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Imaging, Modeling, and Physiology of Aerosols in the Lung

A-122 AEROSOL-DELIVERY TO CRITICALLY ILL PATIENT; A BIG ISSUE EASILY SOLVED BY DEVELOPING GUIDELINES

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Nowadays therapeutic aerosols are commonly delivered to mechanically ventilated patients by nebulizers and pressurized metered dose inhaler (pMDI) attached to an adapter or a spacer.

Studies with asthmatics and chronic obstructive pulmonary disease (COPD) patients have confirmed that aerosol delivery during mechanical ventilation is feasible. They have also reported that the inhaled drugs administered during mechanical ventilation provide greater and faster clinical outcome than when delivering during spontaneous unassisted breathing.

Researchers studied Factors that would affect aerosol delivery during mechanical ventilation. Even though the tremendous amount of publication in this area, still there is no recommendation or guidelines has been released to help respiratory therapists in their decision when delivering aerosol to ventilated patients. Mostly, respiratory therapists read literatures and decide accordingly what to do and which device to be use for their patients. This put the patients at risk of receiving sub-therapeutic or toxic dose of inhaled aerosol.

Some studies raise an alarming sound of physician decision upon reading any released publication related to aerosol delivery in mechanical ventilation without a good trusted recommendations and guidelines. This increases the need of the development of recommendations and guidelines, by trusted board or society, for aerosol delivery to such critically ill patients.

To summarize; inhaled drugs administered to critically ill patients is of benefit compared to taking the patient off the ventilator and delivering during spontaneous unassisted breathing. However, dependable guidelines are needed to optimize aerosol delivery.

A-125 DATA AND OPEN-SOURCE SOFTWARE SHARING THROUGH THE INTERVALS PLATFORM

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Studies on the health impact of inhaled aerosols usually require a high degree of inter- and multidisciplinarity. The comparative assessment of the relative risk of various candidate modified risk tobacco products with respect to that of conventional cigarettes requires establishing assessment strategies of toxicological effects of aerosols, understanding the impact of inhalation on aerosol delivery, and development of aerosol characterization techniques.

Such studies involve a diverse array of products, a variety of laboratory models, and various teams, with the resulting knowledge on toxicity and aerosol inhalation being spread across numerous scientific articles. It is important to fuse the resulting scientific data and knowledge on an open community platform, designed to facilitate the formulation of new hypotheses and weight the evidence. To this end, we have created and are developing INTERVALS (www.intervals.science).

The first case discussed here refers to the recent addition on INTERVALS of a publication (Inhal Toxicol. 30, 159 (2018)) that investigates, via drop-shape method, the physicochemical properties of the direct interaction between lung surfactant and the substances present in the electronic cigarettes liquid mixtures (e-liquids). The second case refers to AeroSolved, an open-source computational fluid dynamics code, based on the OpenFOAM software package, for simulation of the generation, transport, evolution, and deposition of multispecies aerosol mixtures.

A-127 IMAGING 3D NASAL MODELS TO IMPROVE NOSE TO BRAIN (N2B) DRUG DELIVERY

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N2B drug delivery offers potential advantages by avoiding first-pass metabolism and the vascular blood-brain-barrier. Improved imaging techniques are needed to quantitatively evaluate N2B delivery. This project focused on developing imaging techniques to improve intranasal delivery as a platform technology for biomedical applications. Three low-cost nebulizers were successfully modified with 3D-printed accessories (Stratasys, Prairie, MN) for intranasal dosing. Proteins (insulin, albumin) were labeled with IRdye800 and administered as aerosols to the 3D-printed nasal models. One model is a simplified nasal cavity while the other two were derived from a CT scan of a rhesus macaque, with intact and cross-sectioned versions prepared. The models were imaged in multiple 2D positions with the Pearl Trilogy Fluorescent Imaging System (LI-COR Biotechnology, Lincoln, NE). Fluorescent protein deposition was imaged at all locations including at target sites (e.g. olfactory epithelium) and measured by region of interest analyses. Repeated studies were quickly accomplished by rinsing the models with ethanol and water. Quantification showed a range of 10-25% deposition of the aerosol dose in the faux nasal cavity for the modified nebulizers. Results of initial experiments showed the imaging of the nasal models was fast, accurate, and allows for aerosol delivery to be optimized. Future applications include PET and SPECT imaging of the 3D models after dosing with radiolabeled proteins.

New Devices and Emerging Therapies

N-121 TARGETED PULMONARY DELIVERY OF INHALATION AEROSOLS USING MAGNETIC PARTICLES

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The pulmonary route presents an attractive route for topical treatment of lung diseases. Yet, our ability to confine the deposition of inhalation aerosols to specific lung regions still remains hugely insufficient. It has been hypothesized that by coupling magnetic particles to inhaled therapeutics the ability to target points in the lungs (e.g. tumors) can be substantially improved. Although the method has shown promise in seminal in vivo rodent studies, technical challenges have prevented successful targeting in humans. Here, we present the engineering foundations, including transport phenomena of magnetic particle inhalation, to overcome past pitfalls and demonstrate in vitro a path to successfully achieve pulmonary point targeting. First, in silico simulations are used in models of human lungs to demonstrate the feasibility of targeting magnetically-loaded aerosols. Subsequently, an in vitro system is designed, consisting of a smart inhaler coupled with a custom-made ventilation machine, and a true-scale 3D printed airway geometry. Using flow visualization and microscopy, our experiments track the motion of pulsed SPION-laden (superparamagnetic iron oxide nanoparticles) aerosol boli and quantify their deposition on target near the magnet. Our inhalation platform allows for the first time to truly target aerosols to specific lung sites and may pave the way for improved treatment outcomes, including for example in reducing chemotherapy side effects in lung cancer patients.

N-123 IMPLICATIONS FOR PAEDIATRIC ASTHMA CARE FROM GAMIFICATION OF INHALER SPACER TECHNIQUE

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Rafi-Tone (Clin-e-cal) is a CE-marked, sound-analysis, paediatric gamification app designed to make spacer-use instructive and enjoyable. A post-marketing survey (PMS) of 6-10 weeks' use of the app plus Able Spacer whistle-mask (Clement Clarke) has analysed Likert-scale type questionnaire data from 112 asthmatics (age range 1-11y) and parents. 102 subjects were familiar with or always used (66) spacers. Survey foci included confidence, compliance and use of healthcare services.

30 parents (27%) used healthcare apps; 103 (92%, mean child age 6.2y) thought it likely the child would use a game app. Compared with baseline data of 46 (41%) and 41 (36%) respectively, 97 parents (87%) were confident that Able Spacer was delivering a treatment dose and the number of children never feeling upset increased (70, 63%). A child's feelings when using treatment (smiley-face Likert) were ambivalent/happy/very happy (11/25/55) compared with 43/34/15 at baseline: a significant mean change ($p<0.001$). Use of doctor/hospital services reduced from 16/6 at baseline to 4/1, respectively, at follow up. >50% parents were sure the app + Spacer helped their child.

Most asthma apps record use, and provide reminders and videos. Rafi-Tone is the only game app for spacer training and this is the first study to quantify acoustic app use in asthmatic children. This PMS indicates that access by young children and parents to a game-related training app could improve engagement with and confidence in spacer use.

Pediatrics and Cystic Fibrosis

P-128 MECHANISTIC UNDERSTANDING OF HOW HIGH FLOW NASAL CANNULA SIZE AND THERAPY SETTINGS AFFECT PRESSURE SUPPORT USING AN ANATOMICAL REPLICA OF AN INFANT RESPIRATORY SYSTEM

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Despite the increased use of high flow nasal cannula (HFNC) therapy, little has been done to predict airway pressures for a full breath cycle. A 3-month-old infant in vitro model was developed, which included the entire upper airways and the first three bifurcations of the lungs. A breathing simulator was used to create a realistic breath pattern, and high flow was provided using a Vapotherm unit. Three cannulas of varying sizes were used to assess the effects of the inner diameter and nasal occlusion of the cannulas on airway pressures. Using the manufacturer's recommended setting of 8 LPM, based on the infant's weight, end expiratory pressures of 0.821-1.306 cmH2O and 0.828-1.133 cmH2O were produced in the nasopharynx and trachea, respectively. Correlations were developed to predict full breath cycle airway pressures, based on the high flow rate delivered, cannula dimensions, as well as the breathing flow rate, for the nasopharynx and trachea. Pearson correlation coefficients for the nasopharynx and trachea correlations were 0.991 and 0.992, respectively. The developed correlations were then used to determine the flow rate necessary for each cannula to produce pressures commonly used when administering CPAP in hospitals. The correlations accurately predict the regional airway pressure up to and including 7 cmH2O for the entire breath cycle, implying that the rule of thumb for flow per body weight can underestimate the necessary flow to produce effective pressure support.

Environmental/Occupational Health/Toxicology

E-124 E-CIGARETTE AEROSOL TEMPERATURE PROFILES IN UPPER AIRWAY MODELS: RISK FOR EPITHELIAL DAMAGE?

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Introduction: Usage of electronic cigarette (e-cig) devices have risen rapidly among adolescents in the US, with 20.8% (3.05 million) of high school students reporting current use in 2018. While significant attention has been given to chemical toxicity of e-cig aerosols, our preliminary data has shown that aerosol temperatures at the mouthpiece may exceed 160¬oC during normal use, making the potential for thermal injury of the airways unclear.

Methods: To address this, we have quantified the temperature of e-cig aerosols under varying power settings (within the manufacturer's specified range) in a glass anatomical model of the oropharynx and trachea. Data was collected via thermocouples positioned at the mouth entrance, larynx, and carina of trachea in ambient (~25oC, 40%RH) and controlled (~37oC, >70%RH) conditions at a flow of 14 L/min over a 3-second-puff.

Results: The recorded temperatures for a power setting of 160W were 111oC, 67oC, and 47oC at the mouth, larynx, and the carina respectively. For controlled conditions at 160W they were 127oC, 66oC, and 56oC for the mouth, larynx and carina. Recorded temperatures for a power setting of 100W were 84oC, 44oC, and 33oC in ambient conditions, and 84oC, 50oC, and 48oC in controlled conditions.

Conclusions: From these data, we have evaluated an experimental model of the temperature distribution of e-cig aerosols suggesting a possible thermal injury risk to the integrity and function of the upper airway epithelial surface.

E-126 IN VITRO MODEL FOR THE PREDICTION OF RESPIRATORY SENSITIZATION OF INHALED CHEMICALS AND PROTEIN ALLERGENS

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Exposure to chemicals such as acid anhydrides or fragrances can induce respiratory allergies. At present, no in vitro model is validated to reliably detect chemical respiratory sensitizers.

To mimic the lung-blood barrier, we developed a 3D in vitro model allowing the assessment of the respiratory sensitizing potential of inhaled compounds.

The model was cultured at air liquid interface combining alveolar type II epithelial cells (A549), endothelial cells (EA.hy926), macrophage-like cells (PMA-differentiated THP-1) and dendritic-like cells (non-differentiated THP-1). Apically, cells were exposed to nebulized respiratory sensitizers (TriMellitic Anhydride (TMA) and Phthalic Anhydride (PA)) or irritants (Methyl Salicylate (MeSa) or Acrolein (Acr)) at concentrations reducing 25% of cell viability. The exposure to House Dust Mite (HDM) was used as positive control for protein allergens.

Several parameters were evaluated after the exposure, including surface markers of activated DC (e.g. CD54, OX40L, TSLPr) and cytokines (e.g. MCP-1, IL-10. RANTES). In addition, genes related to respiratory inflammation and DC activation were analyzed by qRT-PCR. Exposure to TMA and PA induces DC activation and a specific cytokine release pattern, while irritants do not. OX40L is determined for DC activation to identify high molecular weight allergens.

In conclusion, the presented in vitro model can predict respiratory sensitization, allowing discrimination of chemical sensitizers from irritants.