

In Vitro Evaluation of Radiolabeled Aerosol Delivery
via a Variable Flow Infant CPAP System

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Abstract

Background: Nasal Continuous Positive Airway Pressure (NCPAP) is widely used in neonatal intensive care units. Aerosolized medications such as inhaled steroids and beta-agonists are commonly administered in-line through NCPAP, especially to infants with bronchopulmonary dysplasia (BPD). We hypothesized that aerosol delivery to the lungs via variable flow NCPAP in an *in vitro* model is unreliable, and such delivery depends on the position of the aerosol generator within the NCPAP circuit.

Methods: We used a system that employed a test lung placed in a plastic jar subjected to negative pressure. Simulated inspiration effort was measured by use of a heated wire anemometer. We used TC ^{99m}Tc-DTPA as our aerosol. The nebulizer was placed either close to the humidifier (position A) or close to the nasal prongs (position B) in the circuit and patient effort was simulated at a 0.4 L/min minute-ventilation.

Results: Relative aerosol delivery to the infant test lung using position A was extremely low ($0.3 \pm 0.4\%$); while position B resulted in significantly ($p < 0.001$) improved delivery ($21 \pm 11\%$). Major areas of aerosol deposition in position A vs. B were: nebulizer ($10 \pm 4\%$ vs. $33 \pm 13\%$; $p < 0.001$), exhalation limb ($9 \pm 17\%$ vs. $26 \pm 30\%$; $p = 0.23$), and generator tubing ($21 \pm 11\%$ vs. $19 \pm 20\%$; $p = 0.86$). Position A resulted in $59 \pm 8\%$ of the aerosol being deposited in the inhalation tubing along the heater wire.

Conclusions: Isotope delivery from a generator placed near the humidifier on variable flow NCPAP is negligible in this *in vitro* setup; however such delivery was significantly improved by locating the aerosol generator closer to the NCPAP interface.

Key Words: Bronchopulmonary Dysplasia, Neonatal Respiratory Distress, inhalational administration, respiratory therapy, neonate

Introduction

Bronchopulmonary dysplasia (BPD) is the most common pulmonary complication of prematurity and is associated with significant neurodevelopmental risks.¹⁻³ Numerous interventions have been proposed to treat BPD, including the routine use of nasal continuous positive airway pressure (NCPAP) and administration of inhaled steroids, however data regarding their efficacy are limited.^{4, 5} Many patients with developing BPD receive aerosolized β -agonist therapy, although there is little data on which to base dosing, medication deposition, or clinical response.^{5, 6} It is not clear if the limited evidence of effectiveness of these interventions is due to intrinsic factors or to difficulties achieving measurable deposition in target tissues, especially for those infants maintained on NCPAP.

The Aeroneb Solo aerosol generator is a common method of aerosolized medication delivery in the hospital setting. Studies suggest this generator may be superior to some others at delivering medication to the lung in mechanically ventilated patients.⁷ However, little is known about how much aerosol is actually delivered to the patient's lung when used in-line with a variable flow infant NCPAP system. In addition, nebulizer placement within the NCPAP circuit is limited to either the humidifying chamber or the heater wire-NCPAP generator interface. We hypothesized that placement of the nebulizer closer to the patient's nasal interface (ie further from the humidifier) would increase test lung deposition of aerosolized isotope. We utilized an *in vitro* system consisting of an infant variable flow NCPAP circuit connected to a lung model, where inspiration was triggered by increasing negative pressure around the model lung. We measured isotope deposition using ^{99m}Tc-diethylene tiramine pentaacetic acid (^{99m}Tc-DTPA) scintigraphy.

Methods

The study circuit consisted of a Cardinal Health RT324™ (Cardinal Health, Dublin, OH) heated wire circuit, AirLife 006905 Infant nCPAP Generator Kit (CareFusion, San Diego, CA), a Viasys SiPAP variable flow ventilator (CareFusion, San Diego, CA), a disposable Aeroneb Solo aerosol nebulizer (a new one for each test run) (Aerogen/Nektar, Mountain View, CA), and an institutionally-constructed infant test-lung system. The test-lung was subjected to negative pressure by means of time/valve mechanism connected to a vacuum system. Simulated inspiration effort was triggered by increasing the negative pressure surrounding the test lung and was measured by use of heated wire anemometer (CareFusion, San Diego, CA). The flow signal of the anemometer was then integrated into a volume measurement via an Avea ventilator (CareFusion, San Diego, CA).

We chose to study only the variable flow NCPAP device as it reduces work of breathing in infants and thus is the primary modality within our unit.^{8,9} In particular, we use variable flow NCPAP for all near-term and post-term infants, who comprise those most likely to be prescribed aerosolized respiratory medications in our unit. We tested the device solely in CPAP mode as this is our standard unit practice.

The circuit was assembled and NCPAP settings were as follows: a base flow of about 8 LPM to achieve a CPAP of 6 CM H₂O with no system leak. The test-lung ventilation was set at a tidal volume (V_t) of 45 ml and a minute ventilation of 0.4 l/min. Depending on the size of the infant, this represents a tidal volume of 10-20 ml/kg/breath; while these are larger than typical tidal volumes obtained in healthy preterm newborns, these settings should maximize isotope deposition in the artificial lung, and thereby should minimize the possibility of an artifactual decrease in lung deposition of the isotope. Three ml of ^{99m}Tc-DTPA was delivered for 15 minutes through the nebulizer placed either at the humidifying chamber (Fisher & Paykel, Irvine,

CA) (position A) or 32 cm from the patient prongs (position B) (Figure 1). Position B (the heater wire circuit-NCPAP generator junction) was the closest practical placement of the nebulizer to the nasal interface given the makeup of the circuit, and no commercially available devices exist to place a nebulizer within the NCPAP generator itself. All circuits were placed under a GE Infinia Hawkeye Gamma Camera (GE Healthcare Waukesha, Wisconsin USA) prior to the delivery of the aerosol to ensure a zero exposure baseline (Figure 2).

A total of 15 measurements were obtained. There were 6 measurements taken with the nebulizer placed in position A and 9 measurements were taken with the nebulizer placed in position B. After the isotope was delivered, the circuit was broken up into 5 sections (Nebulizer, Heater wire, Patient, Exhalation, and Generator tubing) and analyzed for isotope deposition using the GE Xeleris™ (Figure 3).

Areas of isotope consolidation were identified with the Infinia Hawkeye camera's companion processing station using the GE proprietary program Xeleris™. Using the Xeleris program, Regions of Interest (ROI) were drawn by the Nuclear Medicine Technologist and then assigned to specific areas of the nebulizer-circuit-patient system.

ROI 0 was identified as the nebulizer, ROI 1 was the heated wire portion of the circuit, ROI 2 was the area associated with the filter representing the patient, ROI 3 was the filter on the exhalation side of the system, and ROI 4 was identified to be the tubing of the Infant Flow™ generator.

Data are expressed as mean \pm standard deviation. Position A was compared to position B using one-way analysis of variance (ANOVA) using SigmaStat (Jandel Scientific, Carlsbad, CA). Differences between the two positions were considered statistically significance when $p < 0.05$.

Results

Placement of the nebulizer at the humidifying chamber (position A) resulted in a deposition of <1% of the measured ^{99m}Tc -DTPA into the test lung system, while placement 32 cm upstream from the patient prongs (position B) resulted in substantial deposition of the isotope in the test lung system (Figure 4). Indeed, when administered from position A in the variable flow NCPAP circuit the vast majority of the tracer was deposited in the nebulizer or in the heater wire on the inhalation side of the circuit, with very little tracer reaching the patient or the exhalation circuit (Figure 3). Placement of the nebulizer 32 cm from the patient prongs (position B), resulted in substantially increased deposition of the tracer in the lungs and exhalation circuit (Figure 3). In addition, significantly more of the tracer remained in the nebulizer in position B than when it was placed in position A (Figure 4).

Discussion

The deposition of radio-labeled isotope to the test-lung representative of the patient in our model of infant flow NCPAP was negligible when the nebulizer was placed at the humidifier (position A), with the majority of tracer deposition occurring on the heater wire. Delivery to the test-lung was markedly improved by placing the nebulizer 32 cm upstream of the nasal prongs (position B), with concomitant reductions in tracer deposition elsewhere in the circuit. Together, these findings suggest that simply placing the nebulizer closer to the patient in the variable flow NCPAP circuit has the potential to improve aerosol delivery.

To the best of our knowledge, this is the first study to examine the delivery of isotope to a test lung *via* a standard variable flow infant NCPAP/nebulizer interface. Position A was chosen

to reflect the circuit set-up used for aerosolized medications in our NICU; under these conditions we found very low deposition of the isotope into the test-lung. This is consistent with *in vivo* and *in vitro* reports demonstrating that the lung deposition of aerosolized medications is often relatively low. For example, O’Riordan et al¹⁰ found in adult patients ventilated through a tracheostomy tube that ~15% of the nebulized charge actually deposited in the lungs using a jet nebulizer. While in ventilated infants with BPD, Fok et al¹¹ found that, using a jet nebulizer, only ~2% of the nebulized dose was deposited in the lung. In our test lung, the deposition of the tracer was significantly improved when the nebulizer was placed in position B, a placement of the aerosol generator much closer to the NCPAP/patient interface. This effect of location closer to the patient in the NCPAP circuit is consistent with other *in vitro* studies examining deposition of aerosolized medications in relation to aerosol generator position with adult ventilators and circuits. For example, Ari et al¹² found that moving the ultrasonic nebulizer from a distal (close to the ventilator) to a more proximal (close to the patient) position increased relative deposition into the test lung from ~5% to ~17%. In a biPAP system with delivered pressures of 10/5 at a rate of 20, when the jet nebulizer was placed close to the biPAP machine the delivered aerosol was ~9% and when placed close to the test lung deposition increased to ~16%.¹³ Thus, although lung deposition of aerosol is relatively small in both adult and infant models, it appears that moving the nebulizer closer to the patient interface substantially improves aerosol delivery.

Although we report that isotope delivery in an *in vitro* model can be improved when using a variable flow infant NCPAP circuit, the evidence for efficacy of aerosolized medications for the prevention and treatment of neonatal lung diseases is mixed. Inhaled steroids, for instance, may improve rates of successful extubation in premature infants, but do not seem to affect rates of BPD.⁵ Inhaled bronchodilators improve airway resistance, but do not reduce the

incidence of BPD.^{5, 14} These disappointing clinical results may reflect either an intrinsic lack of efficacy of these medications or sub-optimal delivery. Thus, we suggest that in future studies of aerosolized medications in neonates, particularly on NCPAP, documentation of drug delivery should be included in the study design.

There are several limitations to this study that should be considered. First, and most obvious, is that our *in vitro* results may not accurately reflect *in vivo* lung deposition given the added complexities of the nasopharynx and airways. Second, the tidal volumes chosen for this study were designed to maximize the potential delivery of the aerosol to the test lung and are therefore larger than typical premature infant tidal volumes. This could limit the clinical applicability of these findings in infants with smaller tidal volumes. Specifically, these findings may be generalized only to the relatively limited population of NICU patients that have similar tidal volumes and minute ventilation. Further, more premature infants with significantly smaller tidal volumes still require substantial bias flows to maintain NCPAP, resulting in a greater ratio of bias flow-to-minute ventilation. It is possible, and perhaps even likely, that tissue deposition will be negatively affected by increasing ratios of bias flow-to-minute.¹⁵ While our study and the study by Ari, *et al* similarly suggest that particle delivery is influenced negatively by increasing bias flows, our data do not confirm their findings with regard to nebulizer placement in the ventilator circuit. Specifically, Ari, *et al*, demonstrated that proximal (near the ventilator) vs. distal (near the patient) placement of vibrating mesh nebulizers was associated with substantially increased delivery of albuterol in a simulated adult model of mechanical ventilation, and increased delivery of albuterol at higher but not lower bias flows in a simulated pediatric model of mechanical ventilation. They hypothesized that these improvements were likely due to a “reservoir” effect within the inspiratory limb of the ventilator circuit.¹⁵ We believe the

differences between the studies are largely due the inherent differences in our models. Specifically, the bias flow necessary to maintain NCPAP is typically much higher (8 vs. 2 or 5 lpm) and our tidal volumes were much lower (45 vs. 100 ml) than those in their study. These differences in our model would likely minimize any potential reservoir effect of the inspiratory limb. Furthermore, deposition of isotope in this model may not reflect deposition of actual medications in live patients, as we were unable to test tagged medications. Finally, another limitation of our study is that we did not measure particle size, which is an important determinant of aerosol delivery. Thus, we believe that our findings, though potentially clinically relevant, must be confirmed with additional *in vitro* and *in vivo* studies.

In conclusion, we show using an *in vitro* model of infant flow NCPAP that the delivery of isotope to a test-lung can be substantially improved by moving the aerosol generator closer to the patient. We believe that our findings, though potentially clinically relevant, should be confirmed in additional *in vivo* studies.

Figure Legends

Figure 1, Positions of aerosol generator within the variable flow NCPAP circuit. Position A is near the humidifier and Position B is 32 cm upstream of the patient interface (Arrows).

Figure 2. GE Infinia Hawkeye Gamma Camera™ with infant lung simulator NCPAP circuit and Carefusion Infant Flow™ driver. The ventilator was used for flow/volume measurements

Figure 3. Typical results showing Aeroneb Solo™ Aerosol generator placed 32 cm from the patient at Infant Flow™ generator connection. Areas of isotope consolidation have been drawn using the GE Xeleris™ program and were labeled as various Regions of Interest (ROI)

Figure 4. Comparison of aerosol deposition (%) by region of interest within the NCPAP circuit or the test-lung. * = $p < 0.001$, ** = $p < 0.00001$, *** = $p < 0.0007$.

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Figure 1

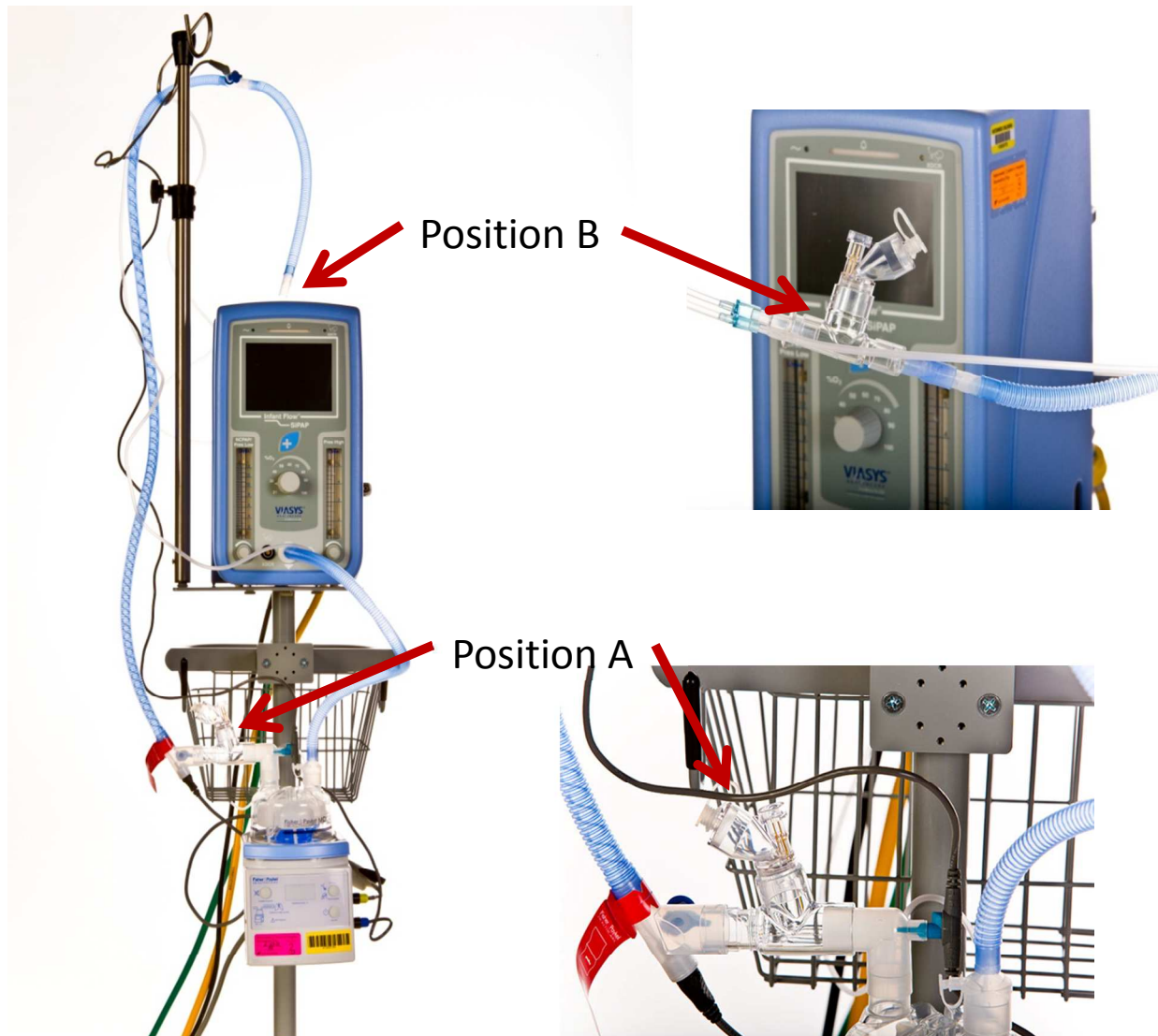


Figure 2.



Figure 3.

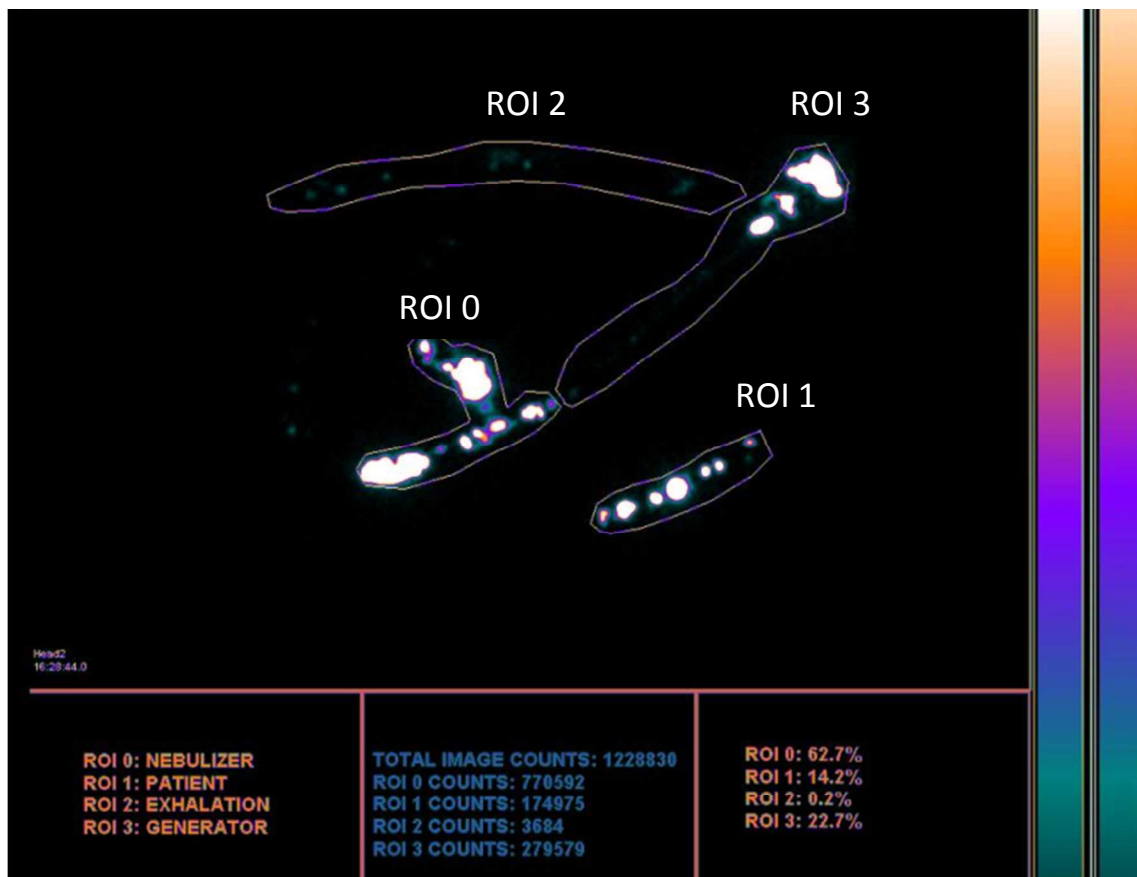


Figure 4.

