

Effect of Tidal Volume and Nebulizer Type and Position on Albuterol Delivery in a Pediatric Model of Mechanical Ventilation

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BACKGROUND: Optimization of factors affecting aerosol delivery during mechanical ventilation in the pediatric population is important. We hypothesized that increasing the tidal volume (V_T), using a vibrating mesh nebulizer, and placing the nebulizer at the ventilator would increase lung dose/delivery efficiency. **METHODS:** Continuous-output jet and vibrating mesh nebulizers loaded with albuterol (2.5 mg/3 mL) were compared when placed before the Y-piece and at the ventilator. The model consisted of a ventilator operated in pressure-regulated volume control ventilation mode at a breathing frequency of 20 breaths/min, PEEP of 5 cm H_2O , F_{IO_2} of 0.4, inspiratory time of 0.75 s, and bias flow of 0.5 L/min with a humidifier ($37 \pm 1.5^\circ C$) and an adult heated-wired circuit. V_T values of 100, 150, 200, and 300 mL were studied. The circuit was connected in series to a 5.5-mm inner diameter endotracheal tube with a filter (lung dose) interposed between them. Delivery efficiency was calculated as a percentage of the nominal dose captured on the filter. Albuterol content was analyzed by spectrophotometry (276 nm). **RESULTS:** No differences in lung dose/delivery efficiency were found at different VT values for the jet nebulizer (both positions) and the vibrating mesh nebulizer (ventilator). Lung dose/delivery efficiency was higher ($P < .02$) at a V_T of 100 mL compared with the other volumes tested. The vibrating mesh nebulizer had higher lung dose/delivery efficiency compared with the jet nebulizer only when placed before the Y-piece. Moving the nebulizers from before the Y-piece to the ventilator increased lung dose/delivery efficiency for all conditions tested except the vibrating mesh nebulizer at a V_T of 100 mL ($P = .36$). **CONCLUSIONS:** Optimization of inhaled drug delivery during pediatric mechanical ventilation should include careful selection of the type of delivery device and its placement in the ventilator circuit. Increasing V_T during nebulization did not increase lung dose/delivery efficiency. *Key words:* tidal volume; mechanical ventilator; drug delivery; aerosol; jet nebulizer; vibrating mesh nebulizer. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Children receiving invasive mechanical ventilation are frequently prescribed in-line nebulized therapy.^{1,2} Drug

delivery efficiency during mechanical ventilation is affected by several factors.³ Some of them are easy to modify (type of delivery device and position in the circuit), but others are not (endotracheal tube [ETT] size).

Although several types of devices are available, continuous-output jet and vibrating mesh nebulizers are the most

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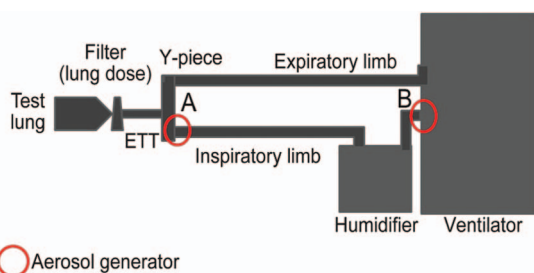


Fig. 1. Experimental setup. Position A is at the inspiratory limb, before the Y-piece, and position B is at the ventilator. ETT = endotracheal tube.

commonly used. The devices can be placed at different positions in the ventilator circuit, with the most commonly used being the inspiratory limb before the Y-piece and at the ventilator.⁴⁻⁹

Drug delivery efficiency data on adult models of mechanical ventilation suggested that higher tidal volume (V_T) resulted in higher lung delivery.^{2,10,11} These results are in agreement with data generated using models of spontaneously breathing children and adults.^{12,13} This information led to the practice of increasing V_T or providing sigh breaths during nebulization.² Previous research using a pediatric model of mechanical ventilation with a jet nebulizer,⁶ and a clinical study in adults,¹⁴ had opposite findings. We hypothesized that increasing the V_T , using a vibrating mesh nebulizer, and placing the nebulizer at the ventilator would increase lung dose and drug delivery efficiency in a pediatric model of mechanical ventilation.

Methods

Mechanical Ventilation Model

This model was similar to one previously published, except we used a lower bias flow (Fig. 1).^{6,7} The model consisted of a ventilator (Servo-i, Maquet, Solna, Sweden) operated in pressure-regulated volume control ventilation mode at a breathing frequency of 20 breaths/min, PEEP of 5 cm H_2O , F_{IO_2} of 0.4, inspiratory time of 0.75 s, and bias flow of 0.5 L/min with a humidifier ($37 \pm 1.5^\circ C$). The following V_T values were studied: 100, 150, 200, and 300 mL. An adult heated-wired circuit (1.83 m long, 22-mm inner diameter [ID]; Evaqua, Fisher & Paykel Healthcare, Auckland, New Zealand) was used. The circuit was connected in series to a 5.5-mm ID cuffed ETT (Mallinckrodt Lo-Pro, Covidien, Pleasanton, California) and a test lung (SmartLung, 600 mL, imtmedical, Buchs, Switzerland) with a low-volume filter holder interposed between them. A new respiratory filter (PARI Respiratory Equipment, Midlothian, Virginia) was used for each run. The cuff was inflated to provide a closed circuit.

QUICK LOOK

Current knowledge

The efficiency of aerosol delivery in pediatric patients is impacted by the type of nebulizer and position in the circuit, ventilator settings, bias flow, breathing pattern, and size of the artificial airway. The optimum position for different types of nebulizers may be different.

What this paper contributes to our knowledge

In a lung model, optimization of inhaled drug delivery during simulated pediatric mechanical ventilation should include careful selection of the type of delivery device and placement in the ventilator circuit. Placement of the nebulizer before the humidifier increased lung dose and delivery efficiency in a pediatric model with low bias flow. Increasing tidal volume did not result in an increase in lung dose or delivery efficiency. Vibrating mesh nebulizers had higher lung dose and delivery efficiency compared with continuous-output jet nebulizers when placed before the Y-piece, but not when placed at the ventilator.

Devices

Four new units of a continuous-output jet nebulizer (Up-Draft II Opti-Neb, Hudson RCI/Teleflex Medical, Research Triangle Park, North Carolina) and a vibrating mesh nebulizer (Aeroneb Solo, Aerogen, Galway, Ireland) were tested (Fig. 2). The jet nebulizer was connected to the circuit with a spring-loaded T-piece (AirLife Valved Tee adapter, Thayer Medical, Tucson, Arizona), and the vibrating mesh nebulizer was connected with its proprietary T-piece adapter. Ventilator settings were adjusted during jet nebulization to compensate for the increase in flow, but no changes were required during vibrating mesh nebulization.¹⁵ The devices were placed in the inspiratory limb before the Y-piece (Fig. 1, position A) and at the ventilator (position B).

Procedure

Devices were loaded with albuterol nebulizer solution (2.5 mg/3 mL; Nephron Pharmaceuticals, Orlando, Florida). At the beginning of each run, a new respiratory filter was used, the filter holder was sealed with Teflon tape, and the returned V_T was checked. Jet (6 L/min) and vibrating mesh nebulizers were operated for 5 and 15 min, respectively.⁷ The length of operation was decided after preliminary testing showed that these intervals allowed complete nebulization of medication within the reservoir

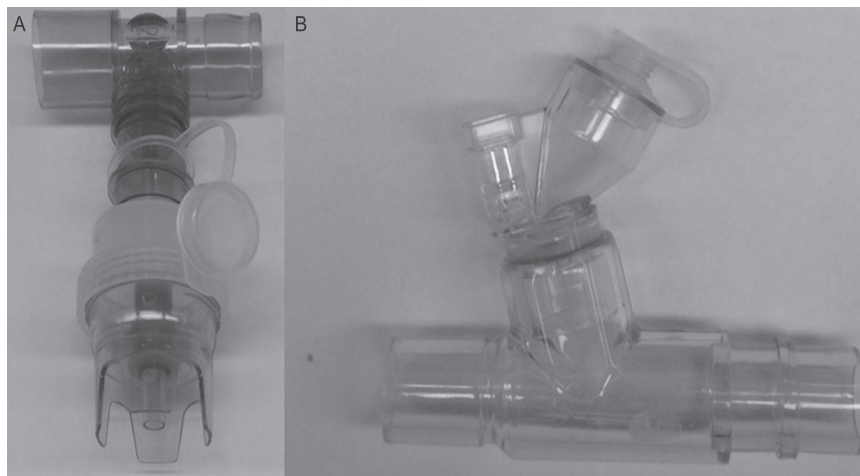


Fig. 2. Devices tested. A: Continuous-output jet nebulizer. B: Vibrating mesh nebulizer.

Table 1. Lung Dose With Different Nebulizers, Positions in the Ventilator Circuit, and V_T

V_T	Lung Dose (μg of albuterol)			
	Placed Before the Y-piece		Placed at the Ventilator	
	Continuous-Output Jet Nebulizer	Vibrating Mesh Nebulizer	Continuous-Output Jet Nebulizer	Vibrating Mesh Nebulizer
100 mL	102 \pm 7	184 \pm 29*†	218 \pm 41‡	238 \pm 128§
150 mL	93 \pm 3	121 \pm 27†	217 \pm 28‡	367 \pm 130‡
200 mL	90 \pm 17	123 \pm 17†	230 \pm 38‡	326 \pm 96‡
300 mL	79 \pm 12	118 \pm 20†	248 \pm 68‡	321 \pm 78‡

* $P < .02$ compared with other tidal volumes (V_T) for the same device/position.
† $P < .04$ compared with the continuous-output jet nebulizer placed before the Y-piece.
‡ $P < .02$ (continuous-output jet nebulizer) and $P < .03$ (vibrating mesh nebulizer) compared with the same device placed before the Y-piece.
§ $P = 0.36$ compared with the same device placed before the Y-piece.

for all devices, and they were also comparable to the intervals used in our previous studies.^{6,7} In addition, the Aerogen control units have settings for 15 and 30 min, and previously published data showed that extending nebulization beyond 5 min did not increase drug output for jet nebulizers.¹⁶

Filters were eluted with ultrapure water, and the washings were tested for albuterol concentration by spectrophotometry (BioMate 3 ultraviolet-visible spectrophotometer, Thermo Fisher Scientific, Waltham, Massachusetts) at 276 nm.⁶ Four units of each type of aerosol generator were tested in each of the 2 positions. The amount of drug captured in the filter (μg) was considered the lung dose. The delivery efficiency was calculated as: % efficiency = (lung dose in $\mu\text{g}/2,500$) \times 100.

Statistical Analysis

Analysis of variance was used to compare lung doses at different V_T values. The Tukey test was used for multiple-

comparison testing. A t test was used to compare different devices at the same position (unpaired with unequal variance) and different positions for the same device (paired). $P < .05$ was considered statistically significant. A statistical software package (KaleidaGraph 4.1, Synergy Software, Reading, Pennsylvania) was used for all calculations.

Results

Data are presented in Table 1 as lung dose (μg of albuterol) and in Figure 3 as delivery efficiency.

Effect of V_T on Lung Dose/Delivery Efficiency

No differences in lung dose/delivery efficiency were found at different V_T values for the continuous-output jet nebulizer when it was placed either before the Y-piece ($P = .08$) or at the ventilator ($P = .75$). The delivery efficiency ranged between 3.6 and 4.1% and between 8.7

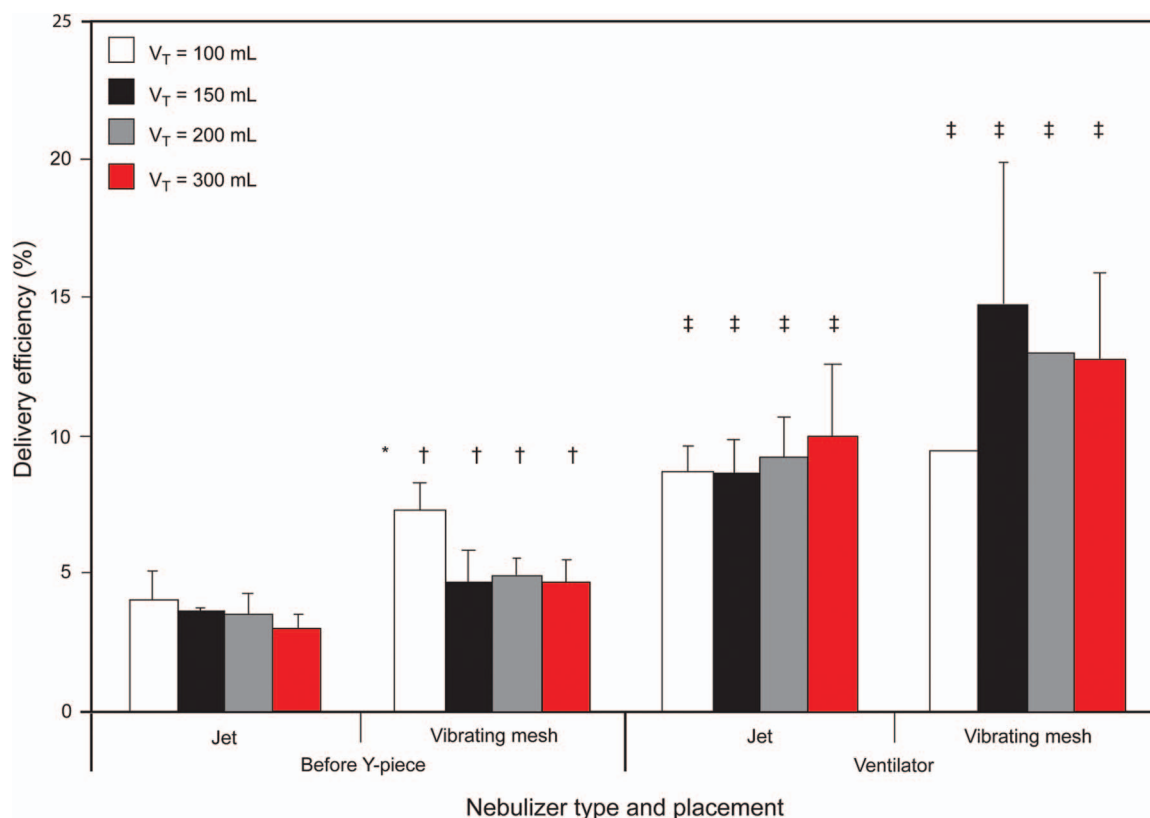


Fig. 3. Delivery efficiency (percent) with different nebulizers, positions in the ventilator circuit, and tidal volumes (V_T). * $P < .02$ compared with other V_T values for same device/position. † $P < .04$ compared with the continuous-output jet nebulizer placed before the Y-piece. ‡ $P < .02$ (continuous-output jet nebulizer) and $P < .03$ (vibrating mesh nebulizer) compared with same device placed before the Y-piece.

and 9.9% for the jet nebulizer placed before the Y-piece and at the ventilator, respectively.

No differences in lung dose/delivery efficiency were found at different V_T values for the vibrating mesh nebulizer when it was placed at the ventilator ($P = .44$). However, lung dose/delivery efficiency was higher at a V_T of 100 mL compared with the other values ($P < .02$) when the vibrating mesh nebulizer was placed before the Y-piece. No differences were found at the other V_T values ($P < .98$). The delivery efficiency ranged between 4.7 and 7.3% and between 9.5 and 14.7% for the vibrating nebulizer placed before the Y-piece and at the ventilator, respectively.

Effect of Nebulizer Type on Lung Dose/Delivery Efficiency

The vibrating mesh nebulizer had 1.3–1.8-fold higher lung dose/delivery efficiency compared with the continuous-output jet nebulizer when placed at the Y-piece ($P < .04$). Although a similar trend was noted when the nebulizers were placed at the ventilator, the difference did not reach statistical significance ($P < .79$).

Effect of Nebulizer Placement on Lung Dose/Delivery Efficiency

Moving the continuous-output jet nebulizer from the Y-piece to the ventilator increased lung dose/delivery efficiency by 2–3-fold at all V_T values ($P > .02$ for each V_T). Moving the vibrating mesh nebulizer from the Y-piece to the ventilator increased lung dose/delivery efficiency by 3-fold at a V_T of 150–300 mL ($P < .03$ for each V_T). Although a similar trend was seen for a V_T of 100 mL, the difference did not reach statistical significance ($P = .36$).

Discussion

We found that moving the nebulizer from before the Y-piece to the ventilator increased lung dose/delivery efficiency in a pediatric ventilator model with low bias flow. We also found that increasing the V_T did not result in an increase in lung dose/delivery efficiency. In addition, we found that vibrating mesh nebulizers had higher lung dose/delivery efficiency compared with continuous-output jet nebulizers when placed before the Y-piece but not when placed at the ventilator.

V_T

Our results are in partial agreement with previously published data using a similar setup except that the bias flow was 2 L/min.⁶ In that study, another brand of continuous-output jet nebulizer was studied when placed before the Y-piece and the humidifier at V_T values of 100 and 200 mL. No differences in lung dose were found between V_T values at either position. Two other studies compared pediatric and adult models but used different size circuits, making the comparison more difficult.^{5,17} Wan et al¹⁷ compared the lung dose generated by a continuous-output jet nebulizer placed at the ventilator during different nebulization modes. The lung dose was 6.3% for the pediatric model (V_T of 160 mL, breathing frequency of 25 breaths/min, inspiratory-expiratory ratio of 1:2 with a 15-mm circuit and a 5.0-mm ID ETT) and 7.4% for the adult model (V_T of 600 mL, breathing frequency of 16 breaths/min, inspiratory-expiratory ratio of 1:2.5 with a 22-mm circuit and a 7.5-mm ID ETT). Their results were similar to ours: 8.7 and 9.9% at a V_T of 150 and 300 mL, respectively. Ari et al⁵ compared a continuous-output jet nebulizer and a vibrating mesh nebulizer placed at the ventilator and 15 cm before the Y-piece on the inspiratory limb. They used an adult model (V_T of 500 mL, breathing frequency of 20 breaths/min with a 22-mm humidified circuit and an 8-mm ID ETT) and a pediatric model (V_T of 100 mL, breathing frequency of 20 breaths/min with a 15-mm humidified circuit and a 5.0-mm ID ETT). The jet nebulizer was operated at 2.5 L/min. Comparison between both models provided different results depending on the device and its placement in the ventilator circuit. No differences between the adult and pediatric models were found when the jet nebulizer was placed before the humidifier and the vibrating mesh nebulizer was placed before the Y-piece. The adult model provided higher lung dose compared with the pediatric model when the jet nebulizer was placed before the Y-piece and the vibrating mesh nebulizer was placed before the humidifier. Comparison is difficult due to the fact that both models differ not only in V_T but also in the IDs of the ETT and ventilator circuit.

Our findings contradict previously published data obtained using adult models.^{10,11} O’Riordan et al¹⁰ found that increasing the V_T from 700 to 1,000 mL resulted in a 12–25% increase in lung dose. Fink et al¹¹ found a progressive increase in lung dose when the V_T was increased from 100 to 800 mL. The different results could be attributed to several differences in the investigational setups. O’Riordan et al¹⁰ evaluated different continuous-output jet nebulizers in an adult model of mechanical ventilation (ETT ID of 9 mm). Fink et al¹¹ used a metered-dose inhaler, a dry circuit, and an ETT with an ID of 8 mm in CPAP mode. The pressure was set at 0, and different V_T values were generated by the breathing simulator.

The effect of different V_T values on lung dose/delivery efficiency depended on the placement of the vibrating mesh nebulizer in the ventilator circuit. Although no changes were noted with the device placed at the ventilator, higher lung dose/delivery efficiency was noted for the lower V_T when the nebulizer was placed before the Y-piece. This could be explained by the presence of a reservoir effect due to the fact that at lower V_T , a higher proportion of the inhaled volume contains aerosol. A different response was reported by Ari et al,⁵ who found that a vibrating mesh nebulizer placed before the Y-piece provided similar lung dose in pediatric and adult models. Conversely, they reported a higher lung dose/delivery efficiency for the adult model when the same nebulizer was placed at the ventilator. The different findings could be explained in part by the differences in the experimental setup, particularly that the nebulizer was placed immediately before the Y-piece in our study, and it was placed 15 cm before the Y-piece in theirs. We speculate that this difference could have decreased the importance of the reservoir effect. The clinical implications of our findings are that clinicians should not consider increasing V_T as a tool to optimize aerosol delivery during pediatric mechanical ventilation because it does not provide any benefits and yet increases the risk of barotrauma and volutrauma.

Delivery Device and Position

The increase in lung dose/delivery efficiency found upon moving the continuous-output jet and vibrating mesh nebulizers from the Y-piece to the ventilator is consistent with previous reports.^{5,7} A similar effect was reported in a previous study for jet and vibrating mesh nebulizers (2.6- and 3.3-fold increases, respectively).⁷ The experimental setup was similar except for a bias flow of 2 L/min and a V_T of 200 mL.⁷ A smaller effect was reported in another study for jet and vibrating mesh nebulizers (1.2- and 1.2-fold differences, respectively).⁵ The experimental setup included a smaller size ventilator circuit (15-mm ID), a slightly narrower ETT (5.0-mm ID), and a higher bias flow (2 L/min). Our lung dose/delivery efficiency at a V_T of 100 mL also increased by similar amounts, but the difference was not statistically significant due to high inter-device variation.

The vibrating mesh nebulizer had a larger inter-unit variation than the jet nebulizer. This is consistent with previous studies that reported a coefficient of variation (SD/mean \times 100) for the vibrating mesh nebulizer placed at the ventilator of 25–30%.^{5,7} Practitioners need to be aware of this phenomenon already reported for jet nebulizers.¹⁸ The findings for the continuous-output jet and vibrating mesh nebulizers were similar to those reported with adult models.^{4,5,9}

The efficiency of the devices cannot be compared without considering their placement in the ventilator circuit. The vibrating mesh nebulizer had higher lung dose/delivery efficiency than the continuous-output jet nebulizer when placed at the Y-piece, as reported previously.^{5,7,8} However, it was lower in this study (1.8-fold) than reported by Ari et al,⁵ Sidler-Moix et al,⁸ and Berlinski and Willis⁷ (2.7-, 3.6-, and 4.4-fold, respectively). The differences in magnitude could be explained in part by differences in experimental setup. Although Sidler-Moix et al⁸ used a similar diameter ventilator circuit and a smaller size ETT (4.0 mm ID), they did not use humidification. The latter would lead to an overestimation of the delivery efficiency.^{4,8} Although Ari et al⁵ used a smaller size heated and humidified ventilator circuit (15-mm ID) and a slightly smaller size ETT (5.0 mm ID), they also used a higher bias flow (2 L/min). In a previous study,⁷ we used a similar experimental setup except for a higher bias flow (2 L/min). Comparison of the data from these 2 studies with those from this study highlights the deleterious effect of bias flow on aerosol drug delivery during mechanical ventilation.⁴ Also, difficulties arise when extrapolating results from one setup to another.

The difference in lung dose/delivery efficiency generated by both devices did not reach statistical significance when the devices were placed at the ventilator. This is in agreement with the results obtained by Ari et al,⁵ who did not find differences in their pediatric model when comparing bias flows of 2 and 5 L/min. In a previous study,⁷ we found a significant difference using a similar setup except for a higher bias flow (2 L/min). We speculate that the relationship between bias flow is not simple and that the size and length of the ventilator circuit, the V_T , and the position of the aerosol generator play a role in the final outcome (lung dose). We speculate that when using an aerosol generator at the ventilator with a 22-mm ventilator circuit, a minimal amount of bias flow is necessary to fill up the inspiratory limb with aerosol during expiration. However, an excess of bias flow results in an increase in impaction against the walls, resulting in lower lung dose.

This study has limitations that are related to the nature of the experimental setup. The in vitro lung dose overestimates the actual dose because the filters do not allow exhalation of the aerosols that are not deposited. However, even with this limitation, this is a well-accepted methodology with already established in vivo/in vitro correlations.^{19,20} Also, we did not measure the particle size of the aerosols that left the tip of the ETT. However, although particle size is a major limitation in bypassing the upper airway, it is not a problem in this context because once the aerosol leaves the ETT, it has already bypassed the upper airway.

Conclusions

Optimization of inhaled drug delivery during pediatric mechanical ventilation should include careful selection of the type of delivery device and its placement in the ventilator circuit. Increasing V_T during nebulization did not increase lung dose/delivery efficiency.

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