

# Albuterol Delivery via Intrapulmonary Percussive Ventilator and Jet Nebulizer in a Pediatric Ventilator Model

Ariel Berlinski MD and J Randy Willis RRT-NPS

**BACKGROUND:** In-line administration of bronchodilators is widely used in pediatric patients receiving mechanical ventilation. We compared the amount of albuterol captured at the end of the endotracheal tube (ETT) with an intrapulmonary percussive ventilator (IPV) versus a Salter 8900 jet nebulizer placed in-line in a pediatric ventilator model, under various operating conditions. We hypothesized that the type of aerosol generator, tidal volume ( $V_T$ ), and position in the ventilator circuit would influence the albuterol delivery. **METHODS:** We connected a ventilator to a heated-wire ventilator circuit (heated to 37°C), to a cuffed 5.5-mm inner-diameter ETT, to a lung model, and ran the ventilator at pediatric ventilation settings: pressure-regulated volume-control mode, respiratory rate 20 breaths/min, PEEP 5 cm H<sub>2</sub>O,  $F_{IO_2}$  0.4, inspiratory time 0.75 s, inspiratory rise time 0.15 s, and flow-triggering at 3 L/min. We collected aerosol with a filter at the distal end of the ETT (ie, between the ETT and the lung model). We tested 3 IPV units run on central O<sub>2</sub> at 50-PSI, with a drive pressure of 25 cm H<sub>2</sub>O, and 3 Salter 8900 units run on central O<sub>2</sub> at 6 L/min. We diluted 5 mg of albuterol in saline, and nebulized 3 mL with the jet nebulizer and 10 mL with the IPV. We studied  $V_T$  (100 mL vs 200 mL), position in the circuit (at the humidifier vs at the Y-piece), and the IPV's "easy" and "hard" percussion settings. **RESULTS:** When positioned at the humidifier, the IPV delivered significantly less albuterol than the jet nebulizer (3.1–3.9-fold difference,  $P = .002$ ). When the IPV was moved to the Y-piece, the albuterol delivery was similar to that of the jet nebulizer at either position. Neither increasing the  $V_T$  nor increasing the IPV settings increased the albuterol delivery. **CONCLUSIONS:** The IPV delivered less albuterol than the jet nebulizer when placed at the humidifier. IPV was equivalent to jet nebulizer when placed at the Y-piece. Doubling the  $V_T$  did not increase aerosol delivery. *Key words:* mechanical ventilation; albuterol; nebulizer; intrapulmonary percussive ventilator; IPV; position; pediatrics; aerosol. [Respir Care 2010;55(12):1699–1704. © 2010 Daedalus Enterprises]

## Introduction

The delivery of therapeutic aerosols to mechanically ventilated patients is a complex process that is affected by

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Ariel Berlinski MD and J Randy Willis RRT-NPS are affiliated with Arkansas Children's Hospital, Little Rock, Arkansas. Ariel Berlinski MD is also affiliated with the Pulmonology Section, Department of Pediatrics, University of Arkansas for Medical Sciences, and with the Pediatric Aerosol Research Laboratory, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas.

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several variables. A simplified approach to understanding this process reveals 4 main components: the patient, the connector, the aerosol generator, and the ventilator.<sup>1,2</sup> The aerosol generator can be either a metered-dose inhaler (with or without a reservoir) or a nebulizer (jet, ultrasonic, or vibrating-mesh).<sup>1-4</sup> The aerosol generator can be placed at different sites between the endotracheal tube (ETT) and the ventilator.<sup>1,2,5,6</sup> Tidal volume ( $V_T$ ) is one of the variables on the ventilator side that can affect the pulmonary drug delivery. The effect of  $V_T$  was previously reported as both positive and neutral.<sup>1,2,7,8</sup>

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Correspondence: Ariel Berlinski MD, Department of Pediatrics, College of Medicine, University of Arkansas for Medical Sciences, 1 Children's Way, Little Rock AR 72202. E-mail: berlinskiariel@uams.edu.

Many mechanically ventilated patients also need airway-clearance therapy, which can be administered via manual chest physiotherapy, high-frequency chest-wall oscillation, or intrapulmonary percussive ventilator (IPV, Percussionaire, Sandpoint, Idaho).<sup>9,10</sup> In some clinical circumstances (eg, with burn patients) IPV can be the only acceptable modality.

The IPV combines a nebulizer and a high-frequency percussive ventilator. The IPV can be used in a noninvasive fashion or in-line in the ventilator circuit. The IPV delivers small bursts of gas at 100–300 cycles/min. Little is known about the effectiveness of the IPV to deliver aerosols. Two previous studies in spontaneously breathing non-intubated patients showed low and variable drug output.<sup>11,12</sup> We are unaware of any peer-reviewed studies on the efficiency of IPV to deliver aerosols via a ventilator circuit.

We measured the albuterol captured at the end of an ETT in a pediatric model of mechanical ventilation, with a heated-wire ventilator circuit. We hypothesized that the type of aerosol generator, the aerosol generator's position in the ventilator circuit, the  $V_T$ , and the IPV percussion setting would influence the amount of albuterol captured at the end of the ETT.

## Methods

The study was performed at the Pediatric Aerosol Research Laboratory, Arkansas Children's Hospital Research Institute, and Arkansas's Children's Hospital, Little Rock, Arkansas. We measured the albuterol captured at the end of the ETT in a pediatric in vitro ventilator model, with 2  $V_T$  settings and 2 different aerosol generators placed in 2 different positions.

### Pediatric Ventilator Model

We operated the ventilator (Servo-I, Maquet, Solna, Sweden) in pressure-regulated volume-control mode with a respiratory rate of 20 breaths/min, PEEP of 5 cm H<sub>2</sub>O, an  $F_{IO_2}$  of 0.4, an inspiratory time 0.75 s, an inspiratory rise time of 0.15 s, a flow-trigger setting of 3 L/min, and a circuit-heater setting of 37°C (range 35.5–38.7°C). We tested  $V_T$  of 100 mL and 200 mL. We connected the heated-wire circuit (Evaqua, Fisher-Paykel, Auckland, New Zealand) to a 5.5-mm inner-diameter cuffed ETT (Mallinckrodt Lo-Pro, Tyco/Mallinckrodt-Nellcor, Pleasanton, California), which we connected to an inhalation filter (Pari Respiratory Equipment, Midlothian, Virginia), in its low-dead-space filter-holder, which we connected to a lung model (SmartLung 600 mL, IMT Medical, Buchs, Switzerland). We inflated the ETT cuff to seal its connection to the filter holder (Fig. 1).

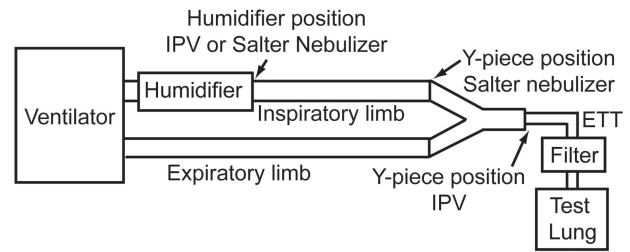


Fig. 1. Experimental setup. ETT = endotracheal tube. IPV = intrapulmonary percussive ventilator.

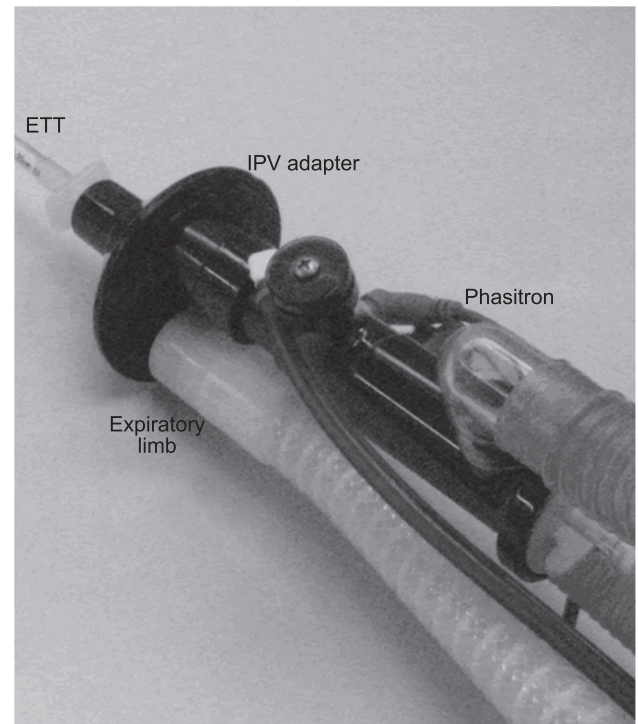


Fig. 2. Endotracheal tube (ETT) attached to the intrapulmonary percussive ventilator (IPV) by cone adapter.

### Aerosol Generators

We studied 3 IPV units (IPV-1C, Percussionaire, Sandpoint, Idaho) and 3 jet nebulizer units (Salter 8900, Salter Labs, Arvin, California). The IPV-1C includes a continuously operated nebulizer connected to the Phasitron (Fig. 2). We operated the IPV on 50-PSI central oxygen and a drive pressure of 25 cm H<sub>2</sub>O for 15 min. The Salter 8900 is a continuously operated jet nebulizer, which we operated on central oxygen at 6 L/min for 5 min. We diluted 5 mg of albuterol sulfate (Nephron Pharmaceuticals, Orlando, Florida) with saline, to 3 mL and 10 mL with the Salter 8900 and IPV, respectively.

We selected the run times based on preliminary experiments that showed the time to the beginning of sputtering.

Table 1. Albuterol Captured at the End of the Endotracheal Tube

Device and Settings	Position in Ventilator Circuit		<i>P</i> *
	At Humidifier (mean ± SD μg)	At Y-Piece (mean ± SD μg)	
IPV on “easy” setting, V <sub>T</sub> 100 mL	53 ± 9	175 ± 46	.01
IPV on “hard” setting, V <sub>T</sub> 100 mL	60 ± 10	189 ± 67	.03
Salter nebulizer, V <sub>T</sub> 100 mL	205 ± 56	230 ± 21	.50
IPV on “easy” setting, V <sub>T</sub> 200 mL	76 ± 12	161 ± 31	.01
IPV on “hard” setting, V <sub>T</sub> 200 mL	90 ± 9	205 ± 32	.004
Salter nebulizer, V <sub>T</sub> 200 mL	236 ± 56	181 ± 9	.17
Overall difference	Salter > IPV ( <i>P</i> < .001)	Salter = IPV ( <i>P</i> = .38)	

\* All the differences between tidal volume (V<sub>T</sub>) of 100 mL and 200 mL were nonsignificant.

ETT = endotracheal tube

IPV = intrapulmonary percussive ventilator

With the jet nebulizer we reduced the V<sub>T</sub> to compensate for the higher flow. With the IPV we decreased the ventilator’s triggering sensitivity to avoid auto-triggering.

We placed the jet nebulizer in-line with a T-piece adapter, in 2 different positions: between the Y-piece and inspiratory limb of the ventilator circuit, and between the humidifier and the inspiratory limb (see Fig. 1). We tested the IPV between the humidifier and the inspiratory limb, using an ad-hoc adapter (IPV adapter kit A50474, Percussionaire, Sandpoint, Idaho). We also placed the IPV at the ETT and connected it with a special adapter (IPV cone interface adapter kit A50474-2, Percussionaire, Sandpoint, Idaho), which has 3 orifices on the ventilator side (inspiratory limb, expiratory limb, and Phasitron) and one orifice on the patient side, which connects to the ETT (see Figs. 1 and 2). We tested the IPV at both its “easy” and “hard” percussion settings, which correspond to frequencies of 300 cycles/min and 100 cycles/min, respectively.

### Albuterol Measurement

Upon completion of each nebulization run we removed the filter and obtained the captured albuterol with purified water. The albuterol concentration was determined via spectrophotometry (Biomate 3, ThermoElectron, Waltham, Massachusetts), at 276 nm, by comparing the sample to a calibrated standard curve.<sup>13</sup>

### Statistics

We compared the outcome variable with analysis of variance, followed by Tukey’s test of multiple comparisons. We express the data as the mean ± SD of 3 tests. A *P* value < .05 was considered statistically significant. We conducted the analysis with statistics software (MDAS 2.0, EsKAY Software, Silver Spring, Maryland).

## Results

### Effect of Choice of Aerosol Generator on Albuterol Delivery

When the aerosol generators were placed at the humidifier and V<sub>T</sub> was 100 mL, the mean ± SD albuterol captured at the end of the ETT ranged from 53 ± 9 μg with the IPV “easy” setting, to 205 ± 56 μg with the jet nebulizer (a 3.9-fold difference) (*P* = .002). When the aerosol generators were placed at the humidifier and V<sub>T</sub> was 200 mL, the albuterol captured at the end of the ETT ranged from 76 ± 12 μg with the IPV “easy” setting, to 236 ± 56 μg with the jet nebulizer (a 3.1-fold difference) (*P* = .002) (Table 1 and Fig. 3).

When the aerosol generators were placed at the Y-piece and V<sub>T</sub> was 100 mL, the mean ± SD albuterol captured at the end of the ETT ranged from 175 ± 46 μg with the IPV “easy” setting, to 230 ± 21 μg with the jet nebulizer (*P* = .41). When the aerosol generators were placed at the Y-piece and V<sub>T</sub> was 200 mL, the albuterol captured at the end of the ETT was 161 ± 31 μg with the IPV “easy” setting, 205 ± 32 μg with the IPV “hard” setting, and 181 ± 9 μg with the jet nebulizer (*P* = .21).

### Effect of Placement in the Ventilator Circuit on Albuterol Delivery

On the “easy” setting, the IPV placed at the Y-piece delivered 3.3 times and 2.1 times more albuterol to the end of the ETT than it did when placed at the humidifier, with V<sub>T</sub> of 100 mL and 200 mL, respectively (*P* = .01 and *P* = .01). On the “hard” setting and at the Y-piece, the IPV delivered 3.2 times and 2.3 times more albuterol to the end of the ETT than when placed at the humidifier, with V<sub>T</sub> of 100 mL and 200 mL, respectively (*P* = .03 and *P* = .004).

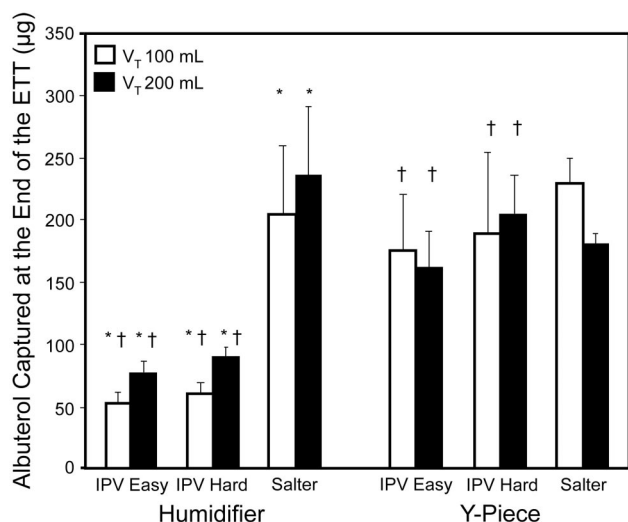


Fig. 3. Albuterol captured at the end of the endotracheal tube (ETT). The data bars and error bars represent the means and standard deviations, respectively. \*  $P = .002$  for IPV placed at the humidifier versus Salter 8900 nebulizer placed at the humidifier. †  $P < .001$  for intrapulmonary percussive ventilator (IPV) placed at the Y-piece versus at the humidifier. The differences were not significant when either position was compared for the Salter 8900 nebulizer or the IPV “easy” or “hard” percussion settings.

There were no significant differences in albuterol delivery when the jet nebulizer was moved from the humidifier to the Y-piece, irrespective of  $V_T$ .

### Effect of Tidal Volume on Albuterol Delivery

There were no significant differences in albuterol delivery when the  $V_T$  was increased from 100 mL to 200 mL, irrespective of aerosol generator or circuit position.

### Effect of Percussion Setting on Albuterol Delivery

There were no significant differences in albuterol delivery when the IPV percussion setting was changed from “easy” to “hard” at any combination of position or  $V_T$ .

## Discussion

Mechanically ventilated patients often require inhaled therapeutic aerosols and airway-clearance therapy, and the IPV is used for both purposes. Compared to the Salter 8900 jet nebulizer, the IPV-1C delivered less aerosol when placed at the humidifier in a pediatric ventilator circuit model. Albuterol delivery improved when the IPV-1C was placed at the Y-piece. We also found that the Salter 8900 and the IPV-1C might have different optimal settings. Increasing the  $V_T$  from 100 mL to 200 mL did not increase albuterol delivery in this pediatric ventilator model.

Our data also confirm that information obtained with adult ventilation models cannot be extrapolated to pediatric scenarios. Although adult in vivo data regarding aerosol delivery during mechanical ventilation are available, only scarce data have been published about children.<sup>1,2</sup> Ethical concerns regarding the use of radionuclide isotopes and large-volume blood draws have limited the research in that area. Although small-animal models have provided some additional information, those data are more applicable to neonates.<sup>2</sup> The bulk of knowledge on how to deliver therapeutic aerosols in a pediatric ventilator setting derives from in vitro data.<sup>2</sup> However, good correlation has been documented between in vivo and in vitro studies.<sup>14,15</sup>

Fok et al, in a animal study<sup>16</sup> and in a neonatal study<sup>17</sup> found that ultrasonic nebulizers had 6-fold and 2-fold higher pulmonary delivery than did a jet nebulizer. Similar data have been reported in the adult literature.<sup>18</sup> Two studies<sup>10,11</sup> compared drug delivery with IPV versus jet nebulizer. Reychler et al compared the pulmonary deposition of technetium-99 from an IPV and from a Sidestream nebulizer in spontaneously breathing healthy adults,<sup>11</sup> and found a 4.2% and 2.5% pulmonary deposition with the Sidestream and IPV, respectively. The IPV had significant inter-subject variability. In the second study, Reychler et al<sup>12</sup> compared amikacin deposition, measured via urinary excretion, between an IPV and a Sidestream nebulizer, and the Sidestream’s deposition was 6-fold higher. And in their in vitro evaluation of the IPV and Sidestream, the Sidestream’s output was 4.4-fold higher.

In our study we found that the Salter 8900 jet nebulizer had a 3.1–3.9-fold higher albuterol delivery to the end of the ETT than did the IPV-1C when the devices were placed at the humidifier. Although the Reychler et al study<sup>12</sup> and our findings favor jet nebulizer, the small difference in magnitude between the studies could be attributed to the fact that ours was done with a ventilator circuit. Furthermore, the Reychler et al study used a gravimetric technique, potentially overestimating the output, but we used chemical determination of drug output.<sup>19</sup> However, the difference in albuterol delivery disappeared when the IPV was placed at the Y-piece. Increasing the IPV percussion setting from “easy” to “hard” did not increase the albuterol delivery. We speculate that the albuterol-delivery difference when the IPV is placed at the humidifier could be attributed to the IPV’s pulsatile characteristics.

We found no difference in albuterol delivery when we increased  $V_T$  from 100 mL to 200 mL, and that result agrees with those of Everard et al,<sup>7</sup> who found no change when they increased  $V_T$  from 11 mL to 22 mL in a neonatal ventilator circuit. Conversely, Fink et al<sup>8</sup> found a positive correlation between  $V_T$  (100 mL, 300 mL, 500 mL, and 800 mL) and albuterol delivery in an adult ventilator circuit with a continuous positive airway pressure mode. These differences could be attributed in part to differences

in ETT size (ie, 3.0 mm, 8.0 mm, and 5.5 mm in Everard's, Fink's, and our study, respectively).<sup>7,8</sup>

In an adult ventilator model, O'Riordan et al<sup>3</sup> also found a positive correlation between  $V_T$  and drug output, which increased 12–25% when  $V_T$  was increased from 700 mL to 1,000 mL with a 9.0-mm ETT. Interestingly, the increase was around 50% when they used a 7.0-mm ETT. There is a complex relationship between ETT size,  $V_T$ , and drug delivery. We speculate that increased albuterol delivery with increasing  $V_T$  may be present only after a certain  $V_T$  is reached. The  $V_T$  we chose in our study (100 mL and 200 mL) are representative of children weighing 16 kg and 32 kg (mean weight for a 4-year-old and a 10-year-old child, respectively).

Previous studies<sup>1,2,5,6</sup> have looked at the effect of nebulizer position on pulmonary drug delivery. Hughes et al,<sup>5</sup> in an adult in vitro study, with a  $V_T$  of 700 mL, found that in continuously operated mode, aerosol output increased when the aerosol generator was placed closer to the ventilator. Quinn<sup>6</sup> compared jet nebulizer output at 3 different positions in an adult ventilator circuit model, with a  $V_T$  of 400 mL: at the Y-piece; at the manifold; and at the ventilator, right after the humidifier. He also found that the closer the aerosol generator was to the ventilator, the higher was the output. In our study the Salter 8900, a continuously operated nebulizer, showed no difference in albuterol delivery when we changed its position from the humidifier to the Y-piece, but the IPV showed a 2–3-fold increase.

The reasons for the differences with the jet nebulizer may include different  $V_T$  in the studies. Also, Hughes et al<sup>5</sup> operated their nebulizer for only 3 min, potentially not achieving the total output. Quinn<sup>6</sup> used a visual colorimetric scale, as opposed to our more accurate spectrophotometric measurements. Our study was conducted with the humidifier on, whereas Quinn's humidifier was turned off and bypassed, and no information on this was reported by Hughes et al. Humidification decreases aerosol delivery.<sup>3,20</sup> Our data agree with those from Moraine et al,<sup>21</sup> who found no difference in aerosol delivery in adult patients on mechanical ventilation when the nebulizer was placed before the Y-piece or before the humidifier.

### Limitations

Our study was in vitro. Capturing the aerosol with a filter at the end of the ETT overestimates in vivo pulmonary delivery because the filter does not allow exhalation of particles, as occurs in vivo. However, our methodology is well-accepted and has shown good correlation with in vivo studies. Another limitation is that the type of ventilator circuit we used does not allow interruptions to place the aerosol generator, so the aerosol generator could only be placed either where the inspiratory limb connects to the

Y-piece or at the ventilator/humidifier. Another limitation is that we did not measure the aerosol particle size leaving the ETT tip. Also, our study addressed aerosol delivery from the IPV, which is not the main reason for the IPV's clinical use. The main use of the IPV is to provide airway clearance.

### Conclusions

The IPV-1C delivered less albuterol to the ETT tip than did the Salter 8900 jet nebulizer when the IPV-1C was placed at the humidifier, in a heated-wire ventilator circuit using pediatric settings. The aerosol delivery from the IPV-1C was equivalent to that of the Salter 8900 when the IPV-1C was placed at the Y-piece. Ventilator circuit position can affect albuterol delivery to the ETT tip, depending on the type of aerosol generator used. Doubling the  $V_T$  did not increase aerosol delivery.

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