrating mesh nebulizer between the mask and the manifold offers a feasible option to improve aerosol delivery and avoid contamination of the nebulizer. Future studies are needed to investigate the cost impact of this setup.

### Limitations of the Study

When CHFO treatment is provided for spontaneously breathing patients at the bedside, a mouthpiece is commonly used, and patients are typically seated upright or in a semi-Fowler position. We substituted a mask for the mouthpiece with the manikin in a supine position, using the extension tubing to connect with the Metaneb device. We believe that the use of a mask instead of a mouthpiece would likely not decrease inhaled dose, and the addition of the tubing did not significantly affect inhaled dose. For patients in the supine position (eg, spinal cord injury patients), they would have to receive CHFO treatment using the extension tubing to keep the nebulizer in an upright orientation.

Similar to other in vitro studies, the manikin has grossly proportional airway anatomy but does not have realistic human function, such as the airway cilia-mucosa system, which heats and humidifies the gas passing through the airway and absorbs the medication deposited in the upper airway. Moreover, the manikin only simulates one size of adult patient. Although this in vitro study provides comparative delivery efficiency with variables studied, the results should not be generalized beyond the parameters studied. Further in vivo studies with CHFO are warranted to confirm our findings.

## Conclusions

Aerosol delivery through the Metaneb device during CHFO with the jet nebulizer in the manifold position for a spontaneously breathing adult was lower than that with a jet nebulizer alone. The in-line placement of a vibrating mesh nebulizer between the manifold and airway could improve aerosol delivery to provide a clinically relevant dose.

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