A 3D Multigeneration Lung Model to Study the Biofluid Mechanics of Intratracheal Drug Delivery

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Statement of Purpose: The lung contains a series of branching airways that lead to the respiratory zone. The respiratory zone houses the respiratory bronchioles and alveolar sacs. A low surface tension at the air-liquid interface of the alveolar sacs is critical to allow for gas exchange.[1] Low surface tension is maintained by the pulmonary surfactant secreted by mature alveolar cells. Pre-term infants have under-developed lungs and insufficient pulmonary surfactant production, causing breathing irregularities and potential lung collapse. This condition is known as Neonatal Respiratory Distress Syndrome (NRDS).[2] NRDS treatment consists of the intratracheal delivery of exogenous surfactant into the lungs known as surfactant replacement therapy (SRT). Although instilled surfactant reduces surface tension to restore normal respiration,[2] there is a high non-response rate of up to 35% to SRT potentially due to inhomogeneous distribution of instilled surfactant. The goal of this study was to develop a 3D, biomimetic neonate lung model and study the distribution of surfactant in airways.

Methods: The 3D computational lung model was designed using morphometric data from human lungs and constructed in SolidWorks. 3D printing was used to fabricate physical models. The resulting model contained eight generations, i.e., z=0-7, of continuously dividing airways (Figure 1a).[3,4] Following printing, the model was subjected to oxygen plasma (Harrick Plasma) for 10 minutes to render its interior hydrophilic. The model was pre-wetted with DI water and a 140 µL plug of Infasurf (ONY, Inc) surfactant was instilled into the trachea. The plug was propagated through the airways at a Capillary number of 0.016. The lung model was positioned at four different roll angles of α=0º, 30º, 60º and 90º to simulate rolling of a neonate during SRT. A distribution index was quantified for the four lobes, upper right (UR), lower right (LR), lower left (LL), and upper left (UL) (Figure 1b).

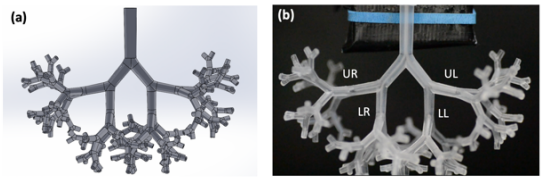

Figure 1. a) Computational multi-generation (z=0-7) neonate lung model developed in SolidWorks. b) Semi-transparent printed model. Four different lobes are labeled.

Results: We found that rolling the model away from its center line at α=0º to α=30º, 60º, and 90º resulted in a significant increase in surfactant distribution to the UR lobe and a decrease to the LL and UL lobes ($p < 0.05$). Our results indicate that as the roll angle was increased, the gravitational force increased the fluid flow to the UR and LR lobes (Figure 2). We also found that the sum of the distribution indices for the four lobes increased as the model was rolled gradually to 90º. This result indicates that as the model was rolled, the surfactant passed through fewer airways, thus depositing less volume onto the walls. This shows that a greater volume may remain inside the airways when the neonate is completely on their side.

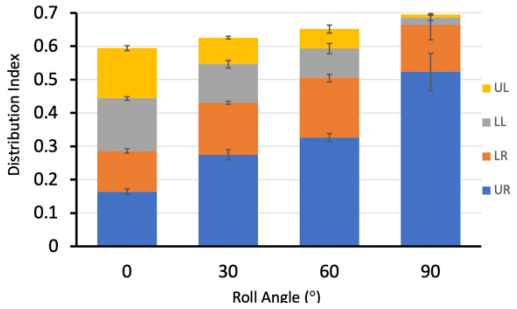

Figure 2. The distribution index for each lobe at various roll angles, representing the volume of surfactant to reach z=2 in each lobe.

Conclusions: Our 3D multigeneration neonate lung airway model enabled simulating surfactant delivery. This case study suggests that when delivering surfactant during SRT, orientation should be considered prior to delivery. Our findings showed that surfactant loss dependence on orientation could affect the clinical success of SRT. This study successfully demonstrated the utility of the model to studies of intratracheal therapeutics delivery under various conditions such as orientation, hydrophilicity, and flow rate. This model has the potential to advance drug delivery studies with respect to simulated environments and offers a device to study therapeutics effects at a cellular level.

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References:

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