Journal of Aerosol Science 110 (2017) 25–35

Contents lists available at ScienceDirect

Journal of Aerosol Science

journal homepage: www.elsevier.com/locate/jaerosci

In vitro assessment of small charged pharmaceutical aerosols in a model of a ventilated neonate

Landon Holbrook[a,1], Michael Hindle[b], P. Worth Longest[a,b,*]

[a] Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, Richmond, VA, United States
[b] Department of Pharmaceutics, Virginia Commonwealth University, Richmond, VA, United States

ARTICLE INFO

Keywords:
Infants
Pharmaceutical aerosols
Mechanical ventilation
Endotracheal tube
Induction charger
Respiratory drug delivery

ABSTRACT

Aerosolized medications may benefit infants receiving mechanical ventilation; however, the lung delivery efficiency of these aerosols is unacceptably low. *In vitro* experiments were conducted to evaluate aerosol delivery through conventional and modified ventilation systems to the end of a 3 mm endotracheal tube (ETT) under steady state and realistic cyclic flow conditions. System modifications were employed to investigate the use of small charged particles and included streamlined components, a reduction in nebulizer liquid flow rate, synchronization with inspiration, and implementation of a previously designed low-flow induction charger (LF-IC), which was further modified in this study. Cyclic flow experiments implemented a modern ventilator with bias airflow and an inline flow meter, both of which are frequently excluded from *in vitro* tests but included in clinical practice. The modified LF-IC system demonstrated superior delivery efficiency to the end of the ETT (34%) compared with the commercial system (~1.3%) operating under cyclic ventilation conditions. These findings indicate that commercial systems still provide very low lung delivery efficiencies despite decades of innovation. In contrast, the modified system increased dose delivery to the end of the ETT by 26-fold. Despite initial concerns, the charged aerosol could be efficiently delivered through the small diameter ETT and reach the lungs. Future studies will be required to determine if the applied particle charge can eliminate expected high exhalation aerosol loss and will require the development of a realistic lung model.

1. Introduction

The extent to which poor lung delivery efficiency of aerosolized medicines limits treatment options for ventilated neonates and infants has been highlighted in numerous studies (Dubus et al., 2005; Fink, 2004; Fok et al., 1996; Mazela & Polin, 2011; Sidler-Moix et al., 2013). Overcoming this limitation and increasing the lung delivery efficiency of pharmaceutical aerosols are expected to improve the clinical effects of existing medications and expand the number of aerosol therapies available for infants in the future (Holbrook, Hindle, & Longest, 2015). Aerosol delivery efficiencies in the range of < 1–14% are common in mechanically ventilated infants, even considering more recent vibrating mesh nebulizer (VMN) devices (Dubus et al., 2005; Fink, 2004; Fok et al., 1996; Mazela & Polin, 2011; Sidler-Moix et al., 2013). In addition to very low aerosol delivery efficiencies, high deposition variability is also a likely reason for poor biological response when infants receive aerosolized medicines (Mazela & Polin, 2011; Shah, Ohlsson, Halliday, & Dunn, 2007).

* Correspondence to: Virginia Commonwealth University, 401 West Main Street, P.O. Box 843015, Richmond, VA 23284-3015, United States.
E-mail address: pwlongest@vcu.edu (P.W. Longest).
[1] Current Address: Center for Environmental Medicine, Asthma, and Lung Biology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

http://dx.doi.org/10.1016/j.jaerosci.2017.05.006
Received 20 January 2017; Received in revised form 11 May 2017; Accepted 12 May 2017
Available online 13 May 2017
0021-8502/

Small diameter connective ventilator tubing, short inhalation periods, and small tidal volumes all contribute to ineffective aerosol delivery to ventilated infants (Fink, 2004; Rubin & Fink, 2001). A significant challenge to aerosol delivery during mechanical ventilation is passing the aerosol through the gas delivery tubing, connection components and patient interface device. Ventilation components are typically designed for gas delivery, not aerosol administration (Longest, Azimi, Golshahi, & Hindle, 2014; Longest, Azimi, & Hindle, 2014). In addition to this, the nebulizer type, location within the ventilation circuit, gas flow, and mode of nebulizer operation are important considerations for increasing aerosol delivery efficiency during mechanical ventilation (Fink & Ari, 2013). Much work is still needed to improve aerosol delivery efficiency and reduce intersubject variability in mechanically ventilated infants, so that the clinical benefit of existing medications can be maximized and new inhaled therapies can be developed (Brion, Primhak, & Yong, 2006; Cole et al., 1999; Fink, 2004; Rubin & Williams, 2014; Shah et al., 2007).

Through the use of VMNs and new ventilation connection components, aerosol delivery efficiency has recently been improved in models of ventilated infants. A macaque animal model of a ventilated infant was used to demonstrate a lung delivery efficiency of 12.6–14% of the aerosolized dose through a 3 mm infant endotracheal tube (ETT) using a VMN synchronized with inspiration and without ventilator bias flow (Dubus et al., 2005). Using a jet nebulizer in an *in vitro* model of a ventilated premature infant, with a new connector to separate nebulizer and ventilation gas bias flow, Mazela et al. (2014) increased albuterol sulfate delivery efficiency from 1% or less through the commercial Y-connector to a maximum of approximately 7% with the improved connector, before the ETT or mask. Additional aerosol losses are known to occur in the infant ETT, which can have an internal diameter as small as 2.5 mm. Similar to the 12.6–14% *in vivo* animal lung model delivery efficiency predictions of Dubus et al. (2005), Longest et al. (2014) used *in vitro,* whole lung, and CFD modeling techniques to predict the lung deposition fraction for a newborn full-term infant under mechanical ventilation through an ETT using commercial connection components (6.8–13.5%). A new streamlined Y-connector was then implemented with synchronized delivery and reduced droplet sizes (~1.8 μm) to improve aerosol deposition in the infant lungs (Longest et al., 2014). For a full term (3.6 kg) infant and 3 mm ETT, maximum total lung delivery efficiency of a polydisperse aerosol with a mass median aerodynamic diameter (MMAD) of 1.8 μm reached 45.2%.

A “small” aerosol with a MMAD of 1.6 μm has been produced with a “high” net charge of approximately 1% of the Rayleigh limit with the intention of reducing the depositional losses before the patient, increasing the mass of drug that reaches the patient, and decreasing the exhaled fraction of the drug (Holbrook et al., 2015). This was accomplished using a novel low flow-induction charger (LF-IC) that incorporated a commercial VMN with a reduced mass output and counter-electrode to produce a charged aerosol through induction charging. The current work will begin with this previously developed LF-IC applied in an infant ventilation circuit containing a 3 mm endotracheal tube during steady state flow conditions and then under cyclic flow conditions.

The purpose of charging the aerosol is to reduce ventilation losses that occur when small particles enter the lungs, lack sufficient inertia and mass to deposit, and are then exhaled. Longest et al. (2014) predicted that these ventilation losses were as high as 40% of the nebulized dose for an infant with a small particle aerosol, even when the delivered dose was synchronized with inhalation. One potential strategy to reduce these ventilation losses is to provide an electrostatic charge to the particles or droplets. Deposition arising from charge is proportional to both conduit diameter and particle or droplet residence time. In theory, the charged aerosol will pass quickly through the ETT and upper airways with insufficient time for depositional loss to increase. As the aerosol penetrates the bifurcating lung network, velocities are reduced and sufficient time is available to increase deposition from electrostatic charge, thereby reducing ventilation losses and increasing aerosol retention in the lungs. However, it is not clear if the charged aerosol can effectively penetrate the nebulizer system and small diameter ETT without large increases in deposition loss.

The objective of this study is to compare the performance of a newly developed LF-IC system to that of a commercially available nebulizer system in an infant ventilation circuit under steady-state and cyclic flow conditions. The LF-IC and commercial device performances are evaluated by the quantification of albuterol sulfate (AS; model drug) mass recovered using high performance liquid chromatography (HPLC) in multiple system components (Fig. 1). After implementing the previously developed LF-IC in an infant ventilation circuit under idealized steady-state airflow, the LF-IC is redesigned to minimize device volume for use with cyclic flow conditions and to allow for the inclusion of a ventilator flow meter (Schena, Massaroni, Saccomandi, & Cecchini, 2015), a new common feature in mechanical ventilation systems that has not adequately been considered in previous studies. This redesigned LF-IC also incorporates a breath actuated nebulizer to increase delivery of aerosolized drug to the patient and reduce the exhaled dose.

2. Materials and methods

2.1. Overview of systems

In this study, commercial and modified aerosol delivery systems were compared for full term neonates receiving invasive mechanical ventilation. Both systems utilized a VMN to produce the test aerosol. The commercial system included a commercial T-connector, commercial Y-connector, and a continuous nebulization signal operating the VMN (Fig. 1a). The modified delivery system included a reduced nebulizer signal to reduce liquid mass output and promote evaporation of the droplets, breath synchronized nebulizer timing, introduction of a streamlined low flow-induction charger (LF-IC) (Holbrook et al., 2015), and a streamlined Y-connector (Fig. 1b) (Longest et al., 2014). Two flow conditions were evaluated with each system, steady state and cyclic ventilation. Steady state flow conditions allow for simplified and idealized experiments to be conducted at the same flow rates of previous characterization studies (Holbrook et al., 2015). The cyclic flow condition better represents clinical use and *in vivo* aerosol delivery during invasive mechanical ventilation. Cases considered are presented in Table 1. Briefly, Systems with 1.* and 2.* designations indicate steady state and cyclic ventilation conditions, respectively. The second number in the designation indicates changes in the charging voltage, run time, nebulization signal, and nebulization timing. An additional case was considered to evaluate the effects of