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Early Airway Structural Changes in Cystic Fibrosis Pigs as a Determinant of Particle Distribution and Deposition

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Abstract

The pathogenesis of cystic fibrosis (CF) airway disease is not well understood. A porcine CF model was recently generated, and these animals develop lung disease similar to humans with CF. At birth, before infection and inflammation, CF pigs have airways that are irregularly shaped and have a reduced caliber compared to non-CF pigs. We hypothesized that these airway structural abnormalities affect airflow patterns and particle distribution. To test this hypothesis we used computational fluid dynamics (CFD) on airway geometries obtained by computed tomography of newborn non-CF and CF pigs. For the same flow rate, newborn CF pig airways exhibited higher air velocity and resistance compared to non-CF. Moreover we found that, at the carina bifurcation, particles greater than 5- μ m preferably distributed to the right CF lung despite almost equal airflow ventilation in non-CF and CF. CFD modeling also predicted that deposition efficiency was greater in CF compared to non-CF for 5- and 10- μ m particles. These differences were most significant in the airways included in the geometry supplying the right caudal, right accessory, left caudal, and left cranial lobes. The irregular particle distribution and increased deposition in newborn CF pig airways suggest that early airway structural abnormalities might contribute to CF disease pathogenesis.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

SUPPLEMENTAL DATA

Videos S1 and S2. Movies show 10- μ m particle flow path and deposition patterns in non-CF (S1) and CF (S2) computational airway geometries. Total duration of the simulation is 400 ms in both groups. Particle color denotes particle states (black = in-transit, red = deposited, blue = escaped).

Keywords

airway narrowing; porcine; computational fluid dynamics

1. INTRODUCTION

Cystic fibrosis (CF) is caused by loss of cystic fibrosis transmembrane conductance regulator (CFTR) function and results in morbidity and mortality due to progressive lung disease (34, 37, 47). While significant efforts have identified a key role for infection and inflammation in CF airway disease, relatively little is understood regarding the early events in airway disease pathogenesis.

We recently developed a porcine model of CF that mimics the phenotype of human CF lung disease, including bacterial infection susceptibility, inflammation, mucus accumulation, airway wall remodeling, and airway obstruction (32, 35, 36, 41). An unexpected finding in the CF porcine model was that, at birth, prior to the onset of infection and inflammation, the CF airways displayed structural abnormalities. These included a reduced caliber, a less circular shape, irregular-appearing cartilage rings, and abnormal-appearing airway smooth muscle bundles (28). Similar observations have been reported in CF mice; and structural abnormalities have also been observed in infants and young children with CF (2, 28).

These observations raised the possibility that early airway structural abnormalities may be important in CF lung disease pathogenesis. In this study, we used the computational fluid dynamics (CFD) technique to investigate airflow characteristics and particle distribution and deposition in newborn non-CF and CF pig airways. CFD analyses were conducted on multi detector row computed tomography (MDCT) airway geometries. We then used in-house CFD programs to predict how the abnormal structure of the CF airway impacts air velocity, airway resistance, and particle distribution and deposition. The outcome of these analyses could have important implications for targeting drug delivery and explain, in part, the regional distribution of lung disease in CF.

2. METHODS

2.1. CT imaging

All animal studies were approved by the University of Iowa Animal Care and Use Committee. We used five non-CF (*CFTR* +/+, birth weight 1.1 ± 0.1 kg, tracheal cross-sectional area 17.9 ± 1.2 mm²) and five CF pigs (*CFTR* -/-, 1.2 ± 0.1 kg, tracheal cross-sectional area 9.9 ± 0.3 mm²) in this study. These pigs were anesthetized initially with intramuscular ketamine (20 mg/kg) and xylazine (2 mg/kg) and maintained with intravenous propofol. Pigs underwent tracheostomy with a 2.0-mm inner diameter endotracheal tube. We used succinylcholine to prevent spontaneous breathing during imaging. All imaging was performed on a dual-source CT scanner (Somatom Definition Flash: Siemens Medical Systems, Erlangen, Germany). Airway geometries were obtained from chest CT imaging performed during a breath hold at a fixed airway pressure of 20 cmH₂O.

Recent studies have shown that flow disturbances in the upper airways on inspiration can affect airflow patterns in the lower airways (1, 4, 9, 24, 29, 49). However, in order to obtain the intra thoracic airway geometry at fixed pressure, the pigs had to have a tracheostomy prior to undergoing a chest CT scan. This eliminated our ability to image the larynx from these animals. Therefore, for most pigs used in this study, prior to tracheostomy, we obtained a CT scan of the laryngeal/upper trachea area and added these regions for each animal to our computational model. At the start of the study a pair of non-CF and CF pigs

were not scanned prior to tracheostomy. Thus we used the larynx from scans of non-intubated non-CF and CF pigs that had similar upper tracheal cross-sectional areas.

2.2. Image analysis

The larynx and intra-thoracic airways were segmented using Amira software (Visage Imaging, San Diego, CA), the average tracheal cross-sectional areas measured, and smoothed using the weighted Laplacian smoothing (Magics, Materialise, Ann Arbor, MI). The smoothed larynx geometry was merged with the fixed pressure intra-thoracic airway tree using the Boolean unite operation (Magics). This operation was performed on both non-CF and CF three-dimensional (3D) airways creating full non-CF and CF airway geometries, including both the larynx and intra-thoracic airways. The terminal branches of the smoothed airway tree were trimmed to ensure that their cross-sectional surfaces were near perpendicular to the centerline. The pig lung includes the left cranial (LCr) and caudal (LCa) lobes, and on the right the cranial (RCr), middle (RM), accessory (RAc), and caudal (RCa) lobes (Figure 1A). The main airways to all of these lobes were included in the non-CF and CF reconstructed airway geometries. The 3D airway tree reconstruction provided a realistic representation of both the porcine larynx and tracheobronchial tree (Figures 1A and 2A). For subglottic area measurements, CT image datasets were imported into Pulmonary Workstation 2.0 (VIDA Diagnostics, Iowa City, IA) and airway area measurements were obtained both at the smallest cross-sectional area in the sub-glottic region for each animal and at a fixed distance of 4.5 mm below the glottic opening.

The smoothed surface geometry of the airway tree was then meshed using Gambit software (Fluent, Lebanon, NH). To verify that the solutions were independent of the mesh size, two unstructured mesh densities were generated and are referred to as the original and refined mesh. The original mesh consisted of $343,027 \pm 54,696$ nodes and $2,111,000 \pm 254,735$ tetrahedral elements. The refined mesh consisted of $1,281,000 \pm 131,796$ nodes and $7,416,000 \pm 842,812$ tetrahedral elements. A grid sensitivity test was then performed. Unless otherwise noted, all of the results presented are based on the refined mesh data, since this provides greater resolution for the analysis of the particle trajectory pattern.

2.3. Computational fluid dynamics solver

The airflow predictions were based on solution of the filtered continuity (eq. 1) and Navier-Stokes (eq. 2) equations of incompressible flow using an in-house large eddy simulation (LES).

$$\frac{\partial u_i}{\partial x_i} = 0 \quad (1)$$

$$\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j} = - \frac{1}{\rho} \frac{\partial P}{\partial x_i} + (\nu + \nu_T) \frac{\partial^2 u_i}{\partial x_j \partial x_j} \quad (2)$$

where u_i is the velocity component in the i direction, P is the pressure, ρ is the fluid density, ν is the kinematic viscosity, and ν_T is the subgrid-scale (SGS) turbulent eddy viscosity. The continuity equation was enforced by solving a pressure-Poisson equation.

The Vreman (46) SGS model was implemented to yield $\nu_T=0$ for laminar flows (8). As ρ is a constant, it can be factored into the pressure gradient and combined with P . For these simulations, ν is set to $1.7 \times 10^{-5} \text{ m}^2 \text{ s}^{-1}$ at ambient conditions. The governing equations were discretized using a characteristic Galerkin approximation together with a fractional

four step algorithm that featured second-order accuracy in both time and space (23). The solver has been verified for flows under various conditions (8, 19, 24, 48).

We considered airflow at peak inspiration. Therefore, a parabolic velocity profile with a constant rate of 15 ml s^{-1} (30) was imposed at the airway inlet. To employ physiologically consistent boundary conditions at the peripheral airway segments, regional ventilation was assessed by measuring the increase in volume in each lung lobe for each pig from 0 to 20 cmH_2O . Flow rate at each boundary outlet was measured by quantifying the airflow ventilation fraction to each lobe (Figures 1A and 1B). If more than one airway in the segmented geometry supplied a lobe (e.g., the right and left caudal lobes), the airflow ventilation fraction to this lobe was divided between these airways based on their outlet diameter. For example, if in our geometry the lobe is supplied by two airways and the outlet diameter for the first airway is double the outlet diameter of the second, then the first airway outlet ventilation fraction would be double that of the second. Reynolds number (Re) was 102.00 ± 0.83 in the CF trachea and 73.43 ± 4.70 in the non-CF trachea ($p < 0.001$) (29). For lobar Reynolds and particle Stokes number calculations, we used the mean airflow velocity and cross-sectional area at the inlet of the airway supplying each lobe.

2.4. Lagrangian particle tracking algorithm

The CFD-simulated flow fields were then used to predict particle trajectories. For this study, spherical particles were used with a density of water (1000 kg/m^3) and ranged in size from $1\text{-}\mu\text{m}$ to $10\text{-}\mu\text{m}$ in diameter. Particle trajectory was computed using a Lagrangian tracking algorithm (29). In general, particle distribution and deposition are dependent on particle size, air velocity, and particle inertia. Since we studied the transport of relatively large particles and the air velocity in the model was constant over time, particle transport was based primarily on drag force and deposition was mainly due to impaction. Therefore, the Brownian motion associated with diffusion of the particles was not considered in the algorithm. The governing equation used to predict particle transport is:

$$\frac{dv_{pi}}{dt} = f_{Di} + \frac{\rho_p - \rho_f}{\rho_p} g_i \quad (3)$$

where v_{pi} is the i-component particle velocity, g_i is the i-component of the gravitational acceleration, ρ_p is the particle density and was set to equal water density, ρ_f is the density of the air in which the particle travels, and f_{Di} is the particle drag force per unit mass. The drag force per unit mass (f_{Di}) was computed as:

$$f_{Di} = \frac{U_l}{Stk \cdot D_l} (\nu_{fi} - \nu_{pi}) \quad (4)$$

where ν_{fi} is the fluid velocity interpolated from the fluid velocity field (u_i) at the particle location, U_l and D_l are the respective local velocity and length scales, and Stk is the Stokes number defined as:

$$Stk = \frac{U_l \rho_p d^2}{18\mu D_l} C_C \quad (5)$$

where d is the diameter of a particle and C_C is the Cunningham slip correction factor. The Stokes number is typically characterized as a ratio of the particle stopping distance to the characteristic dimension of an obstacle (15). Particles with a small Stokes number ($Stk \ll 1$) follow streamlines, while particles with a large Stokes number ($Stk \sim 1$) deviate from curved streamlines.

At the start of every simulation, particles were initialized as a cylindrical bolus consisting of 10,000 particles located at the proximal larynx. All of the particles were distributed in a constant concentration (29). Particles can exist in one of three states: moving, deposited, or escaped. To indicate the states of the particles as they traveled through the airway tree, we used three color codes. The color black indicated that the particle was moving through the airway. Once a particle impacted the airway surface the color changed to red, indicating that the particle had been deposited. Particles were recognized as deposited if the shortest distance from the particle's center of mass to the airway wall was less than the particle's radius. Particles were allowed to move all of the way to the lower tips of the airway model if they were not deposited. Under these conditions, if a particle reached the airway tip without depositing, the particle was considered as escaped and its color changed to blue. If a particle remained moving at the end of the simulation, without depositing or escaping, the color of the particle remained black. The total simulation time was 400 ms and the time step used for the Lagrangian tracking of the particles was 1.65×10^{-6} s, below which there is no real improvement upon the simulation. Since we used a steady-state simulation with a fixed aspiratory flow rate and flow is essentially in the laminar regime in both non-CF and CF airways, a time-dependent fluid field was not required. Particle ventilation fraction was determined for the right lung (particles entering the right mainstem bronchus), left lung (particles entering the left mainstem bronchus), and right cranial lobe (particles entering the right cranial lobe bronchus) divided by the total number of particles entering the right mainstem, left mainstem, and right cranial lobe bronchi. We separated the right cranial lobe from the "right lung" since the right cranial lobe bronchus branches from the trachea and not the right mainstem bronchus.

2.5. Statistical analysis

Data are presented as mean $\pm$ standard error of the mean (SEM). For statistical analyses between groups, Student's *t* or Mann-Whitney tests were used. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1. Airway structures in newborn non-CF and CF pigs

First, we compared the airway structures from five non-CF and five CF newborn pigs. Similar to our prior observations (28), the CF airways had a reduced lumen caliber (Figures 2A and 2B). Specifically, for the airway geometries used in the current study, the non-CF tracheal cross-sectional area was 17.9 ± 1.2 mm² compared to the CF tracheal cross-sectional area of 9.9 ± 0.3 mm² ($p < 0.001$). These measurements are consistent with our previously published findings [tracheal cross-sectional area 15.3 ± 0.6 mm² for non-CF and 8.4 ± 0.4 mm² for CF newborn pigs (28)]. When we measured the subglottic area at a fixed distance below the glottis (4.5 mm), CF was smaller than non-CF (Figure 2B). However, when we measured the smallest cross-sectional airway area in this region, which was the glottic opening (above the fixed distance measurement), we found no difference between non-CF and CF (5.8 ± 0.6 vs. 5.6 ± 0.5 mm², respectively). The right and left mainstem bronchi areas were also reduced in size relative to non-CF (Figure 2B).

3.2. Airflow characteristics in non-CF and CF airways

The main aim of this study was to compare particle behavior in newborn CF pig airways to non-CF. Therefore, we first used CFD to simulate airflow. Although the general outcomes of the simulation were predictable (e.g., smaller sized airways in CF lead to greater airflow velocity), we observed that non-CF:CF differences in airway structure as well as variations in subject-specific airway geometries had significant effects on airflow patterns and secondary flow which altered particle distribution and deposition patterns.

First, we examined airway pressure. While the pressure along the non-CF airway tree remained relatively constant, the narrower CF airway structure caused a greater pressure drop from the larynx to the lower airways (Figures 2A and 2C). For example, in the CF left mainstem bronchus the pressure was -21.00 ± 2.20 Pa compared to -10.35 ± 2.10 Pa in non-CF relative to laryngeal pressure (Figure 2C).

CFD modeling of air velocity revealed a number of differences between non-CF and CF. When a vertical plane of the air velocity contour was examined, a higher velocity was observed in the CF laryngeal region (1.28 ± 0.06 m.s⁻¹) compared to non-CF (0.92 ± 0.18 m.s⁻¹) (Figures 2A and 2D). We also observed the formation of an airflow jet in the glottic area in both non-CF and CF pigs. This jet develops as airflow rapidly accelerates through this narrowed region. Although the airflow velocity at the laryngeal region was higher in CF than non-CF it was not statistically significant. However, the average air velocity in the CF airway geometry was significantly greater than the average velocity in the non-CF airway geometry (1.57 ± 0.06 m.s⁻¹ vs. 0.84 ± 0.12 m.s⁻¹, $p < 0.002$). Finally, the increased velocity profile in the CF airway extended down to the carina region and the mainstem bronchi. Since airway resistance is dependent on both pressure difference and the volume flow rate, we examined the resistance in both non-CF and CF airways. We found that the resistance was significantly higher in CF compared to non-CF airways (Figure 2E). These findings collectively suggest that the narrowed airways in CF uniquely change airflow characteristics.

3.3. Particle distribution and deposition patterns in non-CF and CF airways

Particle distribution of 1, 5, and 10- μ m particles in both non-CF and CF airway models was investigated. Figure 3 shows the distribution pattern for 10- μ m particles at 50 and 400 ms in non-CF and CF airways (Supplemental Data – videos S1 and S2). In the non-CF airway at $t = 50$ ms, most particles were in the glottic region and proximal trachea with minimal particle deposition (less than 50 out of 10,000). At $t = 400$ ms, we observed that particles in the trachea tended to deposit along the anterior surface of the airway tree. This was observed in three out of five non-CF pigs. In the other two non-CF pigs, we observed circumferential deposition around the trachea. In the CF airway at $t = 50$ ms, particles were traveling at a higher velocity compared to non-CF pigs. The higher particle velocity led to significantly higher deposition rate in CF airways at $t = 50$ ms (more than 200 out of 10,000). By $t = 400$ ms in the CF airway, most of the particles were either deposited or escaped from the computational domain (Figure 3). In contrast to the majority of the non-CF airways, particles deposited on both the anterior and posterior airway surfaces in all of the CF pig tracheas (Figure 3B). These differences in particle deposition patterns in both non-CF and CF pigs were caused by structural features in the individual tracheal geometries (Figure 4). Proximal to the tracheal bronchus, the porcine trachea angles posteriorly. We found that the steepness of this angle determined whether particles preferentially deposited on the anterior tracheal surface or not. In non-CF pig tracheas that exhibited anterior particle deposition, this tracheal angle was greater than in pigs with more uniform particle deposition patterns (anterior deposition alone 174.0 ± 0.7 degrees vs. 165.6 ± 1.2 degrees for tracheas with more uniform deposition, $p < 0.05$). The combination of glottic constriction followed by the steeper tracheal angle induces a centrifugal force that skews the axial velocity and leads to the formation of secondary flow (Figure 4, upper panels). The skewed axial velocity near the anterior wall increases the likelihood of the particles traveling in that zone; thereby impacting and depositing along the anterior tracheal wall. In contrast, in two of the non-CF tracheas and all of the CF tracheas the axial velocity did not favor the anterior or posterior walls leading to more even particle deposition along the tracheal surface.

In general, particle ventilation fraction to the right and left lung was similar between genotypes except for 10- μ m particles, in which more particles traveled to the right lung

(excluding the right cranial lobe) instead of the left lung in CF (Table 1). Interestingly, this asymmetry in particle ventilation occurred despite similar airflow ventilation to the right and left mainstem bronchi between non-CF and CF (Figure 1B). Particle Stokes number in the trachea was significantly different for 1- μm , 5- μm , and 10- μm particles (Table 1). However, in CF we only observed greater particle ventilation to the right lung (excluding the right cranial lobe) for 10- μm particles. These data demonstrate that, in the newborn CF pig trachea, the particle ventilation fraction does not equal the airflow ventilation fraction when the particle Stokes number is greater than approximately 0.3 (Table 1). Interestingly, Darquenne et al. reported that when Stokes number was greater than 0.01 particle transport and airflow ventilation fraction were not equal in human airways (11). Differences in absolute Stokes values could be related to variations in porcine vs. human airway geometries, the airway inlet flow rates, or modeling technique employed.

CFD modeling also predicted that deposition efficiency was greater in CF compared to non-CF for 5 and 10- μm particles (Figure 5). These differences were most significant in the airways included in the geometry supplying the right accessory, right caudal, left cranial and left caudal lobes (Figure 6). Collectively these results demonstrate that as particle size increases, particle deposition is greater in CF than non-CF airways. Moreover, the regional differences in particle ventilation and deposition between non-CF and CF.

3.4. Factors that cause higher particle deposition in the CF airway

We observed that the CF airway had a greater efficiency of particle deposition (Figures 5 and 6). With increasing particle size, the Stokes number increased in both non-CF and CF airways (Table 2). Compared to non-CF, we found a significantly greater Stokes number at the inlet of the airways supplying the right middle, right accessory, right caudal, left cranial, and left caudal lobes which could account for the greater particle deposition in these CF airways (Table 2). Particle Stokes number at the inlet of the airway supplying the right middle lobe was also increased despite no increase in particle deposition in this airway. The lack of an increase in particle deposition in the CF right middle lobe airway is in part due to a low Reynolds number (Table 2). Therefore, the reduced airway diameter and increased air velocity in the CF airways increases the likelihood that particles will deviate off the streamline and deposit on the airway surface.

3.5. Enhanced particle ventilation to the right CF lung

We next used our CFD predictions to understand why 10- μm particles preferentially traveled to the right lung in CF despite equal airflow ventilation to both the right and left lungs. Particle trajectory is controlled by both drag and body force (eq. 3). Body force is dependent on gravity; however our initial studies (data not shown) demonstrated that gravity produced a minimal affect on particle deposition and distribution in both non-CF and CF. These findings led us to exclude gravity from simulations and thus ignore the effect of body force on particle trajectory. Therefore, we only focused on drag, which opposes particle motion (eq. 4) (18). Drag is dependent on particle size, inertia, Stokes number, and velocity (eqs. 3 and 4).

We investigated how particle, airway, and airflow characteristics integrate to cause more particles to deviate to the right lung in CF. In general, 10- μm particles in CF had a higher inertia, larger Stokes number, and greater velocity than in non-CF. Analyzing particle trajectory over time, we found that larger particles followed the secondary flow in the CF airways (Figures 7A and 7B). Secondary flow developed, in part, due to a greater glottic constriction ratio (subglottic area/tracheal area) (in CF 1.36 ± 0.04 vs. 0.99 ± 0.11 in non-CF, $p < 0.05$). The effect of the glottic constriction ratio can be observed in Figure 4 where the subglottic narrowing skews axial velocity towards the right side of the trachea causing

secondary flow development in this region. This high velocity zone extended into the CF right mainstem bronchus ($1.51 \pm 0.05 \text{ m.s}^{-1}$ in the right vs. $1.12 \pm 0.07 \text{ m.s}^{-1}$ in the left mainstem bronchus, $p < 0.05$) and particles were preferentially directed towards the right leading to higher particle ventilation to the right lung at the level of the mainstem carina bifurcation (Figures 4 and 7C). This right-left asymmetry in particle distribution was further enhanced by a steeper branching angle of bifurcation for the right mainstem bronchus in CF (Figures 8A and 8B). Figure 8C shows the formation of the particle bolus while entering the right and left mainstem bronchi and highlights the preferential distribution of particles to the right lung in CF.

4. DISCUSSION

This work aimed to study numerically the effect of airway structural abnormalities on airflow characteristics and aerosol particle distribution and deposition patterns in newborn CF pigs. The CFD model predicted that CF airways have a higher air velocity and pressure drop compared to non-CF airways. The higher air velocity increased particle deposition in CF. Moreover, we found that particles larger than $5\text{-}\mu\text{m}$ preferentially distributed to the right lung in CF due to the skewed axial velocity and formation of secondary flow in the trachea. Thus, our computational model shows that the irregular airway structure in CF has a significant effect on the airflow pattern and subsequently on particle distribution and deposition.

Several of our findings provide potential explanations for the observation of enhanced particle ventilation to the right lung. First, the higher air velocity in the CF airway caused particles to travel faster in the trachea. Second, the particle Stokes number was higher in CF airways, suggesting that these particles would not follow the airflow streamline and their transport would be dependent on their inertia impaction. Third, the irregular structure (glottis constriction ratio, tracheal angle, carina angle) of the CF airways drove particles to travel near the wall due to secondary flow. Finally, as the particles traveled near the wall, particle velocity decreased and a greater number of particles followed the airflow streamline to the right lung at the level of the carina bifurcation.

Our study has several advantages and caveats. Advantages include: 1) A numerical model was used because it not only provides accurate predictions for the given boundary conditions, but it also provides potential explanations for the observations. 2) The findings of this study are likely generalizable to newborn CF pig airways since we were able to perform CFD analysis on a number of subjects. 3) We were able to perform CFD modeling on airway trees from newborn CF pigs, thereby studying the primary effect of congenital airway narrowing in CF and eliminating secondary effects from infection, inflammation, and mucus obstruction. While our findings are consistent with recent experimental and stochastic aerosol studies (5, 6, 18, 27, 42, 43), several caveats exist. 1) The airway geometry was assumed to be rigid in this study. Although physiologically the airway structure is deformable, this study only predicts the flow at peak inspiration. Therefore, having a deformable model is much more computationally expensive since we predict the flow at fixed pressure. 2) Our CFD analyses are based upon newborn airway trees that might differ with growth, increasing airway size, and disease progression. Future studies using airway geometries from older CF pigs will likely be informative. 3) It is possible that mesh size influences results of airway and particle behavior. To test the influence of mesh size we conducted a grid sensitivity test on a pair of non-CF and CF pigs (approximately two million versus ten million elements). We found that particle deposition, tracheal airflow velocity, and pressure drop were similar for the two mesh sizes studied [particle deposition efficiency for $10\text{-}\mu\text{m}$ particles in the trachea: 14% vs. 15% (non-CF) and 37% vs 35% (CF); tracheal airflow velocity: 0.82 m.s^{-1} vs. 0.89 m.s^{-1} (non-CF) and 1.53 m.s^{-1} vs. 1.49 m.s^{-1} (CF);

pressure drop: 8.4 Pa vs. 7.3 Pa (non-CF) and 12.5 Pa vs. 13.2 Pa, refined mesh vs. original mesh respectively]. These findings suggest that the observed differences in particle distribution and airflow characteristics are independent of mesh size. Importantly, prior studies have reported good agreement between particle deposition model predictions and measured data, suggesting that our predictions are likely valid (16, 20, 29). 4) Although beyond the scope of the current study, future simulations with transient pulsatile flows will be important to conduct since differences in predicted particle distribution and deposition might be expected to occur when studied under transient flow versus steady-state conditions (current study).

What is the significance of our findings? First, many CFD and CT-based airway geometry studies of airflow and aerosols (therapeutic or pollutant) are based on airway geometries from healthy subjects or used non-physiological based boundary conditions, which may not provide an accurate description of aerosol behavior in diseased airways. Results from our study show that we were able to make predictions on realistic non-CF and CF airway geometries, and that important differences exist dependent upon congenital airway abnormalities. More recently, other groups have used a similar approach to ours (functional imaging based computational fluid dynamics with the same type of boundary conditions) to find the effect of differences in patient-specific airway geometry on inhalational therapy in lung disease, such as chronic obstructive pulmonary disease and asthma (13, 44, 45). Second, many therapeutics for CF airway disease are delivered by inhalation. A better understanding of the CF airway and how airway size and shape influences particle/aerosol deposition and distribution in the lung is critical for targeted delivery of aerosolized treatments to people with irregular airway morphology. Development of submicron particle technology for therapeutic aerosols could be particularly important for lung diseases in which airway narrowing exists, either from a congenital etiology or due to disease progression such as in asthma or CF where mucus accumulation, airway wall thickening, or airway constriction leads to airway narrowing (14, 21, 22, 38). In the setting of airway narrowing in CF, improved drug delivery and deposition to the small airways is more likely to occur with submicron particles. By performing CFD analyses on human- and disease-specific airway geometries, more efficient and better targeting of inhaled therapies may be achieved (7, 10, 13, 25, 44, 45). Third, our comparison of airflow characteristics and particle distribution and deposition pattern in non-CF and CF airways has significant implications for understanding disease pathogenesis in the CF lung.

How do these findings help us better understand the pathogenesis of CF airway disease? First, when bacteria are inhaled into the lung, the airway surface has antimicrobial factors that destroy invading microorganisms. However, both humans and newborn pigs with CF have an impaired ability to kill these inhaled bacteria (33, 37, 41). We hypothesize, based upon results from the current study, that early in CF a significantly greater fraction of inhaled particulate matter and microbes will deposit in the CF airways. This increased microbe deposition on the CF airway surface, combined with the impaired ability to kill bacteria, could overwhelm the airway host defenses and be an important determinant of early CF lung disease. Although no studies have specifically examined this question in early CF, both modeling predictions and experimental results show regional differences in particle deposition in the adult CF lung (5, 6). These findings could correlate to greater bacterial deposition on the airway surface. Furthermore, with disease progression airway lumen obstruction occurs in CF secondary to mucus accumulation and this airway narrowing might be expected to cause similar effects and/or worsen the congenital abnormalities (42). It will be interesting in future studies to determine if particle deposition patterns obtained from newborn CF airway geometries predict the sites of airway disease development later in CF. These studies would be difficult to perform in humans, but feasible in the CF pig model. Second, there is increasing evidence that human CF lung disease, including airflow

obstruction, is present earlier than originally thought; even within months after birth (17, 31, 40). However, technical and ethical constraints limit our ability to investigate the human lung at even earlier time points. Our CFD data predict an increased airway resistance (the presence of airflow obstruction) in CF pigs on the day that they are born. Since we previously reported that the CF pig airways lack infection, inflammation, or mucus accumulation at birth (41), our findings suggest that, in CF, airflow obstruction can occur in the absence of airway inflammation or mucus buildup. These findings have important implications for the timing and type of therapeutics used to treat early CF lung disease. Third, in humans, CF-related lung disease has a known proclivity for the right lung (3, 12, 26, 31, 39). The reason(s) for this right-sided predominance is unknown. Potential explanations have included a higher rate of microaspiration/reflux into the right mainstem bronchus or preferential mucus accumulation and/or impaired mucus removal from the right lung. Alternatively, our modeling data support the idea that secondary flow in the CF airways promotes greater particle ventilation and deposition to the right lung in newborn CF pigs. If a greater number of inhaled particles and bacteria land in the right lung, then this could potentially explain higher rates and more severe disease in the right lung in CF.

5. CONCLUSIONS

In conclusion, our results suggest that early structural abnormalities in the newborn CF airway might contribute to the pathogenesis of CF lung disease and may be a significant determinant of the regional distribution of CF lung disease. Moreover, these findings could have important implications for the development of inhaled therapeutics in CF.

Supplementary Material

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Figure 1. Lung structure and lobar airflow ventilation fraction acquired using computed tomography at 0 and 20 cm H₂O

(A) Front view of non-CF lung at 0 and 20 cmH₂O. The color codes indicate each individual lobe in the pig lung. Gold-right cranial (RCr), blue-right middle (RM), purple-right accessory (RAc), yellow-right caudal (RCa), red-left cranial (LCr), and green-left caudal (LCa). (B) Airflow ventilation fraction to each lobe in newborn non-CF and CF pigs (n = 5 for each genotype).

Figure 2. Computational fluid dynamic modeling of air pressure and velocity in newborn non-CF and CF porcine airways

(A) Air pressure (Pa) and velocity ($\text{m}\cdot\text{s}^{-1}$) in non-CF and CF airways. (B) The cross-sectional area in the subglottis (SG), the average along the trachea (T), the right mainstem bronchus (RMB), and left mainstem bronchus (LMB) in non-CF and CF. (C) The pressure drop at the SG, T, RMB, and LMB in non-CF and CF. (D) The average air velocity at the SG, T, RMB, and LMB in non-CF and CF. (E) The average airway resistance in the area of the SG, T, RMB, and LMB in non-CF and CF. Data for B–E were obtained from horizontal slices extracted from the 3D airway geometry, perpendicular to the centerline using Tecplot. R denotes right side, L denotes left side, A denotes anterior, and P denotes posterior. *

denotes statistical significance between non-CF and CF data ($p < 0.05$) ($n = 5$ for each genotype).

Figure 3. Particle distribution and deposition in non-CF and CF airways
 10- μ m particle flow path and deposition pattern at 50 and 400 ms in non-CF and CF airways. Particle color denotes particle states (black = in-transit, red = deposited, blue = escaped).

Figure 4. CFD prediction of airflow characteristics in non-CF and CF trachea

Shown are tracheal cross-sections at 5 different levels: glottis, above the tracheal angle (above TA), below the tracheal angle (below TA), above the tracheal lobe (above TL), and below the tracheal lobe (below TL). Top panel shows data from a representative non-CF trachea where greater anterior particle deposition was observed. Middle and lower panels show data from a representative non-CF trachea (middle panel) and CF trachea (lower panel) where more circumferential particle deposition was observed. The velocity profile (m.s⁻¹) at each level is shown. A denotes anterior, and P denotes posterior. TA denotes tracheal angle.

Figure 5. Particle deposition efficiency in non-CF and CF airways

The effects of increasing particle size on deposition efficiency to the left and right lung. Particle deposition efficiency was defined as the number of particles depositing in the right (excluding the right cranial lobe since the right cranial lobe bronchus branches from the trachea) or left lung divided by the number of particles that entered the right or left lung, respectively. * denotes statistical significance between non-CF and CF data ($p < 0.05$) ($n = 5$ for each genotype).

Figure 6. Particle deposition efficiency for lobar airways in non-CF and CF airway geometries
 Shown are the effects of increasing particle size on particle deposition efficiency for lobar airways included in non-CF and CF airway geometries. Particle deposition efficiency was defined as the number of particles depositing in a specific lobar airway divided by the number of particles that entered that lobar airway. * denotes statistical significance between non-CF and CF data ($p < 0.05$) ($n = 5$ for each genotype).

Figure 7. 10- μ m particle trajectory in newborn non-CF and CF porcine airways

(A) Particle trajectory in non-CF and CF airways at 0.04 s. (B) Particle trajectory in non-CF and CF airways at 0.055 s. Note the particles tend to travel near the right side of the trachea. (C) Particle trajectory in non-CF and CF airways at 0.065 s. The particles are colored based upon their status - black = in-transit and red = deposited.

Figure 8. The effect of the carina bifurcation angle relative to the trachea on particle ventilation to the right and left lung

(A) Visual comparison between non-CF and CF carina position, and bifurcation angle to right and left main stem bronchi relative to the trachea. (B) The bifurcation angle ratio of the carina relative to the trachea. Note the carina angle ratio was computed by dividing the angle of the left mainstem bronchus by right mainstem bronchus. * denotes statistical significance between non-CF and CF data ($p < 0.05$) ($n = 5$ for each genotype). (C) The formation of the particle bolus while entering the right and left mainstem bronchi. The particles are colored based upon their status - black = in-transit and red = deposited. R denotes right side and L denotes left side.

Table 1

Particle ventilation fraction in non-CF and CF airways

Particle size	Left mainstem bronchus		Right mainstem bronchus		Right cranial bronchus		Tracheal Stokes number	
	non-CF	CF	non-CF	CF	non-CF	CF	non-CF	CF
1 μm	0.42	0.51	0.49	0.42	0.09	0.07	0.0009	0.0021
	0.41	0.43	0.51	0.49	0.08	0.08	0.0006	0.0022
	0.43	0.39	0.52	0.54	0.05	0.07	0.0010	0.0021
	0.43	0.45	0.49	0.47	0.08	0.08	0.0004	0.0067
	0.42	0.47	0.50	0.52	0.08	0.01	0.0011	0.0032
5 μm	0.43 $\pm$ 0.01	0.44 $\pm$ 0.02	0.50 $\pm$ 0.01	0.48 $\pm$ 0.02	0.08 $\pm$ 0.01	0.06 $\pm$ 0.01	0.0008 $\pm$ 0.0001	0.003 $\pm$ 0.0008 #
	0.40	0.52	0.50	0.40	0.1	0.08	0.0225	0.0824
	0.43	0.45	0.49	0.48	0.08	0.07	0.0145	0.0721
	0.40	0.38	0.55	0.56	0.05	0.06	0.0256	0.1161
	0.41	0.40	0.48	0.54	0.11	0.06	0.0109	0.0702
10 μm	0.39	0.42	0.52	0.52	0.09	0.06	0.0184	0.2453
	0.41 $\pm$ 0.01	0.44 $\pm$ 0.03	0.51 $\pm$ 0.01	0.49 $\pm$ 0.03	0.09 $\pm$ 0.01	0.06 $\pm$ 0.01	0.018 $\pm$ 0.003	0.117 $\pm$ 0.033 #
	0.46	0.35	0.40	0.61	0.14	0.04	0.0736	0.3299
	0.44	0.28	0.43	0.56	0.13	0.16	0.0901	0.2885
	0.35	0.30	0.56	0.67	0.09	0.03	0.0579	0.4645
	0.35	0.26	0.57	0.71	0.08	0.03	0.1023	0.2807
	0.35	0.28	0.48	0.68	0.17	0.04	0.0436	0.2813
	0.40 $\pm$ 0.02	0.30 $\pm$ 0.02 #	0.49 $\pm$ 0.04	0.63 $\pm$ 0.03 #	0.12 $\pm$ 0.02	0.06 $\pm$ 0.03	0.073 $\pm$ 0.011	0.329 $\pm$ 0.035 #

The particle ventilation fraction and particle Stokes number in the trachea for each corresponding animal are shown. Particle ventilation fraction was determined for the right lung (particles entering the right mainstem bronchus), left lung (particles entering the left mainstem bronchus), and right cranial lobe (particles entering the right cranial lobe bronchus) divided by the total number of particles entering the right mainstem, left mainstem, and right cranial lobe bronchi. We separated the right cranial lobe from the "right lung" since the right cranial lobe bronchus branches from the trachea and not the right mainstem bronchus. Each line represents data from a pair of non-CF and CF pigs. Mean $\pm$ SEM for the group are in bold.

denotes statistical significance between non-CF and CF data ($p < 0.05$).

Particle Stokes number and Reynolds number at the airway inlet of each individual lobe in non-CF and CF newborn pigs

Table 2

Lobes	Particle Stokes Number						Reynolds number	
	5 μm			10 μm				
	non-CF	CF		non-CF	CF		non-CF	CF
Right Cranial	0.036 $\pm$ 0.007	0.037 $\pm$ 0.004		0.142 $\pm$ 0.030	0.147 $\pm$ 0.018		62.0 $\pm$ 8.3	63.5 $\pm$ 4.6
Right Middle	0.035 $\pm$ 0.008	0.078 $\pm$ 0.014 #		0.140 $\pm$ 0.031	0.316 $\pm$ 0.057 #		64.5 $\pm$ 6.2	87.4 $\pm$ 8.8
Right Accessory	0.038 $\pm$ 0.006	0.073 $\pm$ 0.014 #		0.152 $\pm$ 0.024	0.295 $\pm$ 0.054 #		45.1 $\pm$ 2.7	61.7 $\pm$ 4.5 #
Right Caudal	0.018 $\pm$ 0.003	0.117 $\pm$ 0.033 #		0.073 $\pm$ 0.011	0.469 $\pm$ 0.132 #		144.3 $\pm$ 6.4	276.5 $\pm$ 35.1 #
Left Cranial	0.028 $\pm$ 0.004	0.082 $\pm$ 0.022 #		0.111 $\pm$ 0.015	0.327 $\pm$ 0.089 #		65.8 $\pm$ 6.0	103.3 $\pm$ 8.7 #
Left Caudal	0.017 $\pm$ 0.003	0.064 $\pm$ 0.011 #		0.069 $\pm$ 0.013	0.255 $\pm$ 0.044 #		131.7 $\pm$ 8.6	225.0 $\pm$ 13.1 #

denotes statistical significance between non-CF and CF data ($p < 0.05$) (n = 5 for each genotype).