

# A Method for Increasing Jet Nebulizer Delivery Efficiency for Aerosol Drug Delivery in Ventilated Newborns: An In Vitro Study

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**BACKGROUND:** A substantial percentage of the aerosol produced by a nebulizer is lost down the expiratory limb of the ventilator circuit. We describe a method for the capture, return, and re-aerosolization of that undelivered aerosol. **METHODS:** We designed an expiratory-limb setup in which an “entraining jet” of gas accelerates unused aerosol and propels it toward an impaction surface. The deposited solution is then returned to the nebulizer reservoir via a feedback tube. As a result, more of the initial dose is delivered to the patient. The fraction of the dose delivered to a filter connected to a passive neonatal test lung was measured with and without the aerosol-recycling components activated. We used a  $\Delta P$  (difference between the peak inspiratory pressure and the positive-end-expiratory pressure) of approximately 7.5 cm H<sub>2</sub>O, tidal volume of approximately 6 mL, respiratory rate of 40 breaths/min, and an inspiratory-expiratory ratio of 1:2.3. **RESULTS:** There was a statistically significant improvement with the feedback return to the reservoir, with up to nearly 60% more aerosol delivered. **CONCLUSION:** This improvement in aerosol delivery is encouraging, but more comprehensive studies are needed before such a device could be implemented clinically. *Key words: neonatal, respiratory, drug delivery, inhaled pharmaceutical aerosol, pediatric intensive care.* [Respir Care 2006;51(11):1244–1250. © 2006 Daedalus Enterprises]

## Introduction

A major difficulty with the use of jet nebulizers in neonatal settings is that neonates have extremely small minute volume ( $\dot{V}_E$ ), compared with the flow required to nebulize medications (eg,  $\dot{V}_E$  of approximately 0.5 L, while the nebulizing flow required to achieve optimal aerosol particle sizes is usually 4–6 L/min). As a result, during inspiration, only a small fraction of the nebulized volume of

medicine is delivered to the neonate.<sup>1</sup> For example, only 10% is delivered to a neonate with a  $\dot{V}_E$  of 0.5 L and a 5-L/min nebulizer output, with the remaining 90% of the nebulized volume lost into the expiratory limb. In contrast, an adult would generally have a  $\dot{V}_E$  large enough to include all of the nebulized flow, yielding much higher efficiency than in neonates, although there is still waste, since an adult only inhales during part of the respiratory cycle.

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Numerous authors have examined nebulizer efficiency with existing commercial devices in ventilated pediatric settings.<sup>1</sup> There have been only a few efforts to overcome the low efficiency of jet nebulizers when applied to neonates. One method is to cycle the nebulizing air flow on and off in synchronization with the neonate's breathing

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pattern, with the nebulizer active only when the neonate is inhaling. Improvement by a factor of 1.6 was observed with this approach.<sup>2</sup>

Another method to generate aerosol is the micropump nebulizer technology, which employs a vibrating mesh to nebulize solution and provides higher aerosol delivery efficiencies with neonates (typically > 10%).<sup>3,4</sup> Ultrasonic nebulizers, which employ piezoelectric ceramic elements for nebulization, also provide greater efficiency than a typical jet nebulizer with some solutions.<sup>5,6</sup>

Numerous studies have compared the efficiencies of jet nebulizer to metered-dose inhaler with spacer in neonates.<sup>5,7-10</sup> In clinical trials, metered-dose inhaler with spacer had the same effect on neonatal lung compliance and resistance as did jet nebulizers, while requiring a smaller dose than jet nebulizer, so metered-dose inhaler with spacer had better efficiency. However, jet nebulizers are still used clinically in neonatal ventilation, and it may be useful to consider ways to improve their efficiency in neonatal drug delivery.

One way to improve jet nebulizer efficiency with neonates is to reduce the amount of aerosol lost into the expiratory limb. Since the nebulizing air flow cannot be reduced without negatively altering the aerosol particle size, another method is needed for lowering the amount of aerosol lost to the outflow. To improve jet nebulizer delivery in neonatal ventilation, we studied a method in which aerosol particles in the expiratory limb are collected and returned to the nebulizer reservoir. Once the aerosol mass collected from the expiratory limb is returned to the nebulizer reservoir, the medication is then re-aerosolized. We hypothesized that, for a given dose, nebulizer efficiency would be improved by the decrease in expiratory-limb aerosol loss.

A preliminary examination of this hypothesis can be made by defining  $f$  as the fraction of the total nebulizer output per unit time that can be recovered, *theoretical*  $\eta$  as the theoretical efficiency with aerosol recycling, and  $\eta_0$  as the efficiency without any recycling return to the nebulizer reservoir. Consider a hypothetical collection system that returns the collected drug back to the reservoir after the nebulizer runs out of solution. If the initial dose was  $m_0$ , then the returned dose is  $m_0 f$ . If this continues in an infinite loop, then the maximum total delivered dose  $m_d$  is given by:

$$(1) \quad m_d = \lim_{N \rightarrow \infty} \left( \sum_{n=0}^N m_0 f^n \right) = m_0 \lim_{N \rightarrow \infty} \left( \sum_{n=0}^N f^n \right) = m_0 \left( \frac{1}{1-f} \right)$$

This implies that the theoretical efficiency with aerosol collection and return has an upper limit that can be expressed as

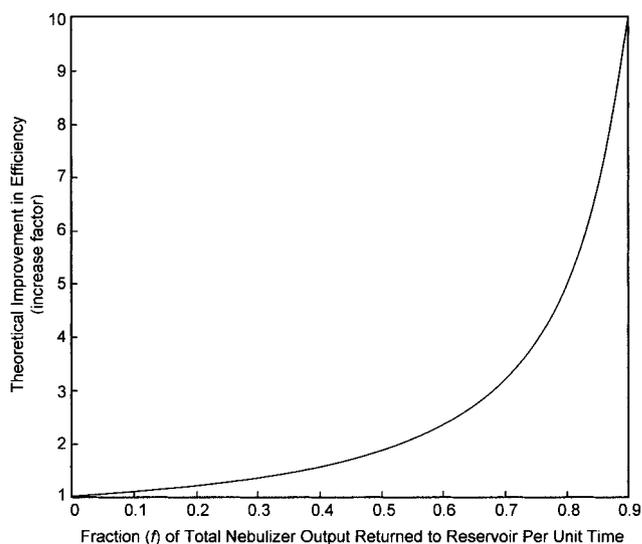


Fig. 1. Maximum theoretical improvement in aerosol-delivery efficiency versus the fraction of the total nebulizer output per unit time ( $f$ ). The maximum theoretical efficiency (theoretical  $\eta$ ) with recycling aerosol from the expiratory limb is bounded by the geometric sum in Equation 1 and shown here. An “increase factor” of 2 means the efficiency is doubled, an increase factor of 3 means the efficiency is tripled, etcetera.

$$(2) \quad \textit{theoretical } \eta \leq \eta_0 \left( \frac{1}{1-f} \right)$$

Figure 1 illustrates the aforementioned maximum scaling of efficiency. Clearly, a very large fraction of the aerosol in the expiratory limb must be recovered to obtain any large improvement in efficiency. Also, it must be emphasized that this is an upper limit to the efficiency improvement, because nebulizers require a minimum volume in the reservoir in order to function.

The above preliminary considerations suggest that improvements in nebulizer efficiency may be possible by recycling expiratory-limb aerosol. The purpose of this article is to explore one possible approach to achieving such improved efficiency.

## Methods

### Modification of the Nebulizer and Circuit

The collection of aerosol particles in the outflow involved 2 steps: entrainment and impaction (Fig. 2). Inclusion of a narrow coaxial “entraining jet” in a rigid outflow tube in the expiratory line provided the entrainment. Inclusion of a solid surface perpendicular to the entraining jet’s axis provided the impaction.

Entrainment occurs when a high-speed air flow exits the narrow jet tube and entrains air in front of the jet exit.

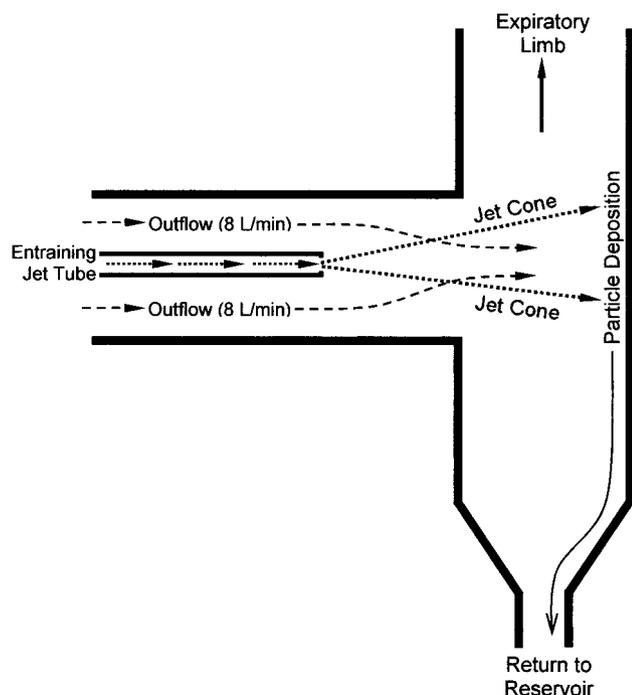


Fig. 2. Entraining jet, aerosol droplet impaction surface, and return-tube feedback system incorporated into the expiratory limb of a ventilator-nebulizer setup. The flow of air from the entraining jet turbulently mixes with the aerosol in the outflow (the flow of gas in the expiratory limb of the nebulizer, excluding the flow from the entraining jet). The aerosol particles, now with a greater velocity than before the interaction with the entraining jet, have enough velocity to deposit onto the impaction surface. When sufficient mass has collected, gravity draws the solution collected on the impaction surface to the return tube.

Aerosol moving in the outflow is drawn, or “entrained,” into the conically-expanding jet. The entrained aerosol particles are accelerated to the same high velocity as the air from the jet. Because the jet of entraining gas expands, the velocity of the jet air and the entrained aerosol decreases with distance.

Impaction is simply the deposition of particles on a surface when particles strike the surface. For impaction to occur, particles of a given mass require a minimum impaction velocity; hence, the requirement of an entraining jet to accelerate the aerosol particles. Particles that approach at less than the impaction velocity simply avoid depositing on the surface. The solution collected from the impaction surface is returned to the nebulizer reservoir through a gravity feed and a narrow tube.

To add the entraining jet, impaction surface, and return-tube feedback system to the nebulizer (Neb-U-Mist II, Hudson, Temecula, California), a modification to the nebulizer top was necessary. Since the feedback tube must be connected to the nebulizer, it was desirable for the entraining jet and impaction surface to be connected to the nebulizer as well. With this in mind, the

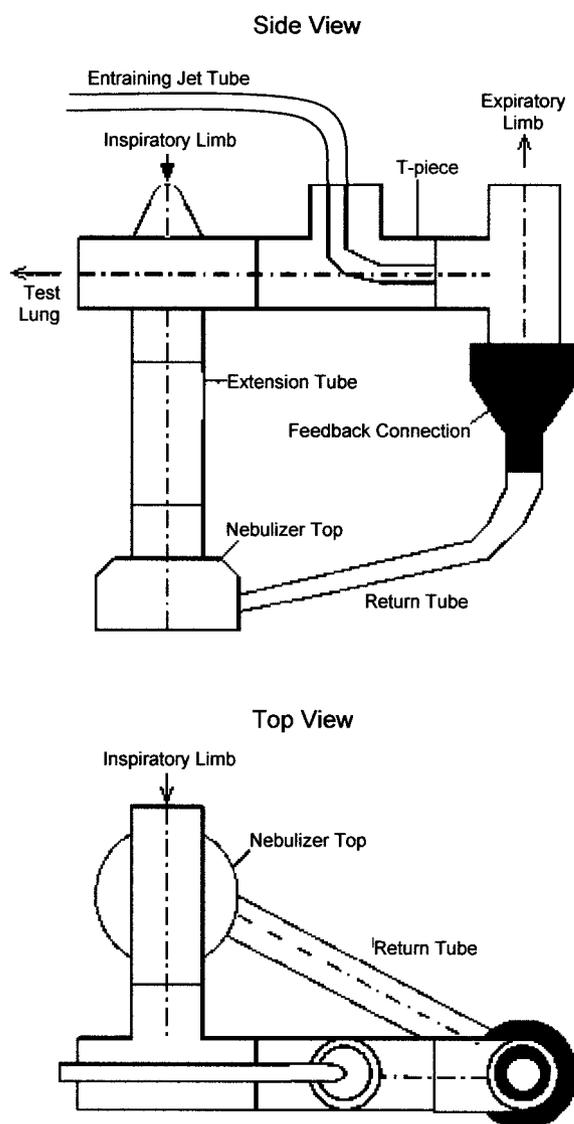


Fig. 3. Modified nebulizer top. The dashed lines indicate the azimuthal axes of the cylindrical geometries in the device.

nebulizer top was extended to include a section of the expiratory limb of the ventilator, which required the inclusion of connections to the inspiratory limb and output to the patient (Fig. 3). Each nebulizer reservoir was used for less than 10 runs.

A hole was cut into the nebulizer top to allow insertion of the feedback tube (R3603, Tygon, Saint-Gobain, Paris, France). (This was the only irreversible modification to the nebulizer.) The feedback tube was connected to the nebulizer baffle and a “feedback connector,” which had a conically sloped interior to return the collected droplets of medical solution without pooling effects. The feedback connector was custom-made from Teflon tubing in the machine shop of the Department of Mechanical Engineering at the University of Alberta.

The feedback connector was connected to a T-piece (61404, B&F Medical, Toledo, Ohio), the inner wall of which acted as the impaction surface. It also allowed for connections to the expiratory line and to the T-piece that held the entraining jet (with a rubber O-ring).

The T-piece was approximately of 1.9 cm inner diameter, 2.2 cm outer diameter, 5.1 cm length, and 3.0 cm height. The extension tube had approximate inner and outer diameters of 2.2 cm and 2.5 cm, respectively. The feedback tube's approximate inner and outer diameters were 6.0 mm and 9.0 mm, respectively. The entraining jet tube had approximate inner and outer diameters of 1.0 mm and 3.0 mm, respectively.

To prevent nebulized droplets from exiting directly to the expiratory line by traveling up the feedback tube, the nebulizer end of the feedback tube was submerged in the solution in the nebulizer reservoir.

The tip of the entraining jet exit was approximately 3.0 cm from the furthest point on the inner wall of the T-piece that acted as the impaction surface. This distance was large enough to meet the requirement for the entrainment of a large fraction of the aerosol in the outflow but small enough to prevent the velocities of most of the particles from dropping below the impaction velocity.

**Additional Equipment and Materials**

An infant ventilator (model IV-100B, Sechrist, Anaheim, California) supplied the ventilation. An air compressor (Proneb Ultra, Pari, Germany) provided the airflow to the nebulizer, at 5.5 L/min, as measured with a dry test gas flow meter (DTM-115, Singer American Meter Company, Wellesley, Massachusetts). The airflow controller and rotameter (FL-3440C-HRV, Omega Engineering, Omega Engineering, Manchester, United Kingdom) for the entraining jet were calibrated. The airflow for the entraining jet were provided by a wall feed. Filters (Respigard II, Vital Signs, Totowa, New Jersey) collected the aerosol.

We used a passive silicone neonatal test lung with a measured compliance of  $(7.8 \pm 2.0) \times 10^{-4}$  L/cm H<sub>2</sub>O at  $\Delta P = 6.5$  cm H<sub>2</sub>O. It consisted of an expanding and contracting volume connected to a narrow tube that had an opening that was connected to a filter, which in turn was connected to the patient output port of the modified nebulizer (Fig. 4).

The nebulized solute was ciprofloxacin hydrochloride dissolved in 0.9% saline solution. The absorbance of the standards and dilutions was measured with an ultraviolet diode array spectrophotometer (8452A, Hewlett Packard, Palo Alto, California). The absorbance of ciprofloxacin in solution is directly proportional to concentration for concentrations in the range of 200 ng/mL to 16  $\mu$ g/mL. The absorbance used was the difference between the peak and

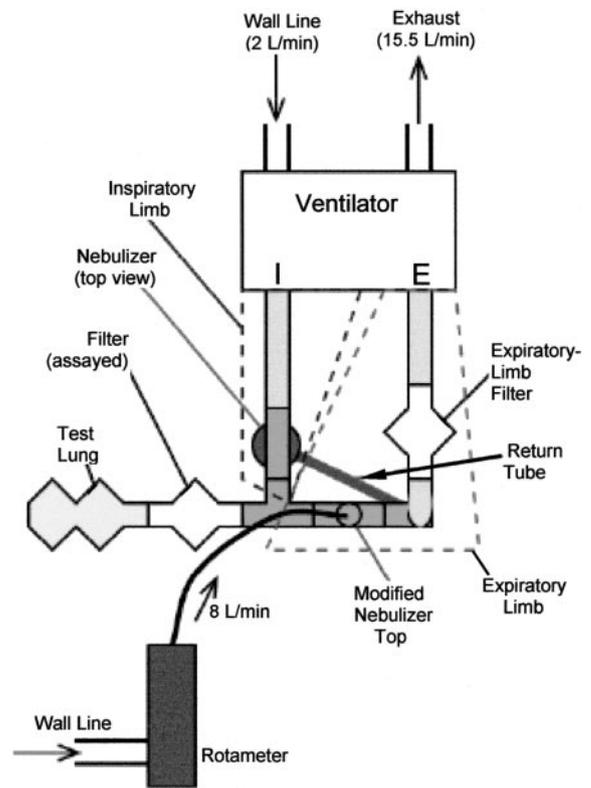


Fig. 4. The ventilator circuit used in the experiments. I = inspiratory. E = expiratory.

baseline absorbance readings, where the peak was recorded at  $\lambda = 272$  nm. The baseline was recorded at  $\lambda = 298$  nm.

No humidifier or endotracheal tube was used in the ventilator circuit in any of the test cases.

**Experimental Procedures**

The modified nebulizer was connected to the ventilator as indicated in Figures 3 and 4. A filter was placed in the ventilator circuit's expiratory limb to prevent release of ciprofloxacin to the ambient air. Another filter was placed between the neonatal test lung and the nebulizer's patient output port.

For each run, 7 mL of ciprofloxacin solution of known concentration was placed into the nebulizer reservoir. Each run was with either (1) the entraining jet off and no aerosol-recycling feedback, (2) the entraining jet on, but with no aerosol-recycling feedback, or (3) the entraining jet on, with aerosol-recycling feedback. The runs were performed in random mixed order, not in the order of the case numbers. Each time the entraining jet was run, the rotameter was used to set a measured dry (relative humidity 0%) air flow of 8 L/min. The flow rate could not be set arbitrarily high to boost the jet exit velocity, because that would increase evaporation effects.

The difference between the peak inspiratory pressure and the positive-end-expiratory pressure ( $\Delta P$ ) ranged from approximately 6.0 cm H<sub>2</sub>O to approximately 7.5 cm H<sub>2</sub>O between runs, which resulted in a tidal volume range of approximately 5–6 mL, which is representative of premature newborns. The data were normalized to a uniform  $\Delta P$  of 7.5 cm H<sub>2</sub>O, assuming linear variation of efficiency versus tidal volume over the small tidal volume range used in this experiment. This is also based on the assumption that the compliance of the test lung is constant over the small range of  $\Delta P$ .

We used a bias flow of  $2 \pm 1$  L/min and simulated a respiratory rate of 40 breaths/min and an inspiration-to-expiration ratio of 1:2.3. The nebulizer was allowed to run for as long as it continued to aerosolize solution. When the nebulizer appeared to have completed nebulization, the nebulizer was perturbed to ensure that no more solution could be nebulized. This ensured a “best case” for each run. At the end of each run, the filter and its casing were assayed. Distilled water was used to extract the captured ciprofloxacin. The filter had numerous holes poked into it with an eyedropper while water was placed onto the filter, which allowed multiple sections of the filter to have collected material extracted. The extract was diluted to 10 mL. All of the water used for dilution was first placed onto the filter. To ensure thorough extraction of the ciprofloxacin from the filter, a second extraction was performed, and each second extract was also diluted to 10 mL.

The nebulizer efficiency was calculated as:

$$(3) \quad \eta_{neb} = \frac{m_{filter}}{m_{dose}} \times 100\%$$

where  $m_{filter}$  is the mass of ciprofloxacin deposited on the filter and the filter casing,  $m_{dose}$  is the dose of ciprofloxacin placed in the nebulizer, and  $\eta_{neb}$  is the nebulizer efficiency.

To determine whether differences between sets of data were statistically significant, we used spreadsheet software (Excel, Microsoft, Redmond, Washington). We used the *t* test for independent samples, to obtain a *p* value for each comparison. Since the changes between cases were predicted, we used one-tailed *p* values. Taking the Bonferoni correction for 3 means into account, where the traditional *p* value for significance ( $p < 0.05$ ) is divided by 3, the null hypothesis was accepted to be true when  $p > 0.017$ , while the alternative hypothesis was accepted when  $p < 0.017$ .

Additionally, for 2 cases with no return to the reservoir, the return was instead fed into a beaker, to measure the volume of aerosol collected due to the entraining jet and impaction surface. It was expected that we would collect no solution in the beaker with the entraining jet off. Additionally, by measuring the absorbance of a dilution from

Table 1. Case 1: Entraining Jet Off and No Return to Nebulizer

PIP (cm H <sub>2</sub> O)	PEEP (cm H <sub>2</sub> O)	$\Delta P$ (cm H <sub>2</sub> O)	Efficiency (%)	Normalized Efficiency (%)
9.5	3.0	6.5	0.84	0.97
9.5	3.0	6.5	0.94	1.08
9.0	3.0	6.0	0.71	0.88
9.0	3.0	6.0	0.71	0.89

PIP = peak inspiratory pressure  
PEEP = positive end-expiratory pressure  
 $\Delta P$  = PIP – PEEP

Table 2. Case 2: Entraining Jet On But No Return to Nebulizer

PIP (cm H <sub>2</sub> O)	PEEP (cm H <sub>2</sub> O)	$\Delta P$ (cm H <sub>2</sub> O)	Efficiency (%)	Normalized Efficiency (%)
12.0	4.5	7.5	0.99	0.99
12.0	4.5	7.5	1.04	1.04
12.0	4.5	7.5	0.92	0.92
11.5	4.0	7.5	1.09	1.09
12.0	4.5	7.5	1.02	1.02
12.0	4.5	7.5	1.42	1.42

PIP = peak inspiratory pressure  
PEEP = positive end-expiratory pressure  
 $\Delta P$  = PIP – PEEP

Table 3. Case 3: Entraining Jet On With Return to Nebulizer

PIP (cm H <sub>2</sub> O)	PEEP (cm H <sub>2</sub> O)	$\Delta P$ (cm H <sub>2</sub> O)	Efficiency (%)	Normalized Efficiency (%)
11.5	4.0	7.5	1.23	1.23
11.5	4.0	7.5	1.82	1.82
11.5	4.0	7.5	1.75	1.75
11.5	4.0	7.5	1.44	1.44
11.5	4.0	7.5	2.47	2.47
11.5	4.0	7.5	1.20	1.20
11.0	4.5	6.5	1.22	1.40
10.5	4.0	6.5	1.19	1.37

PIP = peak inspiratory pressure  
PEEP = positive end-expiratory pressure  
 $\Delta P$  = PIP – PEEP

the collected sample, we calculated the fraction of the initial dose that was collected.

## Results

Tables 1, 2, and 3 show the raw results and the normalized efficiency numbers (normalized to  $\Delta P = 7.5$  cm H<sub>2</sub>O, assuming constant lung compliance for the small variation in  $\Delta P$  between the runs, as aforementioned). The added entraining jet airflow increased both the peak inspiratory

Table 4. In Vitro Nebulizer Aerosol Delivery Efficiency With a Neonatal Ventilator and Test Lung

Case	Number of Runs	Nebulizer Efficiency (mean ± SD %)
1. Entraining jet off and no return to nebulizer	4	0.96 ± 0.09
2. Entraining jet on but no return to nebulizer	6	1.08 ± 0.18
3. Entraining jet on, with return to nebulizer	8	1.58 ± 0.42

Table 5. Comparison of the Cases\*

Comparison	p
Case 1 vs 2	0.12
Case 1 vs 3	0.008
Case 2 vs 3	0.009

\*The comparisons were via *t* test with one-tailed *p* values and the Bonferoni-corrected significance (difference considered significant when *p* < 0.017).

pressure and the positive end-expiratory pressure by ≥ 1 cm H<sub>2</sub>O, compared with the case with the jet turned off. Table 4 shows the aerosol delivery efficiencies. Table 5 shows the results of the *t* tests comparisons of the values from the 3 cases. Table 6 gives data about the solution collected by the entraining jet in the case with the entraining jet on but with no aerosol-recycling return to the reservoir. As expected, no solution was collected when the entraining jet was off, so no data are presented for the case with the entraining jet off and no return to the reservoir.

### Discussion

Case 1 shows a delivery efficiency of approximately 1%, which is similar to that seen by previous authors,<sup>1,2</sup> despite the added volume of the apparatus and placement of the test lung filter.

The nebulization run time increased from approximately 20 min to approximately 28 min with the addition of aerosol-recycling feedback, with a concomitant increase in drug concentration near the end of nebulization. However, the improvement in aerosol delivery with feedback, by a factor of 1.6 (see Table 4), is encouraging.

Initially it was feared that the entraining jet might entrain aerosol that would have otherwise been delivered to the patient, as well as the outflow aerosol, which would have decreased delivery efficiency because less of the aerosol would have been output to the test lung. If that had been the case, the feedback may or may not have made up

for that decrease in efficiency. The Bonferoni-corrected *t* test between the 2 cases, however, showed no significant difference in the means. Apparently, the confinement of the jet in a fairly narrow tube limited the range of aerosol entrainment, so that the entraining jet alone had the desired lack of effect on efficiency.

Although the improvement seen with feedback was expected (as seen in Table 5, the *t* test showed a significant difference in the mean), the relatively efficiency improvement with both the entraining jet and feedback active was unforeseen. A likely explanation is that the entraining jet was somewhat loose, and orientation of the entraining jet probably had a relatively large effect because the jet was a turbulent source. Tighter control of the entraining jet would be expected to reduce the variability, but future work is needed to confirm this hypothesis.

From Table 6 it is clear that the concentration of the returned solution was higher than that of the stock solution, probably because the entraining jet's dry airflow evaporates water from the aerosol particles. Table 6 implies that  $f = 0.50 \pm 0.06$  in Equation 1, so this equation predicts that feedback can yield a maximum efficiency increase of a factor of  $2.0 \pm 0.3$ . Our measured increase of a factor of 1.6 is encouraging, but numerous issues must be investigated before this modified nebulizer can be considered for clinical use. First, the entraining jet increased the peak inspiratory pressure and positive end-expiratory pressure. Such change in flow and pressure would probably lead to complications in setting ventilator parameters and increased expiratory resistance in an actual patient, which would not be observed with a silicone test lung. Furthermore, the concomitant increase in concentration of the returned medicine may pose complications.

Although it was not apparent in this study, the added volume and size of the apparatus could pose problems with respect to compressible volume, dead space, and accidental extubation. In particular, compressible volume and dead space must be studied in greater detail. With our prototype, the output port to the test lung is in close proximity to the bias flow, so there should be little issue with dead space. Regardless, it is possible to build a feedback device with less volume (to reduce compressible volume and dead space) and a better geometry, to further reduce dead space.

Additionally, if a patient is infected with a pathogen, the expiratory gas might carry microbes that would be returned to the nebulizer reservoir, so the nebulizer would need to be carefully cleaned or disposed of to prevent the spread of microbes between patients. The effects of "recycled" microbes in the ventilator circuit needs to be investigated in detail.

Finally, while it was relatively straightforward to include the entraining jet into the ventilation circuit with the ventilator we used, other ventilator models may not allow

## INCREASING JET NEBULIZER DELIVERY IN VENTILATED NEWBORNS

Table 6. Volume and Mass Collected Per Dose in Case 2: Entraining Jet On But No Return to Nebulizer

PEEP (cm H <sub>2</sub> O)	ΔP (cm H <sub>2</sub> O)	Volume Collected/Initial	Mass Collected/Dose
4.5	7.5	0.256	0.562
4.5	7.5	0.263	0.457
4.5	7.5	0.268	0.458
4.0	7.5	0.269	0.574
4.5	7.5	0.273	0.466
4.5	7.5	NA	NA
Mean ± SD		0.266 ± 0.007	0.503 ± 0.059

PEEP = positive end-expiratory pressure  
 ΔP = peak inspiratory pressure minus PEEP  
 NA = not applicable

for a similar modification of the ventilator circuit without disrupting the airflow sensors and their associated control systems.

We made a reasonable effort to determine a geometry that would yield better results, but more optimized geometries should still be possible, since the test apparatus was limited by the fact that the modified nebulizer was composed primarily of a commercially available T-piece, rather than custom-designed parts.

### Conclusion

We studied a method for capturing aerosol in the expiratory limb and returning it to the nebulizer reservoir, in hopes of improving jet nebulizer efficiency for neonatal application. An entraining jet was added to a modified nebulizer, resulting in impaction and collection of aerosol onto a collection wall. The collected drug was then returned to the reservoir via gravity feed, allowing for re-aerosolization of the recycled aerosol.

With our prototype we observed an increase in the deposition of drug onto the filter at the patient output. The average increase was by a factor of nearly 1.6, compared with the performance of the same prototype with the aerosol collection and return function disabled.

Although the observed increase in efficiency is promising, our prototype is not ready for clinical use. Other variables affected by the nebulizer must be investigated before clinical trials could occur, including changes due to the increased airflow, the increase in dead space, and the concomitant increase in the concentration of the medicine in the returned solution.

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