Aerosol Drug Delivery During Noninvasive Positive Pressure Ventilation: Effects of Intersubject Variability and Excipient Enhanced Growth

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Abstract

Background: Nebulized aerosol drug delivery during the administration of noninvasive positive pressure ventilation (NPPV) is commonly implemented. While studies have shown improved patient outcomes for this therapeutic approach, aerosol delivery efficiency is reported to be low with high variability in lung-deposited dose. Excipient enhanced growth (EEG) aerosol delivery is a newly proposed technique that may improve drug delivery efficiency and reduce intersubject aerosol delivery variability when coupled with NPPV.

Materials and Methods: A combined approach using *in vitro* experiments and computational fluid dynamics (CFD) was used to characterize aerosol delivery efficiency during NPPV in two new nasal cavity models that include face mask interfaces. Mesh nebulizer and in-line dry powder inhaler (DPI) sources of conventional and EEG aerosols were both considered.

Results: Based on validated steady-state CFD predictions, EEG aerosol delivery improved lung penetration fraction (PF) values by factors ranging from 1.3 to 6.4 compared with conventional-sized aerosols. Furthermore, intersubject variability in lung PF was very high for conventional aerosol sizes (relative differences between subjects in the range of 54.5%–134.3%) and was reduced by an order of magnitude with the EEG approach (relative differences between subjects in the range of 5.5%–17.4%). Realistic *in vitro* experiments of cyclic NPPV demonstrated similar trends in lung delivery to those observed with the steady-state simulations, but with lower lung delivery efficiencies. Reaching the lung delivery efficiencies reported with the steady-state simulations of 80%–90% will require synchronization of aerosol administration during inspiration and reducing the size of the EEG aerosol delivery unit.

Conclusions: The EEG approach enabled high-efficiency lung delivery of aerosols administered during NPPV and reduced intersubject aerosol delivery variability by an order of magnitude. Use of an in-line DPI device that connects to the NPPV mask appears to be a convenient method to rapidly administer an EEG aerosol and synchronize the delivery with inspiration.

Keywords: computational fluid dynamics, excipient enhanced growth, inline dry powder inhaler, nebulized aerosol, noninvasive positive pressure ventilation

Introduction

NONINVASIVE VENTILATION (NIV) describes several techniques used as alternatives to invasive ventilation, which have gained popularity over the last 30 years, particularly as treatment options for patients with obstructive sleep apnea or chronic obstructive pulmonary disease (COPD).⁽¹⁾ Although

there has been some recent interest in negative pressure ventilation,⁽²⁾ the most prominent forms of NIV are noninvasive positive pressure ventilation (NPPV), traditional nasal low-flow therapy with a nasal cannula, and the more recently introduced high-flow nasal cannula (HFNC) therapy. NPPV is a frequently utilized form of respiratory aid in cases of hypoxemia and acute respiratory failure.^(3–5) A primary

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application for NPPV is use with COPD patients experiencing an exacerbation, where it has been found through controlled trials to provide greater treatment success, reduced durations of hospital stay, a lower need for intubation, and lower mortality rates.⁽⁴⁾

Many patients who receive NPPV may also benefit from the administration of pharmaceutical aerosols, typically bronchodilators, which are best delivered without interrupting respiratory support.^(5–8) A recent survey of 611 physicians representing 70 different countries showed that 99% used some sort of aerosol therapy during mechanical ventilation (including NIV) and that 87% used a nebulizer either exclusively or with a metered dose inhaler (MDI).⁽⁹⁾ Evidence of the efficacy of the combination of nebulized aerosol therapy and NPPV can be found in several *in vivo* studies, which have shown improvements in spirometric data from adult asthmatic patients receiving nebulized pharmaceutical aerosols with NPPV, as opposed to those only receiving aerosol therapy.^(10–12) However, NPPV is generally expected to not improve or even reduce aerosol delivery efficiency to the lung compared with conventional nebulization with a face mask interface based on multiple *in vivo* studies.^(5,8,11,13,14) A recent study by Gupta et al.⁽¹⁴⁾ suggested that the combination of aerosol delivery and NPPV creates a complicated relationship between delivered dose and patient improvement. The results of this *in vivo* study with oronasal mask delivery of bronchodilators to 53 asthmatic patients showed that while intensive care unit and hospital stay durations were decreased by the combination of aerosol therapy and NPPV, as opposed to aerosol delivery alone, no significant differences occurred in the spirometric data, although the mean dose of bronchodilator decreased significantly suggesting that the addition of NPPV reduced the needed amount of bronchodilators.⁽¹⁴⁾

Lung delivery efficiency of nebulized medicines during NPPV administration is expected to be low based on the limited number of studies that have been conducted and measured this metric. While few studies have quantified nebulized drug delivery during NPPV in adults, Parkes and Bersten⁽¹⁵⁾ evaluated the effect of aerosol delivery during a similar procedure, continuous positive airway pressure (CPAP). A combination *in vitro/in vivo* study was performed that showed the addition of CPAP while delivering nebulized bronchodilators reduced *in vitro* mask delivery from 6.9% to 1.3%, but the *in vivo* spirometric data from 10 asthmatic patients showed no significant difference in symptoms, suggesting that aerosol therapy can be conducted without interrupting CPAP.⁽¹⁵⁾ Fauroux et al.⁽¹⁶⁾ observed that 18 children with cystic fibrosis showed increased total lung deposition when NPPV was used with a mouthpiece interface in combination with bronchodilator or corticosteroid delivery, as opposed to aerosol therapy alone. These results are unexpected considering França et al.⁽¹³⁾ found that total lung dose was reduced when NPPV was combined with nebulized aerosol therapy, although the difference may be explained by the use of a mouthpiece for the study conducted by Fauroux et al.,⁽¹⁶⁾ which is expected to alter results compared with a mask. Very recently, Galindo-Filho et al.⁽¹⁷⁾ compared jet and mesh nebulized aerosol lung delivery efficiency during bilevel positive airway pressure (BiPAP) in healthy adult volunteers. The vibrating mesh nebulizer (positioned next to the mask) was shown to provide a lung delivery efficiency of 5.5% (standard deviation; SD=0.9) of the loaded dose vs.

1.5% (SD=0.6) for the jet nebulizer (positioned between the circuit leak and mask).

While lung depositional efficiency of aerosolized medicine administered during NPPV using a conventional method has been shown to be poor, it is expected that variability in this scenario is likely to be high. Deposition variability during NPPV aerosol delivery can be assessed by considering several different factors, including repeatability, intersubject factors, mask design differences, face mask seal, and other system specifics, including nebulizer type and breathing pattern. In addition to the results of Galindo-Filho et al.,⁽¹⁷⁾ only a few studies are known to have reported variability estimates from *in vitro* and *in vivo* studies for aerosol delivery combined with CPAP, BiPAP, or NPPV.^(15,16) Repeatability of bronchodilator delivery during CPAP with a face mask was reported after four *in vitro* trials, with a mean delivered dose at the interface of 1.3% and an SD of 0.37%.⁽¹⁵⁾ High intersubject variability of radiolabeled aerosol delivery through a mouthpiece to 18 children with cystic fibrosis during NPPV was observed by Fauroux et al.,⁽¹⁶⁾ who noted a mean delivered lung dose of 15% with an SD of 8.3%.

Several studies have considered variability of face mask aerosol delivery without NPPV.^(18–20) Smaldone et al.⁽¹⁸⁾ considered repeatability in a study designed to examine the effect of nebulizer type, breathing pattern, and face mask seal on delivered dose through an *in vitro* system without NPPV. Ten nebulizers of a specific brand were purchased and tested, but only five that were within 5% of the mean were selected for use in the study, and three trials were performed on each nebulizer, where it was found for an ideal case that the average delivered dose was 24.3% with an SD of 3.1%.⁽¹⁸⁾ Variability of MDI aerosol delivery due to mask design differences was investigated by Hayden et al.⁽²⁰⁾ through an *in vivo* study with 24 children who used a face mask and a spacer and it was found that while two commercial masks yielded a delivered mask dose of about 30%, another mask only yielded 6%. Additionally, Hayden et al.⁽²⁰⁾ noted poor repeatability with each of the three commercial masks, with coefficient of variation (CV) values of 42%–259%, although these high values of CV may be due to the difficulties associated with ensuring correct usage with pediatric patients. Significant variability due to face mask seal has been reported by the *in vivo* study of Erzinger et al.⁽¹⁹⁾ who noted that a loose mask may reduce lung deposition from 6.5% to 0.3% compared with a normally fitted mask.

Considering the expected low efficiency and high variability of conventional nebulized aerosol delivery during NPPV, a new approach is needed. Excipient enhanced growth (EEG) is a recently introduced method that reduces extrathoracic losses by delivering an initially submicrometer aerosol.⁽²¹⁾ As opposed to enhanced condensational growth, which uses a humidified airstream to produce hygroscopic droplet size increase,^(22,23) the EEG technique uses the formulation to produce aerosol size growth to enable deposition in the naturally humidified human airways by mixing the active pharmaceutical ingredient with a hygroscopic excipient.⁽²¹⁾ Using a combined *in vitro*/computational approach, particle growth for EEG was demonstrated to result in mass median aerodynamic diameter (MMAD) values in the range of 1.6–2.5 μm .⁽²⁴⁾ Regarding variability, a computational approach was used to model the EEG technique as it relates to nebulized drug delivery during HFNC in a set of four nasal

models, and the CV of drug delivered was reduced by a factor of four when compared with a control case.⁽²⁵⁾

While little is known regarding the deposition of aerosolized medicine that is administered during NPPV, evidence in the literature shows that efficiency of conventional aerosol delivery techniques is low and variability is expected to be high. This study uses *in vitro* experiments and computational fluid dynamics (CFD) simulations to examine the predicted lung delivery efficiency in two newly developed nose–mouth–throat (NMT) models that include face mask interfaces for aerosol delivery through a mask during NPPV. Aerosols considered include micrometer-scale nebulized droplets (from a conventional mesh or jet nebulizer) and submicrometer EEG particles produced from a mesh nebulizer^(26,27) or dry powder inhaler (DPI) device.^(28,29)

Materials and Methods

NMT model selection

Prediction of nebulized aerosol delivery through a mask required the creation of new NMT models that each included a realistic facial interface for mask connection. The absence of readily available computed tomography (CT) scan data that included a complete face, nasal cavity, and throat precluded the creation of a larger data set from which the range of dimensional characteristics could be represented. However, the dimensional data compiled in Walenga et al.⁽²⁵⁾ served as a guide for the selection of scan data. Specifically, since the EEG technique is implemented for this study, the nasopharynx exit hydraulic diameter ($d_{h,nasopharynx}$) is used as a characteristic measurement based on a weak inverse correlation that was observed in Walenga et al.⁽²⁵⁾ between $d_{h,nasopharynx}$ and penetration fraction (PF) of EEG-delivered drug through the nasal cavity. The first model was referred to as Subject A and was taken from the same CT scan data that provided the Constricted2 model from Walenga et al.⁽²⁵⁾ The second model, Subject B, was newly extracted from CT scan data obtained from Virginia Commonwealth University (VCU) Medical Center. The demographics for the two models are given in Table 1, where age, height, and weight are available in 10-year, 5-cm, and 5-kg increments. Both subjects were identified as female.

The surface area-to-volume ratio (SA/V) of the nasal cavity and the average hydraulic diameter of the nostril inlets ($d_{h,nostril}$) and $d_{h,nasopharynx}$ of both subjects are given in Table 2, where SA/V is given for each anatomical side of the nasal cavities. The results of Walenga et al.⁽²⁵⁾ indicated that SA/V correlated well with the delivered dose from the nasopharynx when a conventionally sized monodisperse aerosol was modeled, which had an MMAD of 5 μm . Even though

TABLE 1. DEMOGRAPHIC DATA FOR THE SUBJECT A AND B MODELS, INCLUDING AGE, HEIGHT, AND WEIGHT, WHICH WERE AVAILABLE IN 10-YEAR, 5-CM, AND 5-KG INCREMENTS

Model	Age (years)	Height (cm)	Weight (kg)
Subject A	30	180	75
Subject B	20	170	60

Both subjects were identified as female.

TABLE 2. GEOMETRIC MEASUREMENTS OF THE NASAL CAVITY FROM THE SUBJECT A AND B MODELS

Model	SA/V (mm^{-1})		$d_{h,nostril}$ (mm)	$d_{h,nasopharynx}$ (mm)
	Left	Right		
Subject A	1.14	1.05	13.00	8.78
Subject B	0.75	1.33	9.30	4.50

The dimensions tabulated are the surface area-to-volume ratio (SA/V) of the anatomical left and right sides, the average nostril hydraulic diameter ($d_{h,nostril}$), and the nasopharynx exit hydraulic diameter ($d_{h,nasopharynx}$).

Subject A is derived from the same CT scan data as the Constricted2 model in Walenga et al.,⁽²⁵⁾ the SA/V value for Subject A is smaller than what is reported for the Constricted2 model. It was found during the creation of an *in vitro* replica for the Subject A model that the septum would be too narrow for rapid prototyping (3D printing) to capture, so the thickness was increased from about 0.2 to ~ 0.6 mm.⁽³⁰⁾ This small alteration changed the SA/V value of the entire nasal cavity from 1.42 to 1.05 mm^{-1} ,⁽³⁰⁾ which is representative of the mean SA/V value found in Walenga et al.⁽²⁵⁾ For this study, the altered nasal cavity was used for the Subject A CFD model to allow for comparison with the *in vitro* data. The septum in the Subject B model was about 0.6 mm thick or greater, which indicated that no alteration would be necessary for future rapid prototyping. Of note is the large difference between SA/V values on the left and right sides of Subject B, which are 0.75 and 1.33 mm^{-1} , respectively. This difference is most likely due to the presence of nasal cycling, which is described in Lang et al.⁽³¹⁾ Also noteworthy is the value of $d_{h,nasopharynx}$ for Subject B, which at 4.50 mm is smaller than the observed values from Walenga et al.,⁽²⁵⁾ while the value for Subject A (8.78 mm) was just smaller than the upper maximum of observed values in Walenga et al.,⁽²⁵⁾ which was 9.24 mm. As a result, the selected models provide a large range of $d_{h,nasopharynx}$ values while also capturing most of the range in SA/V reported in our previous study.⁽²⁵⁾

NMT model creation

The commercial software package, Mimics 16.0 (Materialise, Leuven, Belgium), was used to extract CT scan data for the creation of the two models, which include face, nose, nasal cavity, and throat regions. For Subject A, the existing surface from Walenga et al.⁽²⁵⁾ was altered to include the face and throat, while the Subject B model was extracted in its entirety. Conversion of the surface files to volumetric files was performed using 3-matic (Materialise), which allowed for the models to be imported into SolidWorks 2011 (Dassault Systèmes Solidworks Corp., Waltham, MA). To facilitate further modification of the models, the SolidWorks file was saved as an .x_t file type and exported to ANSYS Workbench/DesignModeler 14.5 (ANSYS, Inc., Canonsburg, PA, USA).

The mouth pathways were nearly occluded in the CT scan data since patients typically have their mouths closed during imaging. For this study, a closed mouth model was considered appropriate for inpatient NPPV. However, it was

desirable for the models to have mouth pathways to allow for the possibility of an open mouth model in future studies. The mouth pathways visible in the CT scan data were then augmented to similar dimensions as that of the NMT of Golshahi et al.,⁽²⁶⁾ and, to approximate a closed mouth position, the mouth pathway volumes did not join with the volumes defined by the face and mask boundaries. To aid with any future studies that may consider tracheobronchial (TB) regions, the throats were modified to allow for connection with the characteristic TB model developed in Walenga et al.⁽³²⁾ For the CFD calculations, a numerical extension was added to the trachea by extruding the outlet profile by 10 outlet hydraulic diameter lengths. Images and more detailed information regarding the airspace volumes of the nasal valve area, nasal cavity, nasopharynx, mouth, and throat regions in the models are available in Walenga.⁽³⁰⁾

Oronasal mask designs

Two different mask designs based on the commercially available PerformaTrak[®] SE oronasal mask (Philips Respironics, Inc., Pittsburgh, PA) were used in this study, with one mask for nebulized aerosol delivery and a second mask for DPI aerosol delivery. The nebulizer mask was used for both conventional and EEG nebulized aerosols, and similarly the DPI mask was used for both conventional and EEG DPI aerosols. Preliminary *in vitro* testing of a nebulized aerosol delivery system indicated that an unaltered mask best facilitated efficient drug delivery, as opposed to several altered masks that were tested,⁽³⁰⁾ which is the design that was adopted for this study. Regarding dry powder delivery, an aerosol inlet separate from the gas flow inlet was added to the mask, which was angled for direct delivery to the left naris of the Subject A model. The inlet was not altered for the Subject B model to reflect the fact that a manufactured mask would not be perfectly aligned with the left naris entrance for all subjects. The aerosol inlet entrance length was ~ 2.5 cm, while the diameter was 8 mm. Aerosol delivery from an inline DPI was simulated for comparison with corresponding *in vitro* experiments, which implemented the 3D rod array inline design that has been developed by our group, specifically the 2.3-232 version,^(28,33–36) which is actuated with a manual ventilation bag. Only the exit nozzle of the DPI was included in the CFD mask model since the internal particle deagglomeration mechanism was not simulated. An experimentally determined particle distribution was used at the inlet of the mask nozzle.

Computational meshes

To create the computational meshes for this study, the conventional and DPI masks were joined with the Subject A and Subject B models, and the meshing software, ICEM CFD 12.0.1 (ANSYS, Inc.), was used. To test the effect that mask seal with the face may have on drug delivery, the meshes were built with and without a gap at the mask–face interface. In the case of mask leak, a gap distance of 0.5 mm was applied consistently around the mask. A nearly identical meshing procedure compared with Walenga et al.⁽²⁵⁾ was implemented to create the four meshes (conventional and DPI masks without and with a gap). A tetrahedral mesh was applied to the airspace between the mask and the face, as opposed to the hexahedral mesh applied to the tube and

nasal cannula in Walenga et al.,⁽²⁵⁾ because the irregular face surface made the application of a hexahedral boundary intractable. The nasal cavity was also modeled using tetrahedral cells due to its highly complex geometry. A surface mesh was first applied with the curvature-sensitive feature that used smaller elements in regions of greater curvature. A Delaunay mesh was applied to the volume of each nasal cavity with a spacing scaling factor of 1.2–1.3 and a maximum cell dimension of 1 mm. Pentahedral elements were added along the walls to increase the accuracy of the boundary layer simulations and particle deposition. Seven near-wall layers were applied with a near-wall control volume height of 0.011 mm to the Delaunay meshes, where it was found through several iterations of design that these values provided the best combination of flow field resolution and convergence. The four meshes consisted of ~ 6 – 7 million cells. The y^+ values of the near-wall control volumes were checked to ensure mesh independence, and it was found that the maximum value for each case was 2.7 or less, which is within the range ($1 < y^+ < 5$) of accuracy for the turbulence model selected for this study.

Cases considered

Cases of interest include conventional and submicrometer EEG aerosol delivery to Subject A and B models. Sources of both the conventional and EEG aerosols were nebulizer and DPI based. *In vitro* experiments incorporating realistic patient breathing were conducted to validate the CFD model predictions for Subject A receiving nebulizer-generated conventional and EEG aerosols with simulated shallow and deep inhalation patient profiles, and for Subject A receiving a DPI-based EEG aerosol with a simulated shallow inhalation patient profile. To evaluate different medications, albuterol sulfate was used in the *in vitro* nebulizer experiments and the antibiotic ciprofloxacin (CP) was used in the EEG DPI *in vitro* experiments. CFD simulations were first validated using nearly identical conditions and geometries compared with the experiments, including cyclic breathing. Steady-state CFD simulations were then used to consider the full matrix of two subjects receiving conventional and EEG aerosols, with the sources of these aerosols being nebulizer and DPI based. Administration of nebulizer and DPI aerosols required the two different mask designs. As described below, the effect of mask seal leak was also included in some of the simulations.

In vitro experimentation

To validate the CFD model, *in vitro* data collected for this study were used to compare the results of transient simulations for both nebulized and dry powder aerosol delivery to Subject A with a perfect mask seal. Two corresponding *in vitro* models for these cases were constructed using 3D rapid prototyping. To accomplish this, stereolithography (SLA) with a Viper SLA system (3D Systems, Valencia, GA) was used with Accura 60 clear plastic resin. Rapid prototyping was chosen for mask creation because it allowed for both the *in vitro* and CFD models to have identical dead space volumes and geometries.

For the experiments, a Galileo critical care ventilator (Hamilton Medical, Bonaduz, Switzerland) was used to provide NPPV support applied to the *in vitro* patient models. Consistent with a critical care setting, a heated and

humidified dual-limb circuit (no leak port) was selected, and the ventilator was operated using a manufacturer-defined NPPV setting. The NPPV setting defined a pressure support mode, where the peak end expiratory pressure was set to 5 cm H₂O, while the inspiratory positive airway pressure was set to 10 cm H₂O to achieve a mean flow rate of ~ 30 L/min. The ventilator was connected to an *in vitro* NMT model, which was in turn connected to a dual adult test lung (Michigan Instruments, Grand Rapids, MI) controlled with a breath simulation module (Michigan Instruments) and supplied by a tank of pressurized air. A breathing rate of 15 breaths per minute was selected for the dual adult test lung. For shallow patient inhalation, the inspiratory time was 1 second, which provided 400 mL of tidal volume to the system. Similar values for the patient deep inhalation were 2 seconds and 800 mL, respectively. The compliance of the lung was 50 mL/cm H₂O and lung resistance was 5 cm H₂O/(L·s). For conventional and EEG drug delivery, inspiratory and expiratory filters were placed in the system to measure inhaled and exhaled drug dose. High-performance liquid chromatography methods were used to assay albuterol and CP and quantify the drug deposition in the connecting tubing, mask, face, and NMT, together with the inspiratory and expiratory filters.

Conventional nebulized drug delivery was assessed with a 0.5% albuterol (as albuterol sulfate) w/v in water solution and an Aeroneb Pro (Aerogen, Galway, Ireland) mesh nebulizer. The nebulizer was inserted in-line using an Aerogen T-connector and positioned in the inspiratory limb of the dual-limb circuit ~ 25 –30 cm from the face mask. The expiratory filter was placed between the dual-limb junction and the nebulizer. The process diagram is shown in Figure 1. For each experiment, the nebulizer was operated for 2 minutes, consistent with 30 breath cycles. Patient inhalation using the dual adult test lung was simulated using conditions to produce a shallow and a deep inhalation profile. A rapid prototyped version of the commercially available PerformaTrak SE mask was used for all nebulized aerosol experiments, which was applied to the Subject A *in vitro* model with a perfect mask seal.

Considering EEG delivery, the transient flow aerosol mixer–heater developed by our group^(27,37) was modified to

receive inspiratory flow from the ventilator instead of the previously used blowers and was used to produce a sub-micrometer aerosol. The EEG aerosol was a 50:50 combination of albuterol and sodium chloride (NaCl) that was initially dissolved as 0.5% albuterol (as albuterol sulfate) and 0.5% NaCl w/v in water and nebulized with the Aeroneb Pro. The mixer–heater was placed in-line with the inspiratory section of the dual-limb circuit such that air flow from the ventilator passed through the mixer–heater to collect the EEG aerosol before delivery to the Y-connector and entrance to the mask. The inspiratory filter was just downstream of the *in vitro* model, while the expiratory filter was in-line with the expiratory section of the dual-limb circuit. The process diagram for the EEG drug delivery experiments is shown in Figure 2. As in the conventional drug delivery studies, the nebulizer was operated for 2 minutes. Patient inhalation using the dual adult test lung was simulated using conditions to produce a shallow and a deep inhalation profile.

The system used for *in vitro* dry powder delivery was similar to the setup for conventional nebulized delivery with a simulated shallow inhalation profile from the dual adult test lung. The process diagram for the dry powder drug delivery experiments is shown in Figure 3. All of the settings with the Galileo ventilator and the dual adult test lung were the same as described above. To supply the aerosol, an in-line DPI was connected to a side port on the mask with an airtight seal and angled such that the outlet airstream from the DPI was directed at the left nostril (of Subject A). As with the CFD simulations, the inhaler was the in-line DPI based on the 3D rod array design, specifically the 2.3-232 version, which was developed by our group.^(28,33–36) The inlet of the DPI was connected to a manual ventilation bag with tubing, where the bag was actuated manually for ~ 1 second during each inhalation cycle, for multiple cycles. The EEG formulation consisted of submicrometer combination primary particles of a drug:excipient powder⁽³⁶⁾ containing CP, mannitol (MN), L-leucine, and poloxamer 188 (ratio 30:48:20:2). Ten milligrams of formulation was loaded into a size 3 hydroxypropyl methylcellulose (HPMC) capsule; the capsule was pierced and loaded into the in-line

FIG. 1. Process diagram of conventional nebulized drug delivery during NPPV. NPPV, noninvasive positive pressure ventilation.

FIG. 2. Process diagram of EEG drug delivery during NPPV. EEG, excipient enhanced growth.

FIG. 3. Process diagram of dry powder drug delivery during NPPV.

DPI. In addition to collecting drug deposition data in the NPPV model, the emitted particle size distribution from the in-line DPI was measured by a Next Generation Impactor (Copley Scientific Limited, Nottingham, United Kingdom) with the inclusion of makeup air to reach a flow rate of 45 L/min, which was used as the initial polydisperse size distribution entering the mask in the CFD simulations. Importantly, the in-line DPI system and manual ventilation bag are constructed to be airtight such that when connected to the pressurized NPPV mask, humidified airflow cannot flow into the DPI.

For all cases, the Galileo ventilator with a Fisher and Paykel heated humidification unit (MR850) was employed, resulting in heated and humidified air delivered to the *in vitro* model. A sufficient time period (~30 minutes) was implemented to allow the *in vitro* model to equilibrate with the supplied heated and humidified air. The gas delivery temperature at the model inlet was then assumed to be 37°C with a relative humidity (RH) of 99%. Because the aerosol was delivered in a closed system, an environmental chamber was not necessary. For the in-line DPI delivery scenario, heated and humidified gas was used in the model and room air (~21°C and 30%–50% RH) was used in the ventilation bag.

Computational methods and validation

The CFD methods were validated with the collected experimental data through several transient simulations. For nebulized delivery, both the conventional and EEG aerosols were considered, using the experimentally determined shallow and deep flow profiles from the dual adult test lung, where the compositions of the aerosols were the same as with the experiments. Dry powder delivery was modeled with the CP EEG aerosol and shallow inhalation from the dual adult test lung. To simulate the fluid flow for all cases considered, the commercially available CFD package, ANSYS FLUENT 14.5 (ANSYS, Inc.), was used in conjunction with multiple user-defined routines. Using this blend of commercial and custom software, fluid heat and mass transfer were also modeled along with particle deposition,

hygroscopic size change, and trajectories.^(38,39) To simulate both turbulent and laminar flow, a low-Reynolds number *k- ω* model was used because it has been shown to reliably predict flow field properties in human upper respiratory airways, especially in relation to aerosol transport and deposition.⁽⁴⁰⁾ Parallel processing was utilized to enhance solution efficiency.

Lagrangian transport equations were implemented to execute particle trajectory calculations, which included predictions of hygroscopic size change.⁽³⁸⁾ A random walk method was utilized to estimate turbulent dispersion of particle trajectories, and user-defined functions were used to model near-wall corrections of turbulence and fluid velocities. The system was modeled as one-way coupled, in that all influences of the discrete phase on the continuous phase (i.e., mechanical and thermodynamic) were neglected. The governing transport equations used have been described in more detail by Longest et al.⁽⁴¹⁾ and Tian et al.⁽⁴²⁾

Previously established best practices were followed with regard to CFD solution methods in the upper airways.⁽³⁹⁾ Accuracy was improved through the use of double precision for all calculations. The SIMPLEC algorithm was selected to model the pressure–velocity coupling and a second-order upwind scheme was utilized for the spatial discretization of all convective terms. To define flow field convergence, the simulations were monitored to detect both a five order of magnitude reduction in the global mass residual and the approach of mass and momentum residual rates to the numerical precision limit.

To obtain the inlet flow rate conditions for validation simulations, experimental flow rate profiles were sampled from the ventilator flow meter in 0.032-second intervals. The profiles were sampled from a period of ~4 seconds, which were then fit to a series of linear and sinusoidal regressions. The sampled data and accompanying regressions are available in Walenga.⁽³⁰⁾ All of the validation simulations employed a perfect mask seal, which was consistent with the experimental procedures. For all CFD cases, ventilation gas delivery was heated and humidified at an inlet temperature and RH of 37°C and 99%. For the dry powder delivery simulation, flow from the ventilation bag entering the aerosol inlet was modeled at standard room conditions. The flow rate for the aerosol inlet was measured experimentally and a sinusoidal fit was used for the simulation, where the average and maximum flow rates were 7.1 and 11.7 L/min, respectively. This flow rate fit was converted to average velocity and it was initiated after a lag time of ~0.2 seconds, which was done to imitate the experimental procedure where the DPI was actuated manually after the beginning of the inhalation cycle.

Wall surface thermodynamic conditions of the upper airways are difficult to predict and may differ with environmental conditions and respiration rate.⁽⁴³⁾ Martonen et al.⁽⁴⁴⁾ have previously compiled a list of airway surface temperature and RH conditions for the upper airways. After the first few bifurcations, it is generally accepted that airway wall temperature is 37°C and 99%–100% RH. In this study, it was assumed that for a patient breathing heated and humidified air for an extended period, the upper airway conditions would also be 37°C and 99% RH. These wall conditions should maximize aerosol growth in the nose, thereby providing a conservatively high estimate of nasal depositional loss for EEG delivery.

For the nebulized aerosol delivery validation simulations, the conventional aerosol was polydisperse and was assumed to be produced by an Aeroneb Pro nebulizer (Aerogen) with 0.2% albuterol (as albuterol sulfate) w/v at a flow rate of 30 L/min. The polydisperse bolus consisted of 9000 particles. The relevant particle size distribution was reported by Longest et al.,^(45,46) where the MMAD was $\sim 4.8 \mu\text{m}$ with a geometric size distribution of ~ 5.7 . For nebulized EEG drug delivery, drug and excipient combination particles consisting of albuterol and NaCl with a 50:50 ratio were injected into the mask inlet as a monodisperse bolus of 9000 particles, with an assumed initial aerodynamic diameter of $0.9 \mu\text{m}$. This assumption was based on a similar experiment with the steady-state mixer-heater from Golshahi et al.⁽²⁶⁾

For the dry powder aerosol validation simulation, the active ingredient was the antibiotic CP, which was formulated as a combination particle with the hygroscopic excipient MN in a similar manner as described by Longest et al.⁽²⁹⁾ and Son et al.⁽³⁶⁾ For the simulations conducted for this study, the surfactant, poloxamer 188, was omitted, and the new ratio with CP, MN, and L-leucine was 30:50:20. A total of 17,528 particles were used to represent the particle size distribution for the CFD simulations, where the bolus was divided into seven bins to match the experimentally determined distribution from the Next Generation Impactor. The experimentally measured and numerically matched MMAD of the aerosol was $1.53 \mu\text{m}$. A delayed release was implemented, where the entire bolus was released after 0.6 seconds when the inlet velocity at the DPI exit was $\sim 25 \text{ m/s}$. This was done to approximate the theory that the powder would not be released until a critical velocity was achieved and to allow sufficient airflow in the model to entrain the aerosol.

Approximation of inspiratory filter drug deposition with the transient CFD predictions was complicated by the inclusion of a numerical extension in the models. During the transition from inhalation to exhalation, some particles that are entrained in the volume enclosed by the extension reverse course and reenter the volume enclosed by the models. For the sake of comparison, the Subject A model volume is 260.5 mL, while the volume of the extension is 54.7 mL.⁽³⁰⁾ Reentering of the particles into the models does not occur with the *in vitro* setup since the inspiratory filter is directly downstream of the throat exit. However, the extension was included with the CFD simulations to aid with increased accuracy in turbulence modeling at the throat outlet, which is expected to balance to some degree any loss in accuracy due to reentering particles. Moreover, the continuous release of particles (which is consistent with the experiments) ensures that only a small fraction of the total number of particles released may be present in the extension volume at any given moment.

Steady-state simulations

Once validation of the CFD methods for both drug delivery types was complete, steady-state simulations were conducted to allow for relative comparisons of all systems. Since comparisons between nebulized and dry powder delivery and between conventional and EEG delivery were desired, rather than absolute predictions, steady-state conditions were chosen

for their computational efficiency. Conventional and EEG drug delivery were both considered for nebulized and dry powder simulations. The ventilation flow rate for both nebulized and dry powder simulations was 30 L/min, which approximates the mean of the *in vitro* measurements, while the dry powder aerosol inlet was set at 11.7 L/min, which was the maximum measured value. Conventional aerosol delivery was modeled for this study by considering a generic droplet or particle with an initial aerodynamic diameter of $6 \mu\text{m}$ and assuming that size change was negligible, which is considered a reasonable assumption for pharmaceutical aerosols with aerodynamic diameters greater than $3 \mu\text{m}$.^(47,48) This particle size is considered to be typical for mesh nebulizers and DPIs.^(36,46,49,50) It is noted that DPI aerosols are not delivered to NPPV systems in clinical practice due to the absence of a viable delivery device. Therefore, conventional DPI delivery refers to the aerodynamic particle size that would be achieved if a commercial inhaler and powder formulation were integrated into the system with a positive pressure actuation device, as with Tang et al.⁽⁵¹⁾ or Everard et al.⁽⁵²⁾ In contrast, EEG dry powder delivery implements a much smaller initial aerosol size that once inhaled increases in the humid airways due to the inclusion of the hygroscopic excipient.

The effect of mask seal leak was compared with a perfectly sealed system for the nebulized delivery predictions, while the dry powder predictions only considered a system with mask seal leak. Schettino et al.⁽⁵³⁾ evaluated mask sealing during NPPV using a commercial mask with a mannequin at various inlet airway pressure settings and found that the leak flow rate was nearly constant when the difference between the inlet airway pressure and mask pressure was above $1.7 \pm 0.1 \text{ cm H}_2\text{O}$, and that a volumetric air leak of 5.2% was observed at this threshold. Taking this into account, an outflow boundary condition was used for the CFD predictions in this study that applied the leak flow split identified by Schettino et al.⁽⁵³⁾

Deposition metrics

Particle fate in each region was reported as either deposition fraction (DF), lung PF, mask seal loss (MSL), or fraction exhaled (FE). The DF for the *i*th region based on drug mass is calculated on a percent basis as

$$DF_i = \frac{\text{mass of drug depositing in region } i}{\text{mass of drug exiting nebulizer}} \times 100. \quad (1)$$

The values of PF, MSL, and FE were calculated similarly by considering the ratios of mass exiting the NMT model at the trachea, mask seal, or mask entrance to the mass of drug delivered from the nebulizer, respectively, and multiplied by 100 to form a percentage. To calculate these values, an estimate for the amount of drug entering the mask was needed based on the NPPV system employed (i.e., for either conventional or EEG delivery) since the simulations did not model the entire pathway from the nebulizer through the nasal cavity. Several *in vitro* values and assumptions were applied to provide these estimates, which were mainly concerned with estimating deposition on the tubing, nebulizer T-connector, and the mixer-heater (for the EEG case). Further details are provided in Walenga.⁽³⁰⁾

Results

Computational method validation

The nebulized aerosol validation results are displayed for both conventional and EEG delivery in Figure 4, with either a shallow or deep simulated patient inhalation. Overall trends include increases in PF from conventional to EEG delivery and from shallow to deep inhalation. In addition, FE increases from conventional to EEG delivery because improved delivery efficiency with EEG results in more aerosol available to be exhaled. It is also observed that this exhaled fraction during EEG delivery decreases with deep patient inhalation compared with shallow inhalation. The largest absolute difference is between the experimental and predicted values of FE for EEG delivery with deep inhalation (Fig. 4d), with a value of 5.8%, resulting in a relative difference of 23%. For the same case (Fig. 4d), the relative difference for DF is the largest for all metrics and all cases, with a relative increase of 140% from experimental to predicted values, but an absolute difference of only 2.1%. The differences for this case in FE and DF appear to be due to overprediction of DF, which leaves less drug mass available for exhalation. However, DF is underpredicted for conven-

tional delivery with a simulated shallow patient inhalation (Fig. 4a), which highlights the difficulty of balancing simulation parameters to produce meaningful results. Considering that the simulations include transient effects, inhalation and exhalation, and the approximation of effects from the attached NPPV system, the predicted values of DF, FE, and PF were considered to match adequately with the experimental data.

Data for the experimental validation of the dry powder case are provided in Figure 5, which shows DF_{mask} , DF_{FNMT} , FE, and PF; where DF_{FNMT} refers to the DF on the combination of the face and nose–mouth–throat (FNMT) model. The experimental and predicted values for DF and PF match to a very high degree, with relative differences of 4% and 3.4%, respectively. The estimated value of mask DF is underpredicted compared with the experimental value (3% vs. 6.5%), while the predicted value of FE is greater than the experimental value (18.7% vs. 14.6%). It is believed that this discrepancy is primarily due to incomplete information regarding the time release of powder from the in-line DPI, where an approximation was used as described in the Materials and Methods section. However, the metric of greatest interest is lung PF, which is also referred to as the

FIG. 4. Experimental validation of DF, FE, and PF with a sealed nebulized aerosol system and Subject A for conventional drug delivery with (a) shallow and (b) deep simulated patient inhalation and EEG drug delivery with (c) shallow and (d) deep simulated patient inhalation. Transient CFD data are compared with *in vitro* experimental (EXP) results, where the DF values include drug deposited in the mask, face, and NMT. CFD, computational fluid dynamics; DF, deposition fraction; FE, fraction exhaled; NMT, nose–mouth–throat; PF, penetration fraction. Color images available online at www.liebertpub.com/jamp

FIG. 5. Experimental validation of DF, FE, and PF with a sealed dry powder aerosol system and Subject A for EEG drug delivery with shallow simulated patient inhalation. Transient CFD data are compared with *in vitro* experimental (EXP) results, where DF values are reported for the FNMT combination and the mask. FNMT, face–nose–mouth–throat. Color images available online at www.liebertpub.com/jamp

lung delivery efficiency, and indicates a relative difference between CFD vs. experiments of 3.3%.

Steady-state simulations

The steady-state predictions for conventional delivery of nebulized aerosol to Subjects A and B in a perfectly sealed system are given in terms of DF in the mask, face, and NMT in Figure 6. The values of DF for the mask and face are on the order of 1% for both subjects, while the values of DF_{NMT} show a large difference with 25.9% for Subject A and 56.4% for Subject B. Steady-state predictions of EEG

delivery with a nebulized aerosol in a sealed system, shown in Figure 7, indicate that DF values in the mask and face are reduced to values on the order of 0.1%, while the amounts of drug deposited in the NMT are greatly reduced (by a factor of ~ 10) for the submicrometer EEG aerosol compared with conventional delivery. Also notable is that the intersubject difference in the absolute values of DF_{NMT} is greatly reduced for EEG delivery in the sealed system. DF values for both conventional and EEG delivery in the sealed system are also given in Table 3, along with values of PF and outlet MMAD. The EEG case shows improved drug delivery and reduced variability, with PF values of 93.6% and 88.5% for Subjects A and B, as opposed to 69.5% and 39.0% for conventional delivery, respectively. Although it is noted that the largest value of outlet MMAD was for the case of conventional delivery to Subject A, the values of outlet MMAD are more consistent for EEG delivery with 2.46 and 2.45 μm for Subjects A and B, while the values for conventional delivery were 3.14 and 2.29 μm , respectively. In the EEG case, size increase from 900 nm to $\sim 2.5 \mu m$ is sufficient for adequate lung retention, and EEG aerosol size increase is expected to continue in the lungs.

Nebulized aerosol delivery predictions of DF and MSL for both conventional and EEG drug delivery with an imperfect mask seal are given in Figure 8. The mask and face DF predictions are on the order of 1% for both conventional delivery cases (Fig. 8a, b) and range from 0.1% to 0.6% for EEG delivery (Fig. 8c, d). The values of DF_{NMT} are 22.4% and 52.0% for Subjects A and B with conventional delivery (Fig. 8a, b) and 2.9% and 8.5% with EEG delivery (Fig. 8c, d), respectively. Somewhat surprisingly, the amount of drug lost through the seal is nearly the same for all cases, with values of MSL between 3% and 4%. The data are also provided in Table 4, which include predictions of PF and outlet MMAD. Again, the same trends for PF as with a perfectly sealed system are visible here, with significantly increased and less variable values of PF for the EEG cases compared with the conventional delivery cases. The outlet MMAD values with the imperfectly sealed system are nearly the same as with the

FIG. 6. Steady-state CFD predictions of DF with a sealed nebulized aerosol system and conventional drug delivery to (a) Subject A and (b) Subject B. Color images available online at www.liebertpub.com/jamp

FIG. 7. Steady-state CFD predictions of DF with a sealed nebulized aerosol system and EEG drug delivery to (a) Subject A and (b) Subject B. Color images available online at www.liebertpub.com/jamp

perfectly sealed system for the small amount of air leak included (5.3% air escaping through the 0.5-mm gap).

The predictions of DF and MSL for an imperfectly sealed system and conventional dry powder size are displayed in Figure 9. As opposed to the nebulized system, the values of DF_{mask} and DF_{face} vary considerably from Subject A to Subject B, with values that are $\sim 0.5\%$ for Subject A and between 4% and 7% for Subject B. Predictions for DF_{NMT} show values that are similar to the conventional nebulized delivery cases. However, eight times as much drug is predicted to be lost for Subject B than for Subject A, as seen in the values of MSL. The elevated values of DF_{mask} , DF_{face} , and MSL for Subject B are due to a misalignment of the aerosol inlet with the (left) nostril, which are to be expected considering that the inlet was designed to be aligned with the nostril for Subject A and was not altered for Subject B.

TABLE 3. STEADY-STATE COMPUTATIONAL FLUID DYNAMICS PREDICTIONS OF DEPOSITION FRACTION, PENETRATION FRACTION, AND OUTLET MASS MEDIAN AERODYNAMIC DIAMETER WITH THE SEALED NEBULIZED AEROSOL SYSTEM FOR CONVENTIONAL AND EXCIPIENT ENHANCED GROWTH DRUG DELIVERY TO SUBJECT A AND SUBJECT B

	<i>DF</i>			<i>PF</i>	<i>Outlet MMAD</i> (μm)
	<i>Mask</i>	<i>Face</i>	<i>NMT</i>		
Conventional					
Subject A	1.1	0.9	25.9	69.5	3.14
Subject B	1.1	0.7	56.4	39.0	2.29
EEG					
Subject A	0.2	0.3	3.0	93.6	2.46
Subject B	0.2	0.1	8.9	88.5	2.45

All values are presented as a percentage of the initial drug dose. DF, deposition fraction; EEG, excipient enhanced growth; MMAD, mass median aerodynamic diameter; NMT, nose-mouth-throat; PF, penetration fraction.

The misalignment of the aerosol inlet with Subject B complicates the assessment of intersubject variability. One perspective is that misalignment introduces an element of use into the assessment. However, the misalignment results from anatomical differences between Subjects A and B and the fact that the inlet will not properly align with some subjects. With either view, the increased depositional losses associated with misalignment are relatively small ($\sim 10\%$) compared with the increase in depositional losses in the airway of Subject B ($\sim 30\%$). It is further noted that while perfect alignment in Subject B might increase the aerosol fraction entering the nostril, a high fraction of this aerosol will be captured in the NMT region resulting in little change to lung PF.

Considering EEG dry powder delivery in the imperfectly sealed system (Fig. 10), the values of DF_{mask} and DF_{face} are greatly reduced for Subject B and are on the order of 1%, while the values for DF_{NMT} are similar to those predicted for nebulized EEG delivery (Fig. 8c, d). The MSL value for Subject A is approximately the same, while the result for Subject B is reduced from 15.9% to 12.9%. These results suggest that the misalignment of the aerosol inlet can only be partially compensated for by EEG delivery. All the data for dry powder delivery are summarized in Table 5. For a conventionally sized dry powder, PF is reduced for both subjects compared with conventional nebulized delivery, while EEG dry powder delivery produces somewhat similar PF results compared with EEG nebulized delivery. However, the PF value for Subject B is reduced compared with EEG nebulized delivery from 85.0% to 74.7%, presumably due to the increased MSL value. The outlet MMAD results for EEG dry powder delivery are both about $2.9 \mu\text{m}$, which is advantageous for achieving high lung retention.

The lung PF results for both nebulized and dry powder delivery with both conventional and EEG techniques in an imperfectly sealed mask system are summarized in Figure 11. The EEG results are consistently better for both subjects with both nebulized and dry powder delivery. For Subject A, EEG delivery improves lung PF by a factor of ~ 1.3 to 1.5, whereas for Subject B, EEG delivery improves lung PF by much larger

FIG. 8. Steady-state CFD predictions of DF and MSL with the nebulized aerosol system and a 5.2% leak through the mask seal for conventional drug delivery to (a) Subject A and (b) Subject B and EEG drug delivery to (c) Subject A and (d) Subject B. MSL, mask seal loss. Color images available online at www.liebertpub.com/jamp

TABLE 4. STEADY-STATE COMPUTATIONAL FLUID DYNAMICS PREDICTIONS OF DEPOSITION FRACTION, MASK SEAL LOSS, PENETRATION FRACTION, AND OUTLET MASS MEDIAN AERODYNAMIC DIAMETER WITH THE NEBULIZED AEROSOL SYSTEM AND A 5.2% LEAK THROUGH THE MASK SEAL FOR CONVENTIONAL AND EXCIPIENT ENHANCED GROWTH DRUG DELIVERY TO SUBJECT A AND SUBJECT B

	<i>DF</i>					<i>Outlet MMAD (μm)</i>
	<i>Mask</i>	<i>Face</i>	<i>NMT</i>	<i>MSL</i>	<i>PF</i>	
Conventional						
Subject A	1.3	1.1	22.4	3.6	68.4	3.19
Subject B	1.5	0.9	52.0	3.4	39.1	2.31
EEG						
Subject A	0.4	0.3	2.9	3.9	89.8	2.47
Subject B	0.6	0.1	8.5	3.2	85.0	2.45

All values are presented as a percentage of the initial drug dose. MSL, mask seal loss.

factors of 2.2 to 6.4. These results suggest that the EEG technique may be effective with both nebulized and dry powder aerosols for improving efficiency and reducing variability when delivering inhaled medications during NPPV. These data also suggest that while the results with the conventional technique show that the nebulized aerosol performs much better than the dry powder aerosol, with the EEG technique dry powder delivery is comparable and may be a viable alternative.

Discussion

A primary outcome of this study is that the EEG approach can improve aerosol delivery during NPPV in terms of increased lung delivery efficiency (i.e., PF) and reduced deposition variability between subjects. Due to inherent intersubject geometric variability, improvements in lung PF achieved with the EEG approach were different for each subject. With model Subject A, which had relatively high lung PF with conventional delivery, the EEG approach improved lung delivery efficiency for both modes of aerosol

FIG. 9. Steady-state CFD predictions of DF and MSL with the dry powder aerosol system and a 5.2% leak through the mask seal for conventional drug delivery to (a) Subject A and (b) Subject B. Color images available online at www.liebertpub.com/jamp

generation (nebulization and DPI) by factors in the range of 1.3–1.5-fold. For model Subject B, improvements in lung delivery efficiency with EEG compared with conventional delivery were in the range of 2.2–6.4-fold. These findings are based on steady-state CFD predictions; however, similar improvements were observed with the *in vitro* experiments that employed cyclic realistic breathing, as shown in Figure 4 and described further in this Discussion section.

Perhaps more significant than the improved delivery efficiency is the reduction in intersubject aerosol delivery variability achieved with the EEG approach. Based on the use of two subjects, intersubject variability can be assessed as a relative difference in lung PF between Subject A and Subject B. Relative difference is calculated as the range divided by the mean and is therefore similar to the CV used with larger data sets. Considering nebulizer delivery of conventional aerosols with a mask seal leak (Table 4), relative difference in lung PF between Subjects A and B (68.4 vs. 39.1) was 54.5%. The EEG approach for nebulized aerosols reduced this relative difference between Subjects A and B to 5.5%, resulting in an

order of magnitude reduction in intersubject variability of lung-delivered dose. DPI aerosols are currently not delivered during NIV in the clinic. However, recent studies have demonstrated research devices that make this approach possible.^(28,29,51,54,55) Simulating one of these in-line DPI devices and a conventional aerosol size with mask seal leak (Table 5), the relative difference in lung PF between Subjects A and B is 134.3%. EEG delivery reduces this relative difference to 17.4%, again providing an approximate order of magnitude decrease in intersubject aerosol delivery variability. Therefore, intersubject variability in lung PF of conventionally sized aerosols is observed to be high considering two subjects with different anatomical metrics and is substantially (order of magnitude) reduced with the EEG approach implementing both nebulizer and DPI platforms.

A second outcome of this study is that an in-line DPI platform may provide an effective approach for rapid and synchronized aerosol delivery during NIV. As observed by Dhand,⁽⁸⁾ DPI aerosols are not clearly compatible with mechanical ventilation due to possible compromise of the powder

FIG. 10. Steady-state CFD predictions of DF and MSL with dry powder aerosol system and a 5.2% leak through the mask seal for EEG drug delivery to (a) Subject A and (b) Subject B. Color images available online at www.liebertpub.com/jamp

TABLE 5. STEADY-STATE COMPUTATIONAL FLUID DYNAMICS PREDICTIONS OF DEPOSITION FRACTION, MASK SEAL LOSS, PENETRATION FRACTION, AND OUTLET MASS MEDIAN AERODYNAMIC DIAMETER WITH THE DRY POWDER AEROSOL SYSTEM AND A 5.2% LEAK THROUGH THE MASK SEAL FOR CONVENTIONAL AND EXCIPIENT ENHANCED GROWTH DRUG DELIVERY TO SUBJECT A AND SUBJECT B

	DF					Outlet MMAD (μm)
	Mask	Face	NMT	MSL	PF	
Conventional						
Subject A	0.4	0.6	27.7	2.4	59.0	6.00
Subject B	3.8	7.1	60.5	15.9	11.6	6.00
EEG						
Subject A	0.1	0.2	2.0	2.6	88.9	2.90
Subject B	1.1	0.7	8.4	12.9	74.7	2.85

All values are presented as a percentage of the initial drug dose.

by exposure to high levels of humidity used in the ventilator circuits. However, connection of an airtight DPI device in a separate flow pathway and then actuation of the device with an external gas source may solve this problem. Such in-line devices have recently been described by Tang et al.,⁽⁵¹⁾ Pornputtapitak et al.,⁽⁵⁵⁾ Behara et al.,⁽²⁸⁾ and Longest et al.⁽²⁹⁾ The VCU in-line DPI^(28,29) incorporates a new 3D rod array to efficiently deaggregate the EEG powder and was shown to be capable of producing aerodynamically small ($\sim 1.5 \mu\text{m}$) aerosols using low air volumes. Laube et al.⁽⁵⁴⁾ recently reported on the connection of an active DPI to a mask interface for aerosol delivery to infants and found 0.3%–4% lung delivery efficiency with an *in vitro* system. Longest et al.⁽²⁹⁾ recently reported high lung delivery efficiency (up to 63%) with an EEG powder and 3D rod array in-line DPI during HFNC therapy. The current study is the first to report high-efficiency lung delivery during NPPV (or other mask interface systems) using a powder aerosol. CFD results predicted reasonable lung delivery effi-

FIG. 11. Steady-state CFD predictions of PF for nebulized and dry powder drug delivery to Subject A and Subject B for both conventional and EEG drug delivery.

ciency, but high intersubject variability with the conventional powder particle size. Both CFD results and *in vitro* experiments showed high-efficiency lung delivery with the EEG powder system connected to the mask interface. An initial technical challenge was to ensure the in-line DPI system was airtight in the pressurized NPPV setup. However, once the device was engineered to overcome this issue, DPI delivery during NPPV in the *in vitro* experiments was found to be convenient and rapid with good capsule emptying. Importantly, the DPI device was easy to synchronize with inspiration based on visual observation of the ventilator display and did not need additional aerosol delivery-triggering equipment. Furthermore, it is expected that lung delivery efficiency with this system can exceed the current *in vitro* reported value of $\sim 50\%$ (Fig. 5) with continued device optimization, as with similar systems developed by our group.^(28,29)

In this study, steady-state CFD simulations are implemented to determine relative differences in lung delivery efficiency and to assess intersubject aerosol delivery variability. The *in vitro* data with cyclic breathing (and corresponding transient CFD validation simulations) demonstrate similar trends, but (as expected with incorporation of realistic breathing) reduced overall lung delivery efficiency. For example, with cyclic breathing, the *in vitro* data indicate an approximate 2.1–2.6-fold improvement in lung delivery efficiency with nebulized submicrometer EEG aerosols compared with conventional nebulization. Only one subject model was considered in the *in vitro* experiments of this study such that the effects of simulating realistic breathing on intersubject aerosol delivery variability are not available. Trends observed in the *in vitro* data include a higher tidal volume (deep inhalation) increasing the lung PF for both conventional (1.8-fold increase) and EEG (1.5-fold increase) aerosols. In the nebulizer cases, the vibrating mesh nebulizer was operated continuously. Synchronized aerosol generation with inhalation achieved with the DPI *in vitro* experiments improved lung delivery efficiency by an additional factor of twofold. The combination of deeper inspiration and synchronization with inspiration will likely increase lung delivery efficiency during simulated patient breathing to the level that is observed during the steady-state delivery simulations. That is, the combined PF improvement of approximately fourfold that can be achieved with synchronization ($\sim 2\times$) and deep inspiration ($\sim 2\times$) elevates the transient EEG PF prediction of $\sim 25\%$ (Fig. 4c) to the steady-state EEG prediction of $\sim 90\%$ and higher (Table 3).

To enable cyclic ventilation lung PF values approaching the steady-state maximums, system modifications are needed that include synchronizing aerosol delivery to the patient with inspiration, a reduced volume nebulizer system, and deep patient inhalation consistent with NPPV. Previous versions of the mixer–heater used to produce EEG aerosols from a nebulizer have implemented inhalation-synchronized nebulization or airflow.^(37,56) As a result, cyclic delivery has approached steady-state estimates. In the current system, inhalation flow passing through the mixer–heater combined with the dual-limb NPPV setup was viewed as eliminating the need for synchronized generation. Instead of synchronization, the mixer–heater reservoir holds the continuously generated aerosol during the exhalation phase. However, during the *in vitro* experiments, it was determined that bias flow from the ventilator during exhalation passed through the

inspiratory and expiratory limbs, largely reducing the accumulation of aerosol in the mixer–heater unit. As a result, synchronized nebulization is needed in future studies employing nebulizer-generated EEG aerosols from the mixer–heater with NPPV. For synchronization to have the maximum effect and avoid residual aerosol in the system, a reduced volume mixer–heater unit (instead of the current reservoir system) is also needed. An advantage of the DPI system was that synchronization between aerosol delivery and inspiration was easy to achieve by monitoring the flow on the ventilator. Finally, a trend toward large improvements in lung PF was observed with increasing the patient’s simulated tidal volume from 400 to 800 mL (which corresponded to the shallow and deep inhalations in a 4-second breathing cycle). However, compared with clinical data of patients on NPPV, these tidal volumes may be conservatively low. For example, healthy volunteers receiving bilevel NIV are reported to have a tidal volume of 1726 ± 624 mL, which is significantly higher than spontaneous breathing.⁽¹³⁾ For patients during an asthma crisis, tidal volume during NIV is reported to be ~ 1000 mL vs. 600 mL without NIV.⁽¹¹⁾ Future *in vitro* realistic breathing studies of aerosol delivery during NPPV should therefore consider deeper inspirations arising from pressure support, which are expected to further increase lung PF of the aerosol.

It is noted that both shallow and deep inspirations in this study produce the same average inhalation flow rate of 400 mL/s. Correlations that predict extrathoracic deposition as a function of inertial impaction^(57–59) indicate that depositional losses and therefore PF into the lungs should be the same for these two waveforms. However, a number of other factors influence depositional loss and PF in the cyclic breathing cases shown in Figure 4. Different fractions of the nebulized dose are delivered to the NMT model for 1 vs. 2 seconds of inhalation. Furthermore, the model volume for Subject A is 260.5 mL (including the mask), which is over 1/2 the tidal volume for shallow and over 1/4 the tidal volume for deep inspirations. Exhaled doses are less than these dead space-to-tidal volume ratios because of collection of an aerosol bolus before inspiration, jetting of the flow avoiding the full mask volume, and depositional losses. Agreement between the experimental and CFD results provides confidence that the complex interactions of inertial impaction (in the presence of condensational growth), upstream depositional losses, and exhaled dose are correctly captured.

The previous study of Walenga et al.⁽²⁵⁾ considered nose-to-lung aerosol delivery during HFNC therapy at a steady-state flow of 30 L/min, including conventional (5 μ m) and EEG (900 nm) aerosol sizes, which can be compared with the NPPV results of the current study. Walenga et al.⁽²⁵⁾ developed a set of four nasal cavity models, including the Subject A model of the current study. Considering conventional aerosol delivery in the Subject A model, HFNC delivery resulted in an NMT DF of 54.9% compared with 25.9% with NPPV from the current study. As a result, the nasal cannula interface appears to increase depositional loss in the nasal cavity compared with a mask interface for conventional aerosol sizes. In contrast, nasal deposition of the submicrometer EEG aerosol during HFNC was 2.7% vs. 3.0% with NPPV. Therefore, it is observed that the HFNC interface, at the same flow rate, doubles nasal cavity depositional loss of conventional aerosols compared with a mask interface. Moreover, the EEG approach improves delivery

consistency between the HFNC and NPPV platforms. Additional studies with cyclic breathing waveforms are needed to ensure that these differences in nasal deposition values translate to corresponding differences in lung PF.

Limitations of the current study include the use of steady-state calculations, only two airway models, and determining lung delivery with a tracheal filter or similar CFD boundary condition. As described, steady-state simulations are intended to identify trends related to lung delivery efficiency and inter-subject variability. Moreover, these steady-state estimates represent a maximum in lung delivery that can be achieved with adequate device engineering. As with our previous studies, synchronization of aerosol delivery with inspiration and reduced device volume,^(37,56) together with realistic deep inspirations during NPPV, will be required to achieve the steady-state estimates of lung delivery efficiency. While only two airway models were selected to address variability, our previous results enabled reasonable model choices. We selected models that maximized differences in SA/V ratio (which corresponds with conventional aerosol deposition) and had maximum differences in nasopharyngeal hydraulic diameter (which correlates with EEG aerosol deposition).⁽²⁵⁾ As a result, the selected two models are expected to provide a wide range of aerosol depositional losses, and this high variability was observed in the results with conventional aerosol sizes. Still, an expanded analysis of nasal models may increase intersubject variability even further. Finally, a significant limitation of extrathoracic *in vitro* and CFD models is the absence of lung geometry. Particles reaching the tracheal filter are considered to deposit in the lungs, and the potential for aerosols to be exhaled from the lungs is neglected. Due to the inclusion of a hygroscopic excipient and aerosol size increase, EEG aerosols are expected to be retained in the lungs at the same or higher rate than conventional aerosols.^(21,42) Lung-exhaled aerosols may reduce the lung PF values predicted in this study, but the relative trends in delivery efficiency are expected to remain unchanged.

In conclusion, results of this study quantify the effects of multiple factors on the lung delivery efficiency that can be achieved with aerosol administration during NPPV, including the effects of intersubject variability. Based on validated steady-state CFD simulations, lung delivery efficiency values with conventional aerosols were high, but varied largely between the two subject models. Use of EEG aerosols increased lung delivery efficiency compared with conventional aerosol sizes by factors ranging from 1.3 to 6.4-fold. Furthermore, EEG reduced a metric of intersubject variability (relative difference) in lung PF values by an order of magnitude for both nebulizer and DPI aerosols. In-line DPI administration through a mask port was found to be practical with *in vitro* experiments and to provide reasonable lung PF values, which were maximized with EEG delivery. Under steady-state conditions, CFD predicted lung delivery efficiency values with EEG aerosols as high as 80%–90% of the initial dose. Reaching these upper limit values with realistic cyclic breathing will require synchronizing delivery with inspiration, reducing the EEG aerosol production unit’s internal volume, and consideration of realistic NPPV inhalation volumes. These significant improvements in lung delivery efficiency values will enable better knowledge of the lung dose received from current clinical inhalation therapies and may enable the delivery of new high-dose or narrow therapeutic window medications to patients receiving NPPV or other forms of NIV with a mask interface.

Acknowledgment

This study was supported by Award R01 HL107333 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Author Disclosure Statement

Virginia Commonwealth University is currently pursuing patent protection of EEG aerosol delivery, aerosol generation devices, and patient interfaces, which if licensed, may provide a future financial interest to the authors.

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Received on August 28, 2016
in final form, November 2, 2016

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