# Albuterol Delivery Efficiency in a Pediatric Model of Noninvasive Ventilation With a Single-Limb Circuit

Ariel Berlinski and Jeanne Velasco

**BACKGROUND: Pediatric patients treated with noninvasive ventilation (NIV) are frequently given aerosol therapy. Limited pediatric data are available on the efficiency of aerosol delivery efficiency. We evaluated the effect of different nebulizers, positions in the single-limb ventilator circuit, and ventilator settings on the efficiency of aerosol delivery in a model of pediatric NIV. We hypothesized that using a vibrating mesh nebulizer, placing the nebulizer after the circuit leak, and not using the highest inspiratory positive airway pressure would increase aerosol delivery efficiency. METHODS: We connected a breathing simulator in series to a low-dead-space filter holder (lung dose) and to an anatomically correct face/airway model of a 5-y-old child. A mask with an entrainment elbow was connected to a ventilator operated in a NIV bi-level mode and assembled with a single-limb heated-wired circuit. Inspiratory/expiratory pressures of either 15/5 or 20/5 cm $H_2O$ were used. We studied 3 different jet nebulizers and 2 vibrating mesh nebulizers loaded with albuterol solution (2.5 mg/3 mL). Albuterol was measured with spectrophotometry. The outcome measure was the efficiency of aerosol delivery (ie, lung dose expressed as percentage of the nominal dose). RESULTS: Vibrating mesh nebulizers placed after the exhalation port of the circuit had the highest delivery efficiency, even compared with a vibrating mesh nebulizer integrated into the mask. Placing the nebulizer after the exhalation port of the circuit increased efficiency for all nebulizers. Vibrating mesh nebulizers were more efficient than jet nebulizers, regardless of their position in the circuit. Increasing the inspiratory pressure resulted in a variable effect on aerosol-delivery efficiency. CONCLUSIONS: In a model of pediatric NIV using a single-limb circuit, aerosol delivery devices were more efficient when placed after the exhalation port of the ventilator circuit. Vibrating mesh nebulizers were more efficient than jet nebulizers.** *Key words: aerosol delivery; noninvasive ventilation; nebulizer; airway model; lung dose; pediatrics; albuterol.* [Respir Care 2019;64(11):1366–1370. © 2019 Daedalus Enterprises]

## Introduction

Noninvasive ventilation (NIV) is increasingly used in the treatment of pediatric respiratory failure, as well as in status asthmaticus.[1,2] Many patients treated with NIV also receive inhaled bronchodilators. Single-limb and double-limb ventilator circuits are used to deliver NIV. The latter are more commonly used in the pediatric ICU, whereas the former is more commonly used in transport and emergency department settings. Single-limb circuits have an

Dr Berlinski is affiliated with the Department of Pediatrics, Pulmonology Section, University of Arkansas for Medical Sciences, and with the Pediatric Aerosol Research Laboratory, Arkansas Children's Research Institute, Little Rock, Arkansas. Dr Velasco is affiliated with St Christopher's Hospital for Children, Philadelphia, Pennsylvania.

Dr Velasco presented a version of this paper at the American Thoracic Society International Meeting, held May 19-24, 2017, in Washington, DC.

Dr Berlinski has disclosed relationships with AbbVie, Anthera, Aptalis Pharma, Cempra, Janssen Research and Development, Gilead, National Institutes of Health, Novartis, Therapeutic Development Network, Vertex, and the International Pharmaceutical Aerosol Consortium on Regulation and Science. Dr Velasco has disclosed no conflicts of interest.

Correspondence: Ariel Berlinski MD FAARC, University of Arkansas for Medical Sciences, Department of Pediatrics, Pulmonary Medicine, 1 Children's Way, Slot 512–17, Little Rock, Arkansas 72202. E-mail: berlinskiariel@uams.edu.

DOI: 10.4187/respcare.06622

exhalation port at the patient's end of the circuit that allows the release of exhaled gases.[3,4] The effects on delivery efficiency during NIV of different types of aerosol generators, their position in the ventilator circuit, and ventilator settings have been previously studied, but conflicting findings have been reported.[5-7] Pediatric data on NIV are limited to one study done with a single-limb circuit and another study done with a double-limb circuit.[5,6] Both studies found that placing the aerosol-generating device closer to the patient increased delivery efficiency. However, the single-limb study results indicated that a device incorporated into the mask was the most efficient, whereas the double-limb study results did not. Although the double-limb study compared jet nebulizers and vibrating mesh nebulizers, the single-limb study only compared vibrating mesh nebulizers. Studies using models of adult NIV with single-limb circuits found that increasing the inspiratory positive airway pressure (IPAP) resulted in enhanced delivery efficiency.[7,8] However, another study using a pediatric model of NIV with a double-limb circuit did not.[6] More data are needed to help clinicians treating children with NIV choose the type of device and site of placement in a single-limb ventilator circuit that will optimize drug delivery.

In this study, we compared the effects of different types of nebulizers, different positions in the ventilator circuit, and different ventilator settings on the efficiency of aerosol delivery during pediatric NIV with single-limb circuit using an anatomically correct in vitro model of a spontaneously breathing child. We hypothesized that using a vibrating mesh nebulizer, placing the nebulizer after the circuit exhalation port, and not using the highest IPAP would increase the efficiency of aerosol delivery.

**QUICK LOOK**

**Current knowledge**

There is limited knowledge about the drug-delivery efficiency of different aerosol generators placed at different positions on a single-limb circuit, and of the effect of different inspiratory pressures during pediatric noninvasive ventilation.

**What this paper contributes to our knowledge**

Aerosol-generating devices were more efficient when placed after the exhalation port of the ventilator circuit during pediatric noninvasive ventilation using a single-limb ventilator circuit. Vibrating mesh nebulizers were more efficient than jet nebulizers. Increasing the inspiratory pressure had variable effects on the efficiency of aerosol delivery.

## Methods

This study was performed at the Pediatric Aerosol Research Laboratory of Arkansas Children's Research Institute in Little Rock, Arkansas. We used an oronasal mask (AF31, small size, Philips Respironics, Murrysville, Pennsylvania) with an entrainment elbow leak 1 (Philips Respironics) (Fig. 1).[5] We tested 4 units of 5 different brands (Fig. 1). Two vibrating mesh nebulizers were tested: Aerogen Solo and NIVO (Aerogen, Galway, Ireland). Three continuous-output jet nebulizers that operate at different flows were tested: Hudson Updraft II Opti-Neb (Teleflex Medical, Research Triangle Park, North Carolina, 6 L/min), Mini Heart Low Flow (Westmed, Tucson, Arizona, 3 L/min), and Solarys (Monaghan Medical, Plattsburg, New York, 1 L/min). The Solarys generates the aerosol mist at the distal tip of a multi-lumen catheter that interfaces with the ventilator circuit.[9]

### In Vitro Model of a Spontaneously Breathing Child

A previously reported model was used.[6] Briefly, a breathing simulator (Dual Phase Control Respirator, Harvard Apparatus, Holliston, Massachusetts) programmed to deliver a pediatric breathing pattern (tidal volume = 200 mL, breathing frequency = 20 breaths/min, inspiratory to expiratory time (I:E) ratio = 1:3, and inspiratory time = 0.75 s) was connected in series to a low-dead-space filter holder with a 3-dimensional face/airway pediatric model (Fig. 2). The anatomically correct face/airway model of a 5-y-old child was downloaded from https://www.rddonline.com/resources/tools/pediatric_upper_airway_models.php (*Accessed April 1, 2014*) and printed with a 3-dimensional printer.[10] The chosen breathing pattern parameters are similar to previously published model.[6]

### Ventilator Settings

A Trilogy ventilator 202 (Philips Respironics) connected to a humidifier and a single-limb heated-wire circuit (RT219 Evaqua, Fisher & Paykel, Auckland, New Zealand) was used. A single arch exhalation port (Philips Respironics) connected the circuit to the entrainment elbow and mask. The following settings were used: noninvasive bilevel mode with IPAP of 15 cm $H_2O$ and expiratory positive airway pressure (EPAP) 5 cm $H_2O$ and a back-up frequency of 15 breaths/min. Testing was repeated with IPAP of 20 cm $H_2O$ and EPAP of 5 cm $H_2O$ and the same back up frequency.

### Study Procedure

After placing a new aerosol filter (Pari, Pari Respiratory Equipment, Midlothian, Virginia) in the filter holder, the

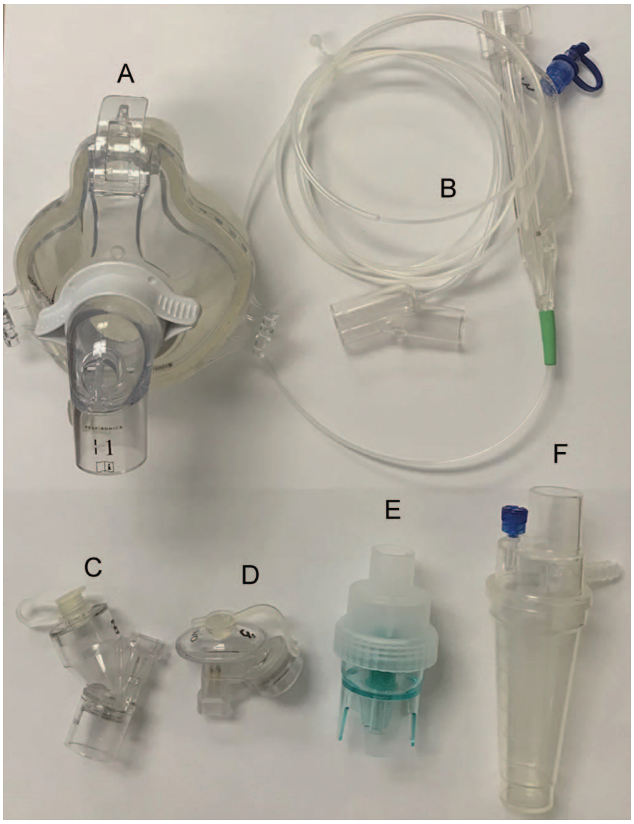


Fig. 1. Interface and delivery devices used in the study. A: Face mask with entrainment elbow. B: Solarys nebulizer. C: Solo nebulizer. D: NIVO nebulizer. E: Hudson nebulizer. F: Mini-heart nebulizer.

breathing pattern was programmed in the breathing simulator. The accuracy of the tidal volume was verified with a mass flow meter (TSI 4043, Shoreview, Minnesota) and its associated software before and after connecting the face/airway model.[11] The face mask was placed on the face/airway model with a gel mask interposed to allow a good seal.[6] The nebulizer was loaded with albuterol sulfate solution (2.5 mg/3 mL) and operated at the predetermined flow using a central air source (50 psi) and a regulated flow meter. All nebulizers were operated for 15 min except for the Hudson (5 min) as per previous evaluations.[6] The Hudson, the Mini-heart and the Solo nebulizers were placed between the exhalation port and the entrainment elbow and on the ventilator (Fig. 2). The NIVO was placed in the entrainment elbow, and the Solarys was placed between the exhalation port and the entrainment elbow. The choice of placement of the different nebulizers was per manufacturer recommendations for the NIVO, and per previous studies and our study design for the others. All scenarios were first run with IPAP/EPAP of 15/5 cm $H_2O$, and then the scenarios were run again with IPAP/EPAP of 20/5 cm $H_2O$. The filter was eluted with deionized water and analyzed via spectrophotometer at 276 nm (BioMate 3 ultraviolet-visible spectrophotometer, Thermo Fisher Scientific, Waltham, Massachusetts).[11] The drug captured in the filter was defined as the lung dose.[6]

### Statistical Analysis

Delivery efficiency (lung dose expressed as percentage of the nominal dose) was the outcome measure. We used analysis of variance followed by the Tukey test for multiple comparisons to evaluate differences in delivery efficiency among different delivery devices at each site of placement. We used the paired *t* test to compare the delivery efficiency of each device at 2 different positions, and of each device/position at 2 different NIV settings. A $P$ value $< .05$ was considered statistically significant. We used a statistical software package for all the calculations (Kaleidagraph 4.1, Synergy Software, Reading, Pennsylvania).

## Results

Data are summarized in Figure 3.

### Effect of Device Selection

Vibrating mesh nebulizers were more efficient than jet nebulizers regardless of where they were placed in the ventilator circuit. The delivery efficiency for the Solo nebulizer was 16.6% and 4.7% at IPAP 15 cm $H_2O$, and 14.9% and 4.3% at IPAP 20 cm $H_2O$, when placed after the exhalation port of the circuit and at the ventilator, respectively. The delivery efficiency for NIVO was 10% and 11.2% when IPAP was set at 15 and 20 cm $H_2O$, respectively ($P = .37$). The delivery efficiency for Solarys was 2.1% and 2% when IPAP was set at 15 and 20 cm $H_2O$, respectively ($P = .93$). The delivery efficiency for the Hudson nebulizer was 5.5% and 2.1% at IPAP 15 cm $H_2O$, and 5.9% and 0.9% at IPAP 20 cm $H_2O$, when placed after the exhalation port of the circuit and at the ventilator, respectively. The delivery efficiency for the Mini-heart nebulizer was 3.9% and 0% at IPAP 15 cm $H_2O$, and 6.7% and 1.9% at IPAP 20 cm $H_2O$, when placed after the exhalation port of the circuit and at the ventilator, respectively.

The Solo nebulizer, when placed at the ventilator, was 2- and 2.3-fold more efficient than the Hudson nebulizer at IPAP of 15 and 20 cm $H_2O$ respectively. The Mini-heart had extremely low efficiency (0.05%). The Solo nebulizer, when placed after the exhalation port of the circuit, was 1.3-, 7.9-, 3-, and 4.3-fold more efficient than NIVO, Solarys, Hudson, and Mini-heart, respectively, at IPAP 15 cm $H_2O$). The Solo nebulizer, when placed after the exhalation port of the circuit, was 1.7-, 7.5-, 2.5-, and

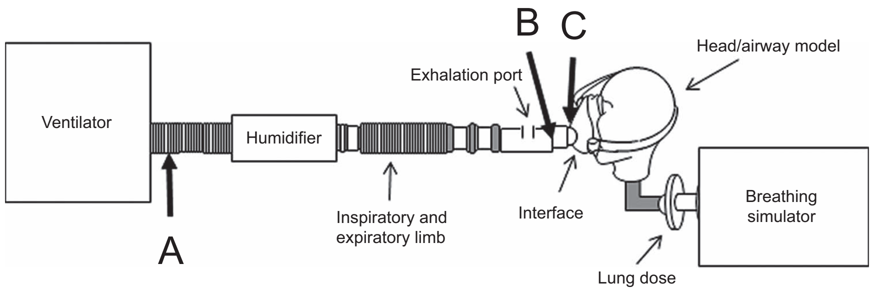


Fig. 2. Experimental setup. Position A: At the ventilator on the inspiratory side. Position B: After the exhalation port. Position C: Incorporated at the elbow that connects to the face mask.

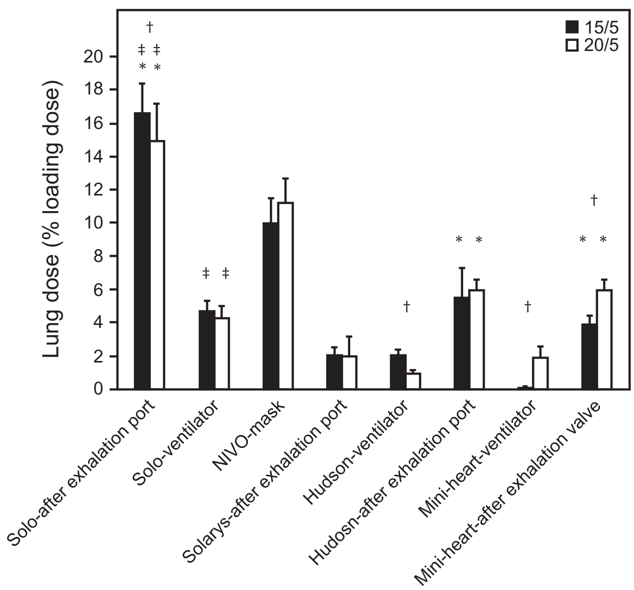


Fig. 3. Delivery efficiency with different devices, positions on the ventilator circuit, and ventilator settings. Columns represent mean values, and error bars show standard deviation. * Delivery efficiency increased when the device was moved from the ventilator to after the exhalation port. † Delivery efficiency changed when inspiratory positive airway pressure was increased from 15 cm $H_2O$ to 20 cm $H_2O$. ‡ Solo had greater efficiency than other devices placed at same position ($P < .001$).

2.2-fold more efficient than NIVO, Solarys, Hudson, and Mini-heart, respectively, at IPAP 20 cm $H_2O$.

### Effect of Device Position

Moving the nebulizer from the ventilator to after the circuit exhalation port resulted in increased delivery efficiency for all units ($P = .002$, $P = .03$, and $P = .001$ for Solo, Hudson, and Mini-heart, respectively) when the IPAP was 15 cm $H_2O$. A similar pattern was observed when IPAP was 20 cm $H_2O$ ($P < .001$, $P < .001$, and $P = .002$ for Solo, Hudson, and Mini-heart, respectively).

### Effect of Increasing IPAP

Increasing IPAP from 15cm $H_2O$ to 20 cm $H_2O$, while keeping the EPAP constant, had variable consequences. It resulted in decreased efficiency for the Solo placed after the circuit exhalation port ($P = .03$), and the Hudson placed at the ventilator ($P = .01$). However, it resulted in increased efficiency for the Mini-heart at both positions ($P = .02$).

## Discussion

We studied the efficiency of aerosol delivery in an anatomically correct pediatric model of a spontaneously breathing child receiving NIV with a single-limb ventilator circuit. We found that choosing a vibrating mesh nebulizer and placing any aerosol generator after the exhalation port of the ventilator circuit increased delivery efficiency. We also found that increasing the inspiratory pressure had a variable effect on the efficiency of aerosol delivery.

Similar to previously reported data obtained with models of pediatric NIV and invasive ventilation, we found that vibrating mesh nebulizers outperformed jet nebulizers.[6,12] Results for nebulizers placed after the circuit exhalation port were similar to those using the same devices placed before the mask in a model of NIV using a double-limb circuit ventilator with a non-vented mask.[6] However, delivery efficiency for the vibrating mesh nebulizer placed at the ventilator was 2.5-fold higher for the double-limb ventilator circuit than for the single-limb ventilator circuit.[6] We speculate that this could be due to the higher bias flow characteristic of the single-limb circuit. In addition to confirming a previous pediatric report, we also provided new data regarding jet nebulizers.

Delivery efficiency of the vibrating mesh nebulizer integrated into the mask (≈10%) was similar to results found in previously published studies.[5,6] Delivery efficiency of a vibrating mesh nebulizer placed at the ventilator (≈4–5%) was also similar to a previous study.[5] However, delivery efficiency of a vibrating mesh nebulizer placed before the mask was 3-fold higher than the study by White et al[5] and similar to our previous work using a double-limb circuit.[6] These differences could be explained in part by differences in the experimental setup. While we used an orotracheal model for both studies, they used an oronasal model.[5,6] These variations produced different alignments between the aerosol paths and the orifice opening.

Our findings that moving the aerosol generator from the ventilator to after the exhalation port of the ventilator circuit are consistent with previous studies using models of pediatric and adult NIV with a single-limb ventilator circuit.[5,7–8,13] This is explained by the aerosol loss that occurs through the exhalation port when the device is placed between the port and the ventilator.[13]

This is the first pediatric study to explore the effect of changing ventilator settings during NIV with a single-limb circuit on the efficiency of drug delivery. Increasing the IPAP/EPAP difference had variable consequences on drug-delivery efficiency. While one jet nebulizer (Mini-heart) improved, the other was either unchanged or decreased (Hudson), and the vibrating mesh nebulizer decreased when placed after the exhalation port but did not change when placed at the ventilator. The difference between both jet nebulizers could be explained in part by the different flows at which they were operated. Our results are in partial agreement with previous studies using non-anatomically correct models of adult NIV and a jet nebulizer.[7,8] One study reported that changing IPAP/EPAP settings from 15/5 cm $H_2O$ to 20/5 cm $H_2O$ resulted in a 10% increase (after the exhalation port of the circuit) and a 34% decrease (at the ventilator).[7] Another study reported that changing IPAP/EPAP settings from 15/5 cm $H_2O$ to 25/5 cm $H_2O$ resulted in a modest increase in delivery efficiency (4 – 7%).[8] These differences highlight the importance of not extrapolating data generated with adult models to pediatric scenarios.

The limitations of our study included an overestimation of inhaled drug due to the in vitro nature of the study, and having used only one breathing pattern and one face/airway model. These limitations are common to most in vitro studies.

## Conclusions

The findings of this study should provide practitioners with objective information to aid in the choice of an aerosol generator and site of placement when delivering NIV with a single-limb circuit to pediatric patients. Nebulizers were more efficient when placed after the exhalation port in a model of pediatric NIV with a single-limb circuit. In addition, we found that vibrating mesh nebulizers were more efficient than jet nebulizers.

## REFERENCES

1. Williams A, Abramo T, Shah M, Miller R, Burney-Jones C, Rooks S, et al. Safety and clinical findings of BiPAP utilization in children 20 kg or less for asthma exacerbations. Intensive Care Med 2011; 37(8):1338-1343.
2. Sorofsky A, Klinowski E, Ilgyev E, Mizrachi A, Miller A, Ben Yehuda T, et al. Noninvasive positive pressure ventilation in acute asthmatic attack. Eur Respir Rev 2010;19(115):39-45.
3. Esquinas A, BaHammam A, Scala R, Arie S, Nasilowski J, Siekmeier R, et al. Aerosol therapy during noninvasive mechanical ventilation: review of key technical factors and clinical implications. Can J Resp Ther 2013;49(1):11-18.
4. Scala R. Bi-level home ventilators for noninvasive positive pressure ventilation. Monaldi Arch Chest Dis 2004;61(4):213-221.
5. White C, Crotwell D, Shen S, Salyer J, Yung D, Zheng J, DiBlasi R. Bronchodilator delivery during simulated pediatric noninvasive ventilation. Respir Care 2013;58(9):1459-1466.
6. Velasco J, Berlinski A. Albuterol delivery efficiency in a pediatric model of noninvasive ventilation with double-limb circuit. Respir Care 2018;63(2):141-146.
7. Chatmongkolchart S, Schettino G, Dillman C, Kacmarek R, Hess D. In vitro evaluation of aerosol bronchodilator delivery during noninvasive positive pressure ventilation: effect of ventilator settings and nebulizer position. Crit Care Med 2002;30(11):2515-2519.
8. Dai D, Kang J, Sun L, Tan W, Zhao H. Influence of exhalation port and nebulizer position on albuterol delivery during noninvasive positive pressure ventilation. J Aerosol Med Pulm Drug Deliv 2013;26: 1-8.
9. Mitchel J, Avvakoumova V, Schneider H, Ali R, Nagel M. The evaluation of a new continuous liquid aerosol delivery system for the patient on mechanical ventilation. Respir Drug Delivery 2013; 373-378.
10. Bickmann D, Wachtel H, Kröger R, Langguth P. Examining inhaler performance using a child's throat model. Respir Drug Delivery 2008;2:565-570.
11. Chavez A, McCraken A, Berlinski A. Effect of face mask static dead volume, respiratory rate and tidal volume on inhaled albuterol delivery. Pediatr Pulmonol 2010;45(3):224-229.
12. Berlinski A, Willis JR. Albuterol delivery by 4 different nebulizers placed in 4 different positions in a pediatric ventilator in vitro model. Respir Care 2013;58(7):1124-1133.
13. Michotte J, Jossen E, Roeseler J, Liistro G, Reychler G. In vitro comparison of five nebulizers during noninvasive ventilation: analysis of inhaled and lost doses. J Aerosol Med Pulm Drug Deliv 2014;27:430-440.