

In Vitro Comparison of Heliox and Oxygen in Aerosol Delivery Using Pediatric High Flow Nasal Cannula

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Summary. Drug administration via high flow nasal cannula (HFNC) has been described in pediatrics but the amount of albuterol delivery with an HFNC is not known. The purpose of this study is to quantify aerosol delivery with heliox and oxygen (O₂) in a model of pediatric ventilation. A vibrating mesh nebulizer (Aeroneb Solo, Aerogen) was placed on the inspiratory inlet of a heated humidifier and heated wire circuit attached to a pediatric nasal cannula (Optiflow, Fisher & Paykel). Breathing parameters were tidal volume (V_t) 100 ml, respiratory rate (RR) 20/min, and I-time of 1 sec. Albuterol sulfate (2.5 mg/3 ml) was administered through a pediatric HFNC with O₂ (100%) and heliox (80/20% mixture). A total of 12 runs, using O₂ and heliox were conducted at 3 and 6 L/min (n = 3). Drug was collected on an absolute filter, eluted and measured using spectrophotometry. The percent inhaled dose (mean ± SD) was similar with heliox and O₂ at 3 L/min (11.41 ± 1.54 and 10.65 ± 0.51, respectively; P = 0.465). However at 6 L/min drug deposition was ≥2-fold greater with heliox (5.42 ± 0.54) than O₂ (1.95 ± 0.50; P = 0.01). Using a pediatric model of HFNC, reducing delivered flow from 6 to 3 L/min increased inhaled albuterol delivery ≥2-fold but eliminated the increase in inhaled drug efficiency associated with heliox. **Pediatr Pulmonol.** 2011; 46:795–801. © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Heliox, a blend of helium and oxygen, has been used in medicine for 70 years to reduce work of breathing with fixed and variable airway resistance. Helium is an odorless, colorless, inert gas with a lower density (0.4 kg/m³) than air (1.20 kg/m³) or oxygen (1.33 kg/m³), but with a similar viscosity (198 μP vs. 183 μP and 204 μP, respectively). This lower density has been associated with a decrease in the Reynolds number and decreased turbulent gas flow through restricted orifices such as narrowed and obstructed airways. As airways and tubings narrow, flow patterns tend to transition from laminar to turbulent, resulting in greater resistance to flow, and greater impactive losses of aerosol.

The penetration and subsequent deposition of inhaled aerosols in the human lung depends on both the physical properties of the particles (including size, shape, and density) and on the flow regime of the carrier gas. Flow regime is affected by the physical properties of the gas (including viscosity and mean free path), and also by the breathing pattern and by the geometry of the respiratory tract.¹

Heliox has been associated with changes in flow patterns from turbulent to transitional, but its benefits persist even under turbulent conditions.^{2,3}

Although flow measurements such as turbulent kinetic energy and velocity magnitude typically differ less than 5% between air and heliox, particle deposition was shown

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Drug name: Albuterol (Salbutamol) Sulfate (2.5 mg/3 ml).

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to be affected by these small differences in the carrier gas. The use of heliox led to less particle deposition for all droplet sizes indicating that heliox will lead to a reduction of in vivo extrathoracic deposition due to the intrinsic properties of the gas phase.⁴

Droplets are conveyed from the nebulizer through the conducting pathway of the HFNC circuit through the action of drag forces imparted by the driving gas. Deposition due to impaction occurs when the steering drag forces are not sufficient to prevent a droplet from following an inertial path that intersect with walls of the conducting pathway or circuit. Drag force, which is dependent on gas density, gas velocity and droplet radius, increases with use of heliox. These higher steering drag forces may improve the conveyance of the aerosol droplets through the conducting HFNC circuit, reducing the likelihood that droplets will deposit due to impaction.⁵

Heliox with aerosol drug administration has been increasingly used in recent years for administration of bronchodilators because of its theoretical ability to carry aerosols deeper than air or oxygen into the airways distal to the sites of airway narrowing and obstruction, resulting in higher lung deposition and greater bronchodilation.⁶⁻⁹ The clinical effects of heliox-carried aerosol drug administration have been studied by several researchers and the findings of these studies differ strikingly. Whereas some researchers found benefits from heliox-carried aerosol drug administration,^{8,10-14} others reported no clinical benefits at all.¹⁵⁻¹⁹ It is clear on closer analysis that the differences between these findings are due to variations not only in research methods and patient characteristics, but also in the technique and duration of both gas and aerosol administration.

Although delivery of aerosol particles with heliox has been reported to result in greater aerosol deposition in adults when compared with air or oxygen, deposition has not been tested extensively in pediatrics. Infants and small children are not simply anatomically scaled-down adults.²⁰ Their rapid growth and transition in relative size of airway structures and breathing parameters, also impact the ability to use and tolerate various aerosol delivery appliances, such as mouthpieces. Therefore, aerosol drug administration differs fundamentally in infants and children. For instance, while the mask is often used for aerosol delivery in adults, it is not well tolerated by up to 47% of young children; therefore, not an optimal way of aerosol drug administration for pediatrics.²¹ Recently, high flow nasal cannula (HFNC) has been used

for the delivery of aerosol medications in children. Previous literature reported that HFNC maintains patent airways, improves gas exchange, and avoids mechanical ventilation.²²⁻²⁹ Recent in vitro work suggests that aerosol from a vibrating mesh nebulizer may administer aerosol with HFNC with relatively high inhaled mass.³⁰

We hypothesize that due to the relatively high flows delivered with HFNC, inhaled drug will decrease as driving gas flow through the circuit and nasal prongs increases. The administration of aerosol with heliox may reduce impactive losses through the conducting circuit and improve aerosol delivery. Therefore, the purpose of this study was to compare heliox and oxygen in aerosol drug delivery via HFNC to a model simulating a pediatric breathing pattern.

MATERIALS AND METHODS

In Vitro Lung Model

A pediatric breath simulator was composed of ventilator (Galileo, Hamilton, Inc., Reno, NV) attached to one chamber of a dual chamber test lung (Michigan Instruments, Grand Rapids, MI) with a rigid connection between the two chambers. Positive pressure applied from the ventilator displaced one chamber, creating a simulated inspiratory, and expiratory gas flow from the other chamber. This chamber was connected to an absolute filter, to collect aerosolized drug, connected to one side of a simulated nares/pharynx, composed of a t-piece with two orifices simulating nares on the distal end, and a cap on the T, in gravity dependent position, to collect any condensate or rainout (see Fig. 1). Since infants and small children receiving HFNC tend to vent excess flow through the mouth or nares, the nares of our model were designed to have a larger inner diameter than the external diameter of the nasal prongs, providing an open system that allows excess gas to enter or exit the model. The internal volume of the t-piece (15 ml) and filter housing to the surface of the filter media (30 ml) was similar or larger than the predicted anatomical dead space of a 14 kg child with the breathing parameters used in this study: Tidal volume (V_T) 100 ml, frequency 20/min, and I-time of 1 sec.

Gases

As shown in Figure 2, each experiment was conducted with 100% oxygen and 80:20% heliox. A heliox calibrated external flow meter (HOR-28016, WT Farley, Inc., Camarillo, CA) with a range of 0–16 L/min was attached to a 50-psi pressure regulator at the outlet of an 80:20 heliox cylinder. Oxygen was delivered through an oxygen-calibrated flow meter (Timeter, St. Louis, MO) with a range of 0–15 L/min, attached to a 50-psi regulator at the outlet of an oxygen cylinder.

ABBREVIATIONS:

Heliox	helium oxygen mixture
HFNC	high flow nasal cannula
RR	respiratory rate
SD	standard deviation

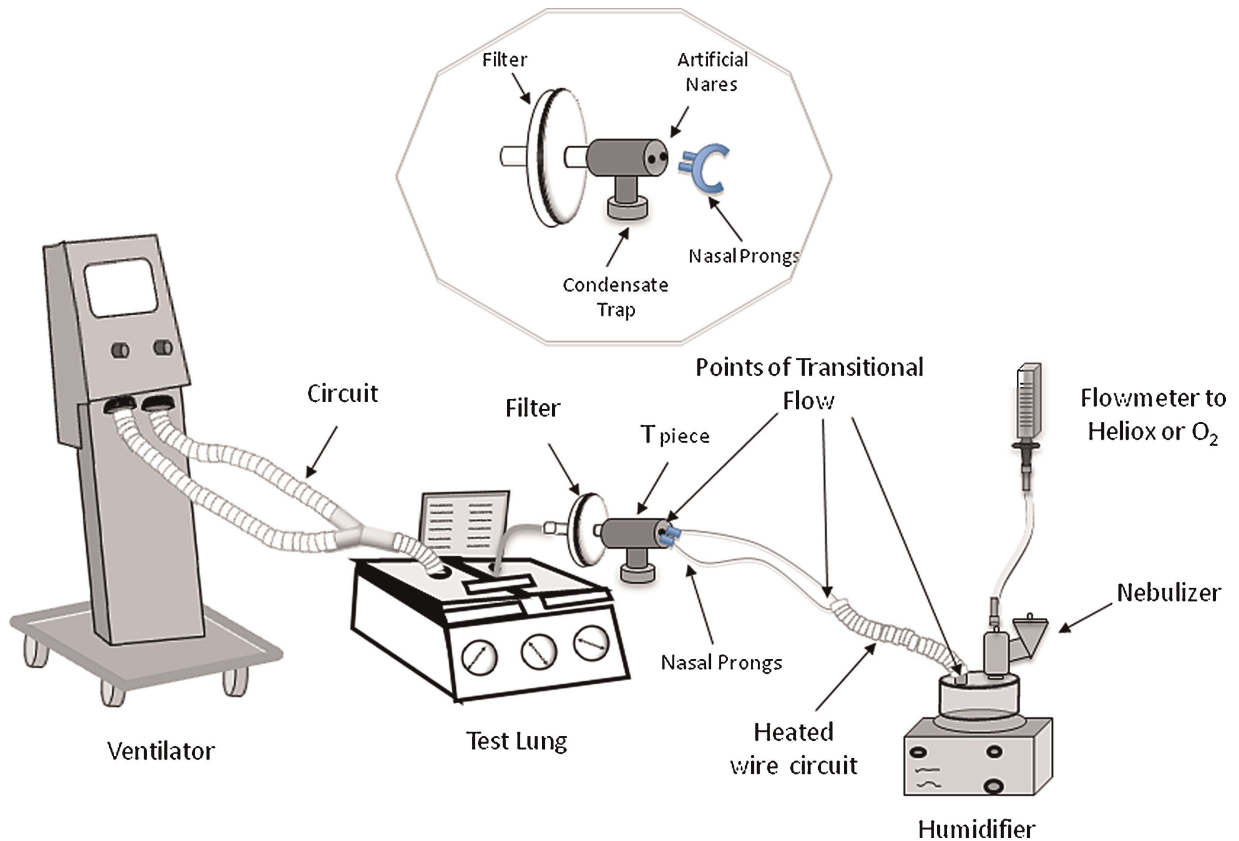


Fig 1. Experimental set-up of the study. Gas from Heliox or O₂ cylinders pass through a flow meter attached to a T-piece with nebulizer at the inlet of humidifier to heated wire circuit and nasal prongs to a T-piece and filter attached to one side of test lung, with rigid bar attached to other test lung compartment attached to ventilator. Ventilation of the test lung compartment moves the other compartment simulating spontaneous breathing pattern. Inset shows exploded view of interface of nasal prong, T-piece with artificial nares, condensate trap, and collecting filter. Three primary points of transitional flow occur while gas passes through the humidifier into the circuit, from the circuit to the nasal cannula, and from the nasal prongs into the artificial nares.

Test gas was connected through an adapter holding a vibrating mesh nebulizer (Aeroneb Solo, Aerogen, Inc., Galloway, Ireland) placed on the inspiratory inlet of a heated humidifier and heated wire circuit attached to a pediatric nasal cannula (Optiflow, Fisher and Paykel Healthcare Corporation, Auckland, New Zealand). Albuterol sulfate (2.5 mg/3 ml) was placed in the nebulizer medication reservoir and the aerosol administered through a pediatric HFNC, with prongs placed in the nares of the model.

Flow Rates

In this in vitro study, the flow rates were set at 3 and 6 L/min, using heliox and oxygen (Fig. 2). These flow rates are commonly used with the pediatric HFNC with oxygen and heliox during the treatment of children.

Data Collection

A total of 12 runs, 6 using oxygen and 6 using heliox were conducted at each flow rates ($n = 3$).

In Vitro Measurements

The absolute filter distal to the nares and pediatric HFNC was used to collect aerosolized albuterol with each run. Drug was eluted from the filter with 0.1 M normal hydrochloric acid for 3 min with gentle agitation, and analyzed via spectrophotometry (Beckman Instruments, Fullerton, CA), at a wavelength of 276 nm. The spectrophotometer was calibrated before the trials to determine wavelength accuracy, and set to zero, using the solvent alone before each analysis. Albuterol eluted from the filter was quantified and expressed as a percent of drug delivered from original dose placed in the medication reservoir of the aerosol generators.

Data Analysis

The amount of drug deposited in the filter was expressed as a percentage of the total inhaled drug mass delivered from each aerosol generator during each trial experiment. Descriptive statistics were calculated for the means and standard deviations (SDs) of each gas type and flow rate

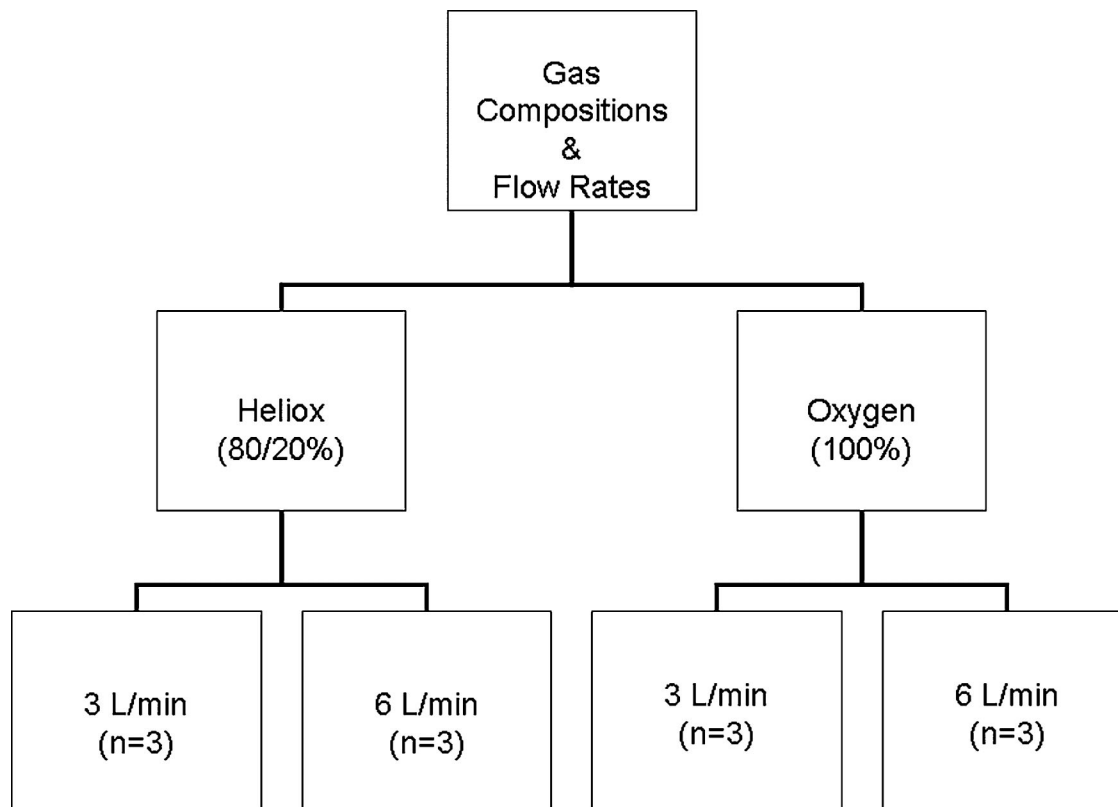


Fig 2. A scheme of variables and experiments utilized in the study.

used in this study. Paired-samples *t* tests were performed to determine significant differences between the percent inhaled dose measures caused by 3 and 6 L/min, using heliox as well as oxygen. Independent samples *t* tests were conducted to compare aerosol delivery with heliox and oxygen at each flow rate. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

The inhaled dose expressed as the mean \pm SD percent of the total dose and *P* values of heliox and oxygen at 3 and 6 L/min are shown in Table 1.

As shown in Table 1, the mean percentage of inhaled dose delivered was greatest for both heliox and oxygen at 3 L/min. There was a wide difference in the mean percentage of inhaled dose between heliox and oxygen

at 6 L/min but not at 3 L/min. Decreasing flow rate from 6 to 3 L/min increased aerosol delivery by 210% with heliox (*P* = 0.028) and 546% with oxygen (*P* = 0.002). Mean treatment time to end of nebulization was 6.2 min, with no difference noted between gas flow or composition.

DISCUSSION

Infants and small children pose unique challenges for effective aerosol drug delivery. One of the greatest challenges is finding an aerosol delivery appliance that small children will tolerate without fussing. Nasal cannulas, commonly used for both high and low flow oxygen seem to be better tolerated by children than aerosol masks. Only recently have researchers suggested that nasal cannulas may be a reasonable appliance for aerosol delivery to this population. When Bhashyam et al.³⁰ reported aerosol

TABLE 1—Percent of Albuterol Collected on the Filter at the End of Nebulization From the Vibrating Mesh Nebulizer With the Pediatric Simulated Breathing Pattern

Gas/flow	3 L/min	6 L/min	<i>P</i> -Value
Heliox (80/20%)	11.41 \pm 1.54	5.42 \pm 0.54	0.028
Oxygen (100%)	10.65 \pm 0.51	1.95 \pm 0.50	0.002
<i>P</i> -Value	0.465	0.01	

delivery with oxygen at low flow (3 L/min), the question arose as to the impact on aerosol delivery with the range of oxygen flows commonly delivered by HFNC to infants and small children (up to 6 L/min).

As total flow through the HFNC increases, the inhaled dose decreases with both gases and a smaller proportion of the emitted aerosol is inhaled. The vibrating mesh nebulizer produces consistent output of aerosol/minute over the 6.2 min average run time. Consequently, the concentration of aerosol/L in the carrier gas decreases by 50% as the flow is increased from 3 to 6 L/min. With a set minute ventilation of 2 L/min, the amount of drug inhaled by the model would be dependent on the concentration of drug/L of gas inhaled.

Because heliox has lower density than oxygen, it has theoretical potential to create less turbulent flow than oxygen at a given flow through the path allowing for better ventilation and aerosol delivery to the distal airways.^{2,9,31} Reduced impactive aerosol losses have been associated with less turbulent gas flow, and less drug loss within the delivery system may result in an increase in aerosol delivery to the lungs.³¹⁻³³ Due to the narrow diameters of the nasal prongs, we hypothesized that the use of heliox should reduce transitional and turbulent flows through the apparatus, reducing impactive aerosol loss. In studies of the human larynx and trachea Dekker identified turbulence at flows as low as 6.0 lpm.³⁴ Even with a >2-fold reduction in the Reynolds numbers associated with low density heliox, some amount of turbulence is likely.³¹ This hypothesis was supported with the higher flow tested in which heliox did improve aerosol delivery twofold compared to oxygen. However, the impact of heliox versus oxygen on aerosol delivery decreased as flow rate was decreased. This may be because the lower flow of oxygen passing through the cannula did not produce sufficient transition or turbulent flow to substantially reduce aerosol passing through the cannula. Alternatively, the lower delivered gas flow (less than model's inhaled flow of 6 L/min) likely resulted in up to 50% the inhaled gas being entrained from ambient room air, diluting the helium concentration to the point that the effects of heliox were diminished.

Goode et al.³² using a model of conventional volume controlled mechanical ventilation and a blender to dilute heliox with various proportions of oxygen, reported that the higher the concentration of helium, the greater the aerosol delivered through the airway, down to a concentration of 50% helium. Similarly, Garner et al.³⁵ using an infant model of mechanical ventilation reported that heliox mixtures of 70:30, 60:40, and 50:50 all improved aerosol delivery from a pMDI compared to room air, but with no significant difference between the heliox concentrations tested.

Kim et al.⁹ stated that patients would benefit from helium concentrations as low as 40–50%, Kim et al.

further suggest increasing the percentage of helium in the mixture as the patient's hypoxemia improves.

The key to effective administration with heliox appears to be meeting or exceeding the inspiratory flow of the patient, so that the heliox concentration is not diluted with room air. The flow rates used in this study represent the range of flows recommended for HFNC by the manufacturer of the system. With other respiratory parameters held constant, the inspiratory flow rate of the model remained constant, and exceeded the output of the HFNC. As the flow output of the HFNC decreased, a greater proportion of room air would be entrained, reducing the heliox concentration inhaled.

Heliox 80:20 was used to optimize effect, but can be problematic clinically, especially in patients with hypoxia or severe asthma exacerbations. In these cases, adding oxygen to the inhaled gas will increase the FiO₂ but may lead to less aerosol deposition in the peripheral airways at the higher flow rate studied.

Our findings, at the lower flow tested, were in agreement with Bhashyam et al.³⁰ reporting an inhaled dose of $8.4 \pm 2.3\%$. They noted that the aerosol particle size distribution emitted by the vibrating mesh nebulizer was 5 μm , while aerosol leaving the nasal prongs was less than 2 μm , suggesting substantial losses of aerosol in the circuit and nasal prongs. This rainout in the inspiratory limb and cannula can result in a sputtering of liquid from the nasal prongs, which could be annoying to the patient.

Placement of the nebulizer at the inlet of the humidifier was chosen to allow rainout of the larger particles in the humidifier, prior to entering the inspiratory limb. This resulted in minimal sputtering and condensate being emitted from the nasal prongs.

The vibrating mesh nebulizer uses a piezo ceramic element to vibrate a plate with 1,000 funnel shaped apertures to generate aerosol was selected for this study because the particle size distribution and output rate of aerosol generated is relatively independent of the density and flow of the carrier gas. In addition, the vibrating mesh nebulizer is electronically operated and does not add gas that might cause dilution of the heliox gas mixtures. Using laser diffraction techniques, Fink reported similar particle size and output from a vibrating mesh nebulizer at three levels of flow with both oxygen and heliox.³⁶ In contrast, operating jet nebulizers which generate aerosol using gas driven through a jet to draw medication from a reservoir and shear medication into aerosol particles, with heliox at the same flows as air or oxygen has been shown to reduce aerosol output rate and change the size of aerosol particles emitted.^{31,37,38} O'Callaghan et al.³⁷ compared jet nebulizers using heliox to vibrating mesh nebulizers in the delivery of albuterol and reported that the total amount of inhaled mass obtained with the vibrating mesh nebulizer was consistently higher than that of the jet nebulizer.

Limitations of This Study

Characterization of the particle size of aerosols was not included with this study. While jet nebulizers have been associated with flow related changes in both output and particle size with heliox, there is some disagreement as to the relationship.^{37,38} One issue may be how the cut points of the different impactors were calculated to compensate for in the changes of gas density. O'Callaghan et al.³⁷ reported a reduction in aerosol size from the vibrating mesh nebulizer (Aeroneb Pro) from $4.5 \pm 0.13 \mu\text{m}$ with oxygen to $3.99 \pm 0.12 \mu\text{m}$ with heliox. Total nebulization time ranged from 6.0 to 7.0 min, with no changes in treatment times associated with gas composition or flow. The changes in particle sizes generated by the vibrating mesh nebulizer were marginally smaller ($0.5 \mu\text{m}$) with heliox, with a greater proportion of aerosol $<3 \mu\text{m}$. This might suggest that a greater percent of the drug reaching the inspiratory filter may be respirable. Bhashyam, using a similar setup with a similar vibrating mesh and oxygen reported MMD less than $2 \mu\text{m}$ exiting the pediatric size nasal prongs at 3 L/min.³⁰ The particle size would presumably be even less at higher gas flows secondary to impactive losses in the tubing. Consequently, it may be reasonable to assume that aerosol exiting the nasal prongs would be $\leq 2 \mu\text{m}$ under the conditions tested, with a very high fraction of particles less than $3.5 \mu\text{m}$. Fink reported no difference in aerosol generated from a vibrating mesh nebulizer into a gas stream flow of 5, 10, and 15 L/min with oxygen and 80:20 heliox with volume median diameter ranging from 2.94 ± 0.05 to 3.17 ± 0.01 , and a mean of $3.1 \mu\text{m}$ with both oxygen and heliox.³⁶ Total nebulization time differed for each vibrating mesh nebulizer but was consistent for each nebulizer, with both oxygen and heliox. This was consistent with our observations. Future efforts to determine the changes in aerosol size and volume distribution measured at different points in the delivery system may provide valuable insights into the mechanisms involved, but the modification and validation of impactor cut points was beyond the scope of this study.

This was an *in vitro* study with a simple model to simulate the nares and nasopharynx with a "pediatric" patient. Pediatric patients range from preterm infants to teenagers, with a wide range of tidal volumes and breathing patterns. Inhaled mass will vary with these parameters. For example, this model used an I:E ratio of 1:2 which may not be representative of the range typical of small children. As the I:E ratio shifts toward 1:1, the percent of emitted aerosol inhaled would increase. Additional breathing patterns should yield greater insights into the variables impacting aerosol drug delivery with HFNC.

This study is the first to suggest that administration of aerosol via nasal cannula at the low range of driving gas flows to infants and small children provides similar

inhaled dose efficiency whether the driving gas is O₂ or Heliox. These findings have implications beyond the use of HFNC, with potential for administration of aerosol with low flow oxygen commonly administered via nasal cannula to children who may not tolerate administration of aerosol via mask. Although inhaled mass of drug entering the "nares" was similar at low flows, it is unclear as to whether heliox may improve pulmonary deposition.

Further studies are needed to determine if the improved albuterol delivery with heliox enhances clinical response in pediatrics receiving aerosol therapy through HFNCs.

CONCLUSION

Our results indicate that a pediatric HFNC can be a useful and relatively efficient option for aerosol drug administration across the range of driving gas flows commonly used in clinical practice. As flow rate increased from 3 to 6 L/min, heliox increases aerosol delivery by >2 -fold compared to oxygen. Reducing flow rate increases albuterol delivery in this model of pediatrics but decreases impact of heliox. The ability to efficiently deliver inhaled aerosols via nasal cannula may expand clinical options to administer medical aerosols to treat children who will not tolerate the use of masks.

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