

Aerosol Delivery through Nasal Cannulas: *An In Vitro* Study

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ABSTRACT

In most circumstances, a nasal route for the delivery of pulmonary aerosol medications is rarely considered; however, in specific instances, this route may be quite useful. Consider, for example, the delivery of aerosol treatments during humidified high-flow nasal cannula use in pediatric critical care, or continuous aerosol delivery via cannula for medications with short durations of action. The goal of this study was to evaluate the potential for delivering aerosols via nasal cannula through *in vitro* studies of aerosol output and size. The system utilized for testing included an Aerogen *Solo* nebulizer downstream of a heater/humidifier system, followed by a nasal cannula and an aerosol collection apparatus. Adult, pediatric, and infant cannulas were tested with and without an inhalation-only breathing simulator. The cannulas were driven by 3 lpm (50 psig) oxygen flows. Dose quantification was performed using radioisotope techniques. Total cannula output and system losses were measured. Aerosol size measurements were made from the nebulizer, from the heating tube, and from the prongs of the adult and pediatric cannulas, using laser-diffraction techniques. Total cannula output ranged from 8.4–25.1% and 18.6–26.9% of loaded dose, without and with the addition of inhalation flows. Volume median diameters were $2.2 \pm 0.2 \mu\text{m}$ from the adult cannula and $1.9 \pm 0.3 \mu\text{m}$ from the pediatric cannula. Ninety percent of the aerosol volume was in sizes smaller than $4.2 \pm 0.4 \mu\text{m}$ (adult) and $3.8 \pm 0.5 \mu\text{m}$ (pediatric). System losses were highest in the nebulizer–humidifier connectors, heated tube, and humidifier. Losses in the nebulizer were very low (2.2–3.5%). This study demonstrates that aerosols can be efficiently delivered through a humidified high-flow nasal cannula system. Further study is required to determine if this route is viable for pulmonary delivery.

Key words: bench testing, nebulizer, cannula

INTRODUCTION

THE NOSE IS RARELY CONSIDERED as an optimal route for aerosol delivery to the lungs. Under certain circumstances, however, this mode of delivery may be very convenient and useful. In pe-

diatric critical care, for example, humidified high-flow nasal cannula (HHFNC) use is common as a means of maintaining patent airways, enhancing gas exchange, and avoiding mechanical ventilation.^(1–8) This technique uses flows of 2–8 lpm of humidified oxygen that provide supportive

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pressure in the upper airways. In this setting, for example, the cannula could be utilized to deliver aerosol treatments for bronchiolitis, which would otherwise be delivered via a nebulizer using a face mask.^(9,10) Infants under the age of 4 months are typically obligate nose breathers,⁽¹¹⁾ making nasal delivery the only option regardless of the delivery system. Systemic delivery of inotropic support could also be considered via a nasal cannula as an alternative to i.v. therapy, especially in situations where i.v. access is challenging. In adult populations there is a potential to utilize aerosol delivery via a nasal cannula to continuously or intermittently dispense inhaled doses of short-acting medications, especially for conditions that may already require oxygen therapy via a cannula. Ideally, this delivery would be continuous and passive, allowing the patient to receive treatments without interruption to their daily routine.

Using a nasal delivery route presents obvious challenges. From an *in vivo* perspective, the nose is a potential site of substantial aerosol deposition. Heyder et al.⁽¹²⁾ considered nasal aerosol inhalation in adults. Maximum alveolar deposition occurred with a 2- μm aerosol with 18–40% of the starting dose being deposited in the deep lung, depending on breathing conditions. Deposition in the nose was substantial, ranging from 33–65%.

Increasing aerosol size to 5 μm resulted in 67–88% deposition within the nose, with proportional decreases in airways and alveolar dose. Jet flows from the cannula prongs might also cause regions of high local deposition within the nose. Drug delivery through a humidified nasal cannula also presents challenges in terms of the delivery system itself. The small-diameter tubes of the cannula have the potential for substantial internal deposition. Humidification use in ventilator circuits has been shown to decrease aerosol delivery,⁽¹³⁾ and the presence of a heating wire within the circuit adds an additional surface for deposition.

The goal of the current study was to evaluate the potential for delivering aerosols via nasal cannula through *in vitro* studies of aerosol output and aerosol size from a cannula aerosol delivery system. This system was assembled based on equipment used in the pediatric intensive care unit for humidified high flow gas delivery. A micropump nebulizer was added to the circuit downstream of the heater-humidifier (see Fig. 1). Radioisotope techniques were utilized to determine the percentage of loaded nebulizer dose delivered through the prongs of adult-, pediatric-, and infant-sized cannulas. An inhalation-only breathing simulator was later added to the circuit to estimate the effects of inspiratory flows on the delivered dose. Aerosol losses in system compo-

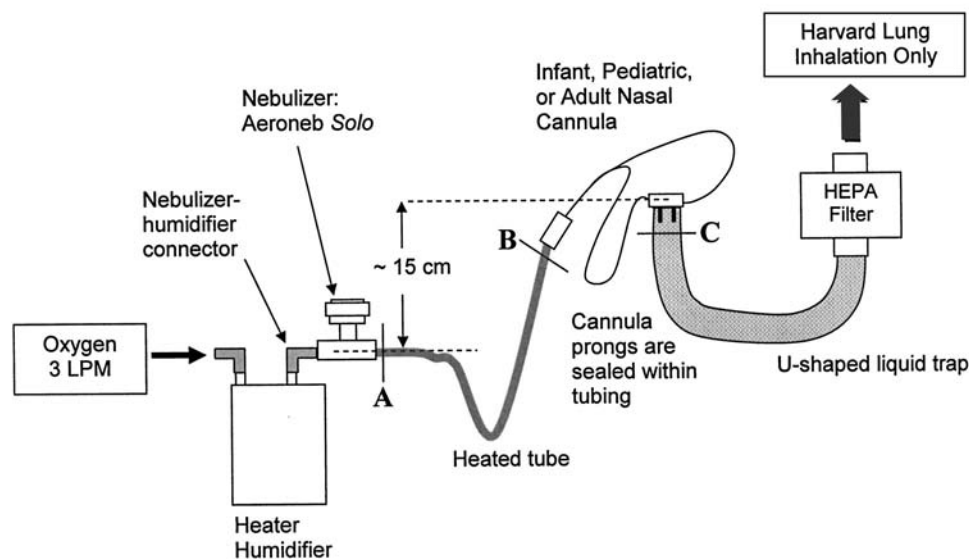


FIG. 1. Nasal cannula aerosol delivery system. All cases utilized a 3 lpm oxygen flow through the circuit. Harvard lung cases included inspiratory flows appropriate to the patient group associated with each cannula. Aerosol output dose was captured by the HEPA filter at the end of the circuit. A liquid trap collected nonaerosol dose delivered through the system (i.e., dripping). Adult, pediatric, and infant cannulas were tested. Aerosol sizing measurements were made at points A, B, and C (in open air).

nents were measured or estimated. Aerosol sizing was also performed to quantify aerosol size at various points in the delivery system.

METHODS

The system utilized for *in vitro* testing is shown in Fig. 1. An Aerogen Solo nebulizer (Aerogen/Nektar, Mountain View, CA) was placed downstream of a Fisher Paykel heater-humidifier system (Fisher & Paykel Healthcare Inc., Irvine, CA), followed by the nasal cannula. The heater-humidifier included a heated tube section containing a thermostatically controlled heating wire. The device was set to 37°C and 100% relative humidity (RH). Adult-, pediatric-, and infant-sized cannulas were tested. An approximately 4.5 cm-long corrugated tubing assembly was placed over, and sealed around, the prongs of the cannula for testing. This short tube segment was then connected to a longer piece of corrugated tubing that was curved into a "U"-shaped trap to collect the liquid that was delivered through the cannula in nonaerosol form (dripping). A single cartridge HEPA filter (HEPA-Lites, Teleflex Medical, Temecula, CA) was placed at the end of the U-tube. This filter provided a measurement of the total aerosol output dose delivered through the circuit (Fig. 1). The entire filter assembly was raised approximately 15 cm above the rest of the delivery apparatus to minimize gravity-driven dripping.

Dose quantification was performed using radioisotope techniques. Approximately 2 mCi of Technetium (Tc-99m) DTPA in 4 mL of deionized water was added to the nebulizer at the start of testing and nebulized until dry. Radioactivity was measured in the aforementioned output filter, the heated tubing of the heater/humidifier circuit, the "U"-shaped trap, the cannulas, the connectors joining the nebulizer to the humidifier, and in the nebulizer itself. All measurements were made using a nuclear medicine dose calibrator (Radioisotope Calibrator CRC-4, Capintec Inc., Ramsey, NJ). All doses are presented as a time-corrected percentage of the dose loaded into the nebulizer. *Aerosol output dose* was assessed based on the total activity found only in the output filter. The lost dose in the delivery system components was determined based on specific measurements, except for losses in the humidifier. Because the humidifier was too large to be assessed in the dose calibrator, it was assumed

that all activity not found in other components was deposited there. This dose is reported as *losses in heater/humidifier (assumed)*. Adult-, pediatric-, and infant-sized cannulas were tested using oxygen flow rates of 3 lpm (at 50 psig). Two test cases were considered. In Case 1, aerosol was delivered through the circuit using only the 3 lpm driving oxygen flow. In the second case, inspiratory flows were applied to the circuit using a Harvard Lung at settings appropriate to the population associated with each cannula type. Inspiration only flows were utilized on the assumption that a large portion of cannula and normal expiratory flows would vent through the mouth. This venting has been demonstrated in studies of nasal (prong delivered) CPAP in newborns.⁽¹⁴⁾ Three trials were run for each test case with each cannula. The nebulizers were run until dry and the *run time* was noted.

Aerosol size measurements were also made using laser-diffraction techniques. A Malvern MasterSizer S (Malvern Instruments, Southborough, MA) was utilized to make open-air measurements of aerosol size as delivered from the humidifier and nebulizer (point A, Fig. 1), from the heater tube of the circuit measured just upstream of the cannula (point B, Fig. 1), and from the prongs of the adult, pediatric, and infant cannulas (point C, Fig. 1). For nebulizer and heated tube measurements the circuit was opened at the points shown on Figure 1, and aerosol size measurements were made in open air. For the cannula size measurements, the cannula prongs were placed into a standard mouthpiece and sealed in order to optimally spread the jet stream emitted from the cannula for measurement by laser diffraction. Each result is based on 10 individual size measurements. Volume median diameter (VMD) and 90% volume diameter $D_v(90)$ are reported. Half of aerosol volume is in sizes smaller than the median diameter, while 90% of total volume is in sizes smaller than $D_v(90)$.

A two-factor ANOVA was used to consider the effects of cannula type and the addition of inhalation flows from the Harvard lung on aerosol output dose and losses in specific portions of the delivery system. A single-factor ANOVA was used to consider changes in median aerosol size during passage through the delivery system. Individual comparisons of output results and median size comparisons between cannulas were made using unpaired two-sided *t*-tests. In all cases significance was based on $p \leq 0.05$.

TABLE 1. SUMMARY OF AEROSOL OUTPUT DOSE AND DELIVERY TIME FOR THE NASAL CANNULA AEROSOL DELIVERY SYSTEM SHOWN IN FIGURE 1

	<i>Infant cannula</i>		<i>Pediatric cannula</i>		<i>Adult cannula</i>	
	<i>No Harvard lung</i>	<i>Harvard lung</i>	<i>No Harvard lung</i>	<i>Harvard lung</i>	<i>No Harvard lung</i>	<i>Harvard lung</i>
Aerosol output dose (%)	8.4 ± 2.3	18.6 ± 4.0	18.1 ± 4.2	25.4 ± 1.7	25.1 ± 5.0	26.9 ± 4.9
delivery time (min)	13.1 ± 2.5	10.8 ± 0.7	13.0 ± 0.0	10.9 ± 1.4	12.5 ± 0.4	12.1 ± 0.8

Aerosol output dose is the percentage of the loaded nebulizer dose delivered into the HEPA filter at the end of the circuit. For the Harvard lung cases, inspiratory flows appropriate to the patient group associated with each cannula were utilized. Three trials were performed for each case. All values ± SD.

RESULTS

In all cases, a substantial portion of the dose added to the nebulizer was delivered through the cannula assembly. Average aerosol output dose ranged from 8.4–25.1% of loaded dose with oxygen flows alone, and from 18.6–26.9% when inspiratory flows were added with the Harvard Lung (see Table 1). Aerosol output dose varied significantly by cannula type and with the use of the Harvard lung (ANOVA: $p = 0.0004$, $p = 0.005$). Compared individually, the pediatric and adult cannulas had significantly higher output doses versus the infant cannula without the Harvard lung (t -test: $p = 0.04$ and 0.02). When the Harvard lung was in use these differences were not significant. The addition of inspiratory flows from the Harvard Lung significantly increased total output dose from the infant cannula (t -test: $p = 0.03$), and had no statistically significant effect with the adult or pediatric cannulas. Doses

collected in the U-shaped trap designed to catch liquid delivered through the cannula system in nonaerosol form ranged from 1.0–3.8% of loaded dose, and did not vary significantly based on cannula type or the use of the Harvard lung (ANOVA). Run times varied from 10.8–13.1 min.

Losses within the cannulas ranged on average from 3.5–12.3% of loaded dose, and were generally increased within the adult cannula (ANOVA: cannula type $p = 0.03$, Harvard Lung $p = \text{NS}$) (see Table 2). Losses in the heater/humidifier were quite varied across test cases ranging from 1.7–26.7%, and were increased in the infant cannula (ANOVA: cannula type $p = 0.004$, Harvard lung $p = \text{NS}$). Losses within the nebulizer remained extremely low in all test cases varying from 2.2–3.5%. Substantial losses were noted in the connection point between the humidifier and the nebulizer, varying from 17.3–27.8%. Losses in the heated tube were also substantial varying from 27.1–37.3%. None of these values varied sig-

TABLE 2. SUMMARY OF COMPONENT LOSSES FOR THE NASAL CANNULA AEROSOL DELIVERY SYSTEM SHOWN IN FIGURE 1

	<i>Infant cannula</i>		<i>Pediatric cannula</i>		<i>Adult cannula</i>	
	<i>No Harvard lung</i>	<i>Harvard lung</i>	<i>No Harvard lung</i>	<i>Harvard lung</i>	<i>No Harvard lung</i>	<i>Harvard lung</i>
Losses in cannulas	3.5 ± 2.0	7.5 ± 1.1	7.8 ± 5.2	6.6 ± 3.1	12.3 ± 5.0	10.8 ± 2.9
Losses in nebulizer	2.2 ± 0.3	3.4 ± 0.6	3.5 ± 1.1	2.7 ± 0.8	2.8 ± 1.4	2.4 ± 0.6
Losses in nebulizer–humidifier connectors	25.6 ± 5.9	20.4 ± 17.7	27.8 ± 12.7	17.3 ± 11.9	26.0 ± 16.2	20.7 ± 8.2
Losses in heated tube	30.7 ± 4.3	32.1 ± 7.8	37.3 ± 2.5	35.0 ± 11.6	27.1 ± 1.7	28.5 ± 2.5
Losses in U-shaped liquid trap	3.0 ± 3.8	1.0 ± 1.0	3.8 ± 3.0	1.8 ± 0.5	1.1 ± 0.4	2.1 ± 1.5
Losses in heater/humidifier (assumed)	26.7 ± 3.7	17.1 ± 8.8	1.7 ± 1.1	11.1 ± 5.4	5.6 ± 11.8	8.7 ± 5.8

For the Harvard lung cases, inspiratory flows appropriate to the patient group associated with each cannula were utilized. Three trials were performed for each case. Values represent the percent of the dose loaded into the nebulizer. All values ± SD.

TABLE 3. AEROSOL SIZE MEASUREMENTS AT DIFFERENT POINTS IN THE NASAL CANNULA AEROSOL DELIVERY SYSTEM

Meas. point		VMD μm	Dv90 μm
A	Exit of nebulizer	$5.0 \pm 0.2^{*,**}$	8.9 ± 0.8
B	Exit of heater tubing	$4.2 \pm 0.7^{*,**}$	6.8 ± 1.5
C	Adult cannula	$2.2 \pm 0.2^{*,***}$	4.2 ± 0.4
C	Pediatric cannula	$1.9 \pm 0.3^{*,***}$	3.8 ± 0.5
C	Infant cannula	NM	NM

Specific measurement points are shown in Figure 1. Measurements were made in open air using laser diffraction. Results based on the average of 10 measurements each. VMD, volume median diameter; Dv90, 90% volume diameter. NM, not measured due to aerosol density below instrument limit.

$^{*,**}p < 0.0001$ by ANOVA; $^{***}p < 0.02$ by *t*-test.

nificantly based on cannula type or Harvard lung use (ANOVA).

Changes in median aerosol size during transit through the circuit are presented in Table 3. Median aerosol size decreases during passage through the circuit with the largest reductions occurring within the cannulas. Aerosol size from the infant cannula could not be measured because aerosol density was below instrument limits.

Ninety-percent of the aerosol volume delivered from the prongs of the adult nasal cannula was in sizes smaller than $4.2 \mu\text{m}$. The fraction of aerosol volume delivered from the nebulizer in sizes smaller than $4.2 \mu\text{m}$ was approximately 37%. The percentage of the total nebulized dose recovered from the outlet filter was $\sim 26\%$ —approximately two-thirds of what would be anticipated if the delivery system was acting as an absolute inertial filter with a cut point equal to Dv(90) at the cannula outlet. Similarly, 90% of the volume delivered from the pediatric cannula was in sizes smaller than $3.8 \mu\text{m}$. The portion of aerosol volume delivered from the nebulizer in sizes smaller than $3.8 \mu\text{m}$ was approximately

30%, with $\sim 20\%$ of the nebulized dose being recovered in the output filter. This result would also seem to indicate a removal of larger size classes, and some percentage loss ($\sim 33\%$) of volume in the sizes classes that do generally transit the delivery system.

DISCUSSION

The goal of the current study was to evaluate the potential for delivering aerosols via a nasal cannula through *in vitro* studies of aerosol output and aerosol size. The results demonstrated 8.4–25.1% transport of the loaded dose through the delivery circuit without an inhalation flow and 18.6–26.9% transport of the loaded dose when an inhalation flow from a breathing apparatus was present. These percentages were based on filter collection following transit through a “U”-shaped tube designed to trap dripping liquid, and are therefore indicative of aerosol dose only. This is surprisingly efficient delivery given the large potential for internal deposition within the circuit. The delivered doses in the best cases are similar to what one might expect with oral inhalation from a nonbreath actuated jet nebulizer.⁽¹⁵⁾ Low internal losses within the micro-pump nebulizer contributed substantially to this efficiency.

Delivery using only the driving oxygen flow of 3 lpm was considered as the first case, and then a Harvard lung breathing apparatus with an appropriate inhalation-only breathing pattern for the cannula in use was connected to the outlet filter and delivery was reassessed. Adding inspiratory flows increased aerosol delivery with the smallest cannulas, likely by increasing flow through the circuit and limiting the potential for aerosol back-flow into the humidifier. The inspiration-only model likely overestimates delivered

TABLE 4. HARVARD LUNG BREATHING APPARATUS SETTINGS USED TO PROVIDE INHALATION FLOWS TO NASAL CANNULA DELIVERY SYSTEM SHOWN IN FIGURE 1

	Infant cannula	Pediatric cannula	Adult cannula
Tidal volume (mL)	150 ^a	300	550
Respiration rate (breaths/min)	25	18	15
Inhalation: exhalation ratio	50/50	50/50	50/50

Pediatric values estimated using empirical equations of Hoffman.¹⁸

^aApproximate tidal volume of a 4-year-old child was used based on limits of simulator.

dose in the clinical setting. Mouth-venting of CPAP flows delivered through nasal prongs has been demonstrated in (normally nasal-obligate) newborns.⁽¹⁴⁾ The potential for different flow paths makes it difficult to model exhalation at the nose during cannula use. Also, the limits of the breathing simulator used prevented the simulation of the true tidal volume conditions of an infant, likely resulting in further overestimates (see Table 4).

The most substantial losses within the delivery circuit occurred within the heated tube, the connection between the heater-humidifier and nebulizer, and within the heater-humidifier itself. Likely all of these losses were the result of high nebulizer output and relatively low conducting gas flow rates. Such losses might be reduced by the addition of a reservoir in place of the simple t-piece used to connect the nebulizer to the circuit. The heating wire within the heated tube most likely contributed to increased losses that were observed there. Losses within these components were somewhat variable by test case. This variability seemed to represent a tradeoff in losses among the components that ultimately did not result in much variability in the output dose.

The changes in median aerosol size and the relative changes in volume distribution measured at different points in the delivery system seem to indicate an almost absolute filtering of larger droplet size classes, and some percentage loss of volume in the smaller "passable" size classes, most likely due to inertial impaction within the delivery system. We estimate that the transit time for a droplet in the current experiment would be of the order of 6 sec, which would also seem to indicate a potential for gravitational sedimentation. (Both mechanisms would favor the loss of larger droplets.) The potential for aerosol size changes and subsequent aerosol deposition changes based on thermodynamic effects such as evaporation or hygroscopic growth is present as well. The combination of aerosol heating and a humid environment is likely to produce a complex dynamic that would affect the smallest droplets most quickly and profoundly. Larger droplets would be less significantly and more slowly affected. (The time scale for changes to a 2- μm droplet due to hygroscopic effects is of the order of 10 sec⁽¹⁶⁾.) It is difficult to speculate whether thermodynamic effects played a major role in these experiments, but their potential contribution should not be excluded, especially if aerosols with very high solute concentrations are

being considered. Importantly, we must consider the limitations of our aerosol size measurement methods. The use of a laser diffraction instrument necessitated that the circuit be opened at points A and B (Fig. 1) in order to measure aerosol size in the open air. Although we believe that upstream phenomena will dominate, these alterations may have affected aerosol size dynamics, and therefore the accuracy of our measurements.

The high delivered doses from the cannulas suggest the potential for substantial pulmonary drug availability, but could also suggest the potential for substantial local delivery and possibly toxicity within the nose. Favorably, even with the cannula prongs pointed straight down, the liquid delivered by the system in nonaerosol form (i.e., dripping), was minimal. Lacking data from an anatomical model, we can predict aerosol deposition only based on the size of the aerosol at the cannula prongs. This aerosol was small in all cases considered: all volume median diameters were $\leq 2.2 \mu\text{m}$, and all 90% volume diameters were $\leq 4.2 \mu\text{m}$. Past studies involving the nasal inhalation of different monosized aerosols have demonstrated that maximum alveolar deposition occurs with sizes in the range of 2 μm , with deposition fractions as high as 40%.⁽¹²⁾ Nasal deposition fraction could vary substantially based on the exact orientation of the cannula prongs within the nose. Also, no data is available on the optimal aerosol size for nasal delivery in pediatric subjects.

Our study demonstrates that aerosols can be delivered efficiently through the current equipment used for humidified high flow nasal cannula gas delivery. This mode of delivery would seem to merit further investigation and development, because it would already be in place in many pediatric patients, and because the only obvious alternative for nebulized delivery to these patients is the use of a mask. Our study does not directly consider the deposition of the aerosols after inhalation, which obviously requires further investigation. Measurements of local delivery and toxicity should be addressed through studies with accurate anatomical models.⁽¹⁷⁾ A new design of equipment specifically for this application would benefit from a prong design that would prevent orientations that might result in locally high deposition.

A less explored, potential application for nasal aerosol delivery would be passive, continuous delivery of aerosols over extended periods to

adult subjects. This could be considered for drugs with short half-lives that would otherwise require multiple daily oral inhalation treatments. Obviously, this application would require even more specific system design and extensive clinical study, but the potential for the development of a system for continuous aerosol delivery is attractive.

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