Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Towards a multi-scale computer modeling workflow for simulation of pulmonary ventilation in advanced COVID-19

Shea Middleton, Elizabeth Dimbath, Anup Pant, Stephanie M. George, Veeranna Maddipati, M. Sean Peach, Kaida Yang, Andrew W. Ju, Ali Vahdati

Keywords: Pulmonary mechanics, COVID-19, Pulmonary ventilation, Computer modeling, Acute respiratory distress syndrome, SARS-CoV-2, Lung mechanics

1. Introduction

Coronavirus Disease 2019 (COVID-19) infection due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus can cause extensive damage to many tissues and organs, including the lungs. Millions of lives have been lost to the disease, while others face long-term effects of this viral infection [1,2]. Though computer models may assist with managing and tracking the spread of COVID-19, yet new variants of the SARS-CoV-2 virus may spread more easily and can pose an increased risk of severe disease and other complications linked to COVID-19 [3,4]. Alveolar damage is seen in imaging and histopathological studies of COVID-19 infected lungs [5], and heterogeneous damage throughout the acinar regions of the lung is observed in computed tomography (CT) images [5]. In particular, CT imaging can provide useful spatial information on patterns of lung injury, including ground-glass opacities (GGO) and areas of consolidation [6]. Also, some patients suffering from COVID-19 acute respiratory distress syndrome (ARDS) exhibit increased hypoxemia compared to typical acute respiratory distress syndrome (ARDS) [7]. However, there is currently little quantitative information on how acinar level patho-mechanics contribute to whole lung function in COVID-19 patients. A better understanding of how COVID-19 impairs regional ventilation may give insight into overall lung dynamics specific to CARDS.

To provide a four-dimensional view of airflow patterns in the lung, CT images can be used to develop geometric models of the lung, which can then be combined with fluid flow and tissue mechanics physics-based models. Such physics-based computer models of the lung present an opportunity for gaining valuable insights into pulmonary ventilation dynamics [8,9]. For instance, computational modeling of lung dynamics across multiple spatial scales may allow a deeper understanding of how mechanical changes at the alveolar and acinar levels affect lobar and whole-lung dynamics in CARDS. Previous physics-based computer models of the lung have provided a detailed four-dimensional view of pulmonary ventilation in both healthy and disease states. In the...
aforementioned computer models, CT images were used to determine lobar volumes and airway branching patterns of large airways with small peripheral airways constructed utilizing volume-filling tree-generating algorithms \cite{10,11} and the coupling of airway trees to compliant acinar regions provided realistic flow distribution among the lung lobes \cite{12}. Along with realistic geometries for airways and compliant acinar regions, in silico models have also incorporated other factors such as tissue deformation, gravity, acinar-level interdependence, and surface-tant all of which contribute to distribution of ventilation in the healthy lung \cite{13–15}.

Disease can lead to remodeling of airways and parenchymal tissue thus inducing changes in airflow patterns and tissue mechanics that can be implemented in in silico models \cite{16}. Insight into the effects of disease on ventilation and pressure distribution of the lung has been gained through modification of model geometry and mechanics in previous studies \cite{17,18}. Additionally, information on distribution and manifestation of damage throughout the lung is important for realistic representation of disease states \cite{18}. Registration of high resolution and 4D CT images has been used to identify damaged areas of parenchyma and changes in airway geometry and regional ventilation in disease states \cite{16,19}. Utilization of imaging techniques also opened the door for patient-specific modeling of airflow and pressure distribution \cite{10,18}. Multi-scale in silico lung models with geometries resolved from CT imaging have proven useful in understanding various pulmonary diseases like cystic fibrosis, chronic obstructive pulmonary disease (COPD) and asthma \cite{18,20,21}. However, there is a need for computer modeling studies on pulmonary ventilation dynamics in COVID-19 patients.

The main objective of this study is to develop a physics-based in silico modeling workflow for studying the pulmonary ventilation of COVID-19-infected lungs by bringing existing methodologies for coupling airflow and lung tissue mechanics together \cite{10,11,22}. The presented in silico modeling approach is the foundation and first step towards a virtual hypothesis testing platform for a better understanding of COVID-19 pulmonary dynamics utilizing 4D CT data from COVID-19-infected lungs and accounting for patient-specific lung geometry and disease distribution with varying levels of damage. In addition, we aimed to develop an in silico multi-scale approach to simulate and compare the regional changes in lung dynamics associated with heterogeneous subject-specific COVID-19-induced damage in the parenchyma of the lung. To this end, we present an investigation of the effect of various levels of inflammation in a meso-scale acinar mechanics model on global lung dynamics.

2. Methods

2.1. Imaging

This study utilized the 4D CT scan of a male patient recently hospitalized in Vidant Medical Center (Greenville, North Carolina, USA) for an advanced case of COVID-19. The 4D CT scan was obtained during tidal breathing using an Optima CT850 RT scanner (GE Healthcare, Waukegan, WI). The methodology used in this paper was approved by the East Carolina University and Medical Center Institutional Review Board (UMCIRB) with study ID 20–001447. Informed consent was obtained from the patient. Sorting of the CT images into phases of the breathing cycle was accomplished using the Varian 4DCT Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA). When a series of CT images was attained over a time comparable to that of a normal breathing cycle, the Varian RPM camera captured the patient’s real-time external chest motion amplitude, and Advantage 4D (GE Healthcare, Waukega, WI) software retrospectively sorted the CT data into corresponding phases of the respiratory cycle from 0% to 90%, with 0% corresponding to end-inspiration and 50% corresponding to end-expiration \cite{23}. The images were taken at 120 kVp, 300 mAs, and 20 mm collimation and were reconstructed through a 512 × 512 matrix with a 2.5 mm slice thickness and reconstructed retrospectively to a slice thickness of 1.25 mm.

2.2. Segmentation

Following imaging, the geometry of the major airways visible in CT and lungs lobes was segmented. The major conducting airway geometry was segmented from the end-inspiratory phase using a combination of dynamic region growing and manual editing in Materialise Mimics 23.0 (Materialise NV, Belgium) (Fig. 1a). Centerline detection and extraction as described in Bordsa et al.’s work \cite{10} for the major airways were also achieved using Mimics 23.0. Five different lung lobe (right upper, right middle, right lower, left upper, and left lower) geometries were segmented at the end-inspiratory phase and end-expiratory phase using the Chest Imaging Platform \cite{24} available in 3D Slicer \cite{25,26}. Total segmented lobe volume was validated against total segmented lung volume. 3D Slicer was used to segment the COVID-19 affected GGO and consolidated regions of the lungs at end-inspiratory and end-expiratory phases using the LungCTAnalyzer \cite{27} extension of the Chest Imaging Platform (Fig. 1b). This segmentation was based on Hounsfield unit (HU) values in the CT images. Inflated lung Hounsfield unit thresholds were determined based on the study by Kassin et al. \cite{28} with a range of –1000 to –650 HU. The difference between ground glass opacities and consolidated regions were determined based on the 3D Slicer Chest Imaging Platform \cite{24} and Lung CT Analyzer \cite{27} (https://github.com/rbmm/SlicerLungCTAnalyzer) extensions preset values for COVID-19 lung analysis.

2.3. Geometry

Segmented major airway geometry was limited to the first four to six generations. Further airway segmentation was constrained by CT image resolution. Subsequently, a space-filling airway generation algorithm with random heterogeneity based on the work of Tawhai et al. \cite{11,29} was used to create up to 16 generations of conducting airways. Airway diameter, length, and branching angles were based on the segmented geometry and lung lobe models (Fig. 1c) following the methods described in Refs. \cite{29–31}. The number of acini per lung was approximately 15,000 \cite{32}. The lumen diameter for each one-dimensional line segment was assigned based on the Horsfield number \cite{10,11}:

\[
\log D(x) = (x - \text{Max}) \log R_{h} + \log D_{\text{Max}}
\]

where \(x, D, \text{Max}, D_{\text{Max}}\) represented the current Horsfield order, the airway diameter, the maximum Horsfield order and the maximum diameter, respectively. \(R_{h}\) represented the anti-log slope of airway diameter plotted against Horsfield order and was assigned to be 1.15.

2.4. Airflow and acinar mechanics model

Here, our multi-scale computational models of the lung are developed through the C++ simulation package CHASTE (Cardiac, Heart, and Soft Tissue Environment) \cite{10,33}. Airflow in the airway tree geometry was described by a reduced dimensional airway model implemented in CHASTE, which was coupled to the tissue mechanics acinar models \cite{10,34}. The flow was presented as a modified Poiseuille flow following the approach developed by Swan et al. \cite{13} and Ismail et al. \cite{12} and by assuming isotropic expansion of acini. Corrections to the dynamic resistance based on work by Pedley et al. \cite{10,35} were applied as shown in Equation (2):

\[
R = \frac{1}{\log \left( \frac{D_{\text{aw}}}{I_{\text{aw}}} \right)^{1/2}} R_{p}
\]

where \(R\) is the dynamic resistance, \(R_{p}\) is the Poiseuille resistance, \(D_{\text{aw}}\) and \(I_{\text{aw}}\) are the diameter and length of an airway, respectively, \(R_e\) is the Reynolds’s number, and \(\gamma\) was set to be generation-dependent based on the work of van Erbruggen et al. and Ismail et al. \cite{12,36}.
Atmospheric pressure was assigned at the trachea, hence airflow into the lungs was driven by variations in the volume of acini as a function of changes in the transpulmonary pressure during breathing. All nodal pressures and edge fluxes were solved for simultaneously using multi-frontal lower-upper factorization solver UMFPACK. Flow from the airway model was fed into each acinar model to calculate the change in acinar volume using the stretch ratio during each time step taken by the solver.

A sigmoidal acinar mechanics model based on the work of Fujioka et al. and Venegas et al. [37,38] was coupled to the generated airway tree in the simulations (Fig. 2).[55,309] In this model, as shown in Equation (3), $V_a$ is the acinar volume, $P_a$ is the transpulmonary pressure for each acinus (defined as the difference between pressure in the acinus and the pleural pressure), and $A$, $B$, $C$, and $D$ are constants that vary based on surfactant level and consequently tissue compliance:

$$V_a = A + \frac{B}{1 + e^{-C(P_a - D)}}$$  \hspace{1cm} (3)

Time-derivative of equation (3) was solved at the end of each terminal bronchiole, where an acinus was connected to an airway, thus coupling the pressure in the airway tree and the acinar model.

2.5. Boundary conditions and simulation settings

2.5.1. Boundary and loading conditions

Pulmonary ventilation dynamics during tidal breathing was simulated in accordance with the aforementioned coupled airway-acinar model. To simulate tidal breathing, a varying pleural pressure was applied at the acini while a constant atmospheric pressure boundary condition was applied at the trachea. The varying pleural pressure was assumed to be [12,40]:

$$P_{pl} = P_{pl\ max} + \frac{\Delta P_{pl}}{2} \left( 1 - \cos \left( \frac{2\pi\ t + \Phi}{T} \right) + \pi \right)$$  \hspace{1cm} (4)

where $P_{pl\ max} = -5 \text{cmH}_2\text{O} (-490 \text{ Pa})$, $\Delta P_{pl} = -3.2 \text{cmH}_2\text{O} (-314 \text{ Pa})$, and the phase shift $\Phi = \pi/11$.

2.5.2. Simulation of COVID-19-afflicted lungs

The coupled airway-acinar model was used to simulate COVID-19 lung damage based on the segmented CT images and the associated region-specific levels of damage, corresponding to GGO and consolidated regions. Since the CT images were obtained from a patient recovering from advanced COVID-19, hypothetical healthy lung simulations were also performed to provide a basis for comparison of the results. To simulate the changes between healthy and COVID-19 afflicted lung function, different mechanical behavior of the sigmoidal acinar model (Fig. 2) was implemented based on the amount of surfactant and compliance of the acinar units.

Simulations were run for the healthy case considering the normal amount of surfactant. The COVID-19 affected lung simulations considered the reduced amount of surfactant and decreased compliance in both GGOs and consolidation regions [41–43].

Previously segmented GGO and consolidated regions in lung CT images were used to identify acinar regions affected by COVID-19. We assumed GGOs to represent partial filling of airspace while consolidated regions may signify more severe damage where a large proportion of airspace is filled with liquid and inflammatory infiltrates [5,6]. While the airspace becomes compromised and inflamed, as seen in CT images of GGO and consolidation regions, the amount of surfactant and compliance of the acini can be altered [38,44,45]. Different acinar properties were applied to the GGO and consolidated regions to simulate these varying levels of tissue damage. Two simulations were run to visualize the effects of varying levels of COVID-19 severity: for the first simulation, a 20% reduction in the surfactant amount was used for the...
GGO regions, and 40% reduction in the surfactant for the consolidation regions was considered. For the second simulation, a 20% reduction of surfactant in the GGO regions and a 60% reduction in the consolidated regions was considered (Fig. 2).

Coefficients for the healthy sigmoidal model were fit to physiologically relevant coefficients based on patient-specific lung volumes [39]. Lung volumes were estimated based on the gender, height, and age of the COVID-19 positive patient used for CT scans in this study: male, 167.6 cm, 51 years, and 88.5 kg, respectively [46].

The following equations from Boren et al. [47] were used to estimate lung capacities and volumes for a healthy adult male:

\[
TLC = 0.078H - 7.30
\]  
\[
FRC = 0.032H - 2.94
\]  
\[
RV = 0.019H + 0.0115Ag - 2.24
\]  
\[
VC = 0.052H - 0.022Ag - 3.60
\]

where TLC is the total lung capacity in liters, \( H \) is the subject’s height in centimeters, FRC is functional residual capacity in liters, RV is residual volume in liters, \( Ag \) is the subject’s age in years, and VC is vital capacity in liters. Based on these equations for the patient in this study, we found that TLC = 5.77 L, FRC = 2.42 L, RV = 1.53 L, and VC = 3.99 L. Estimated lung volumes were then used to define coefficients A and B, as A is approximated by the residual volume and B is approximated by the vital capacity [39]. The values of \( C \) and \( D \) in the sigmoidal model correspond to the inflection point of the curve and the pressure range in which the volume change takes place, respectively [39]. As such, \( C \) and \( D \) are not as easily determined by available physiological data and were estimated such that in the healthy case, they were estimated based on the calculated FRC and the total volume pressure range.

Then, to define the regions of GGO and consolidation, \( C \) and \( D \) coefficients signifying reduced surfactant as reported by Fujioka et al. [38], were scaled to fit our patient data. Fujioka et al.’s [38] coefficients were limited to normal surfactant, 20% reduced, and 40% reduced surfactant amounts. Coefficients for 60% reduced surfactant was not directly available. Hence, the coefficients for 60% reduced surfactant were extrapolated. Assumptions for extrapolation were based on work by Fujioka et al. [38] that only coefficient \( C \) varied markedly when surfactant level was changed (Table 1).

Three different simulations were executed for this study:

1. A hypothetical control study where the lung was assumed to be healthy; GGO and consolidated regions are considered to be normal inflated regions with normal surfactant levels.
2. COVID-19-afflicted lung with 20% reduced surfactant for the GGO region and 40% reduced surfactant for the consolidated region.
3. COVID-19-afflicted lung with 20% reduced surfactant for the GGO region and 60% reduced surfactant for the consolidated region.

The total simulation time was 12 s, with each breathing cycle assumed to be 4 s between consecutive end-inspirations. The time step used by the solver was 0.001 s, and data were saved every 100 time steps. A smaller 0.0001 s time step was also tested for the healthy case and showed no significant difference in results other than an increase in simulation time. Three breathing cycles were executed, with the first two cycles discarded so that only steady-state conditions were analyzed. Following the onset of steady-state conditions, the data from that breathing cycle was used to calculate the flow rate at the trachea, flow rate into the individual lobes, total tidal volume of the lungs at different time points, the flow rate through individual lobes. Flowcharts summarizing the entire model development and simulation process are shown in Figs. 3 and 4, respectively.

### 3. Results

In total, three simulations were performed consisting of a hypothetical healthy lung with normal surfactant levels as well as two COVID-19-afflicted simulations created through reduction of surfactant levels based on the degree of damage present in the CT images. The first simulation will be referred to as the hypothetical “healthy” case, while the second and third simulations will be referred to as “diseased 20–40” and “diseased 20–60” cases, respectively.

Airflow during the simulations was generated due to the negative pressure as a result of the acinar expansion. Fig. 5 shows the flow rate of air at the trachea and into each lobe after reaching steady-state over an entire breathing cycle. Different colored lines represent each simulation scenario, with the highest flow rate in the healthy simulation and the lowest in the diseased 20–60 simulation. The lobar flow rate values were determined by calculating the flow rate at the first airway branch that enters each lobe.

The flow rate at various points in the lung can be integrated to determine the total and lobar tidal volumes (Fig. 6). The maximum values of tidal volumes for the whole lung and each lobe are also reported in Table 2, in addition to the percent change in tidal volumes in diseased cases versus the hypothetical healthy case. From Table 2, it can be seen that the healthy, diseased 20–40, and diseased 20–60 simulation tidal volumes were 0.592 L, 0.392 L, and 0.248 L, respectively. Thus, the results in Fig. 5 and Table 2 demonstrate that the tidal volume of the whole lung decreases as the severity of COVID-19 in the affected consolidated regions increases. It can also be seen in Table 2 that the right middle lobe shows the least difference in its tidal volume between the healthy and diseased simulations.

The volumes of GGO and consolidated regions calculated from CT images at end-inspiration were also quantified and are presented in Table 3. As previously described, these volumes were determined directly by thresholding the CT images. Note that actual COVID-19 affected volumes are likely to be slightly larger than presented, as very small unconnected “islands” of damage had to be excluded from analysis for volume meshing purposes. In Table 3, “COVID-Afflicted %” is the combined portion of consolidated and GGO regions. It can be seen that at end-inspiration, the right middle lobe shows the lowest percentage of damage by COVID-19, followed by the left upper lobe by a large margin. The two lobes with the smallest volume of air and the highest amount of damage in both states are the left and right lower lobes (Table 3).

Table 4 compares the share of ventilation that goes into each lobe during tidal breathing for each of the three simulated scenarios versus the values calculated from the CT using images at end-inspiration and end-expiration. Based on these results, it can be seen that the right middle lobe which shows the lowest COVID-19 inflation of 29.6% at end-inspiration, demonstrates a 10% increase in tidal volume percent share as the simulations progress from healthy to the diseased 20–40 and 20–60 states. The left upper lobe which has a relatively low 45.1% inflation at end-inspiration, shows an increase in tidal volume percent share with COVID-19 progression, though not as drastically as the right middle lobe, with only a 3.4% increase (Table 4). At end-inspiration, the right upper, right lower, and left lower lobes demonstrated remarkable COVID-19-induced damage with 58.7%, 78.2%, and 75.0% affliction, respectively, and each lobe showed a decrease in tidal volume percent share with disease progression. The less-afflicted right upper lobe

### Table 1

| Surfactant Level       | A (L) | B (L) | C (Pa)  | D (Pa) |
|------------------------|-------|-------|---------|--------|
| Healthy                | 1.53  | 4.24  | 1078.73 | 449.14 |
| 20% reduced surfactant | 1.53  | 4.24  | 1420.00 | 451.11 |
| 40% reduced surfactant | 1.53  | 4.24  | 1818.15 | 356.96 |
| 60% reduced surfactant | 1.53  | 4.24  | 2359.48 | 356.96 |
showed a far more minor change in tidal volume (−1.6%) than the right lower lobe (−6.5%) or the left lower lobe (−6.5%).

Additionally, Table 4 contains a column showing lobar air volume fraction, averaged over inspiration and expiration and converted to a percentage, as defined in a Jahani et al. [48] study investigating regional healthy lung deformation and ventilation with 4D-CT. This column was added for validation purposes to show a general agreement with our healthy model and CT-based estimations of lobar ventilation distribution. Note that lungs differ from person to person morphologically, but general trends in shape persist in most lungs; in this case, our healthy simulation successfully predicts that the left upper lobe is the largest, followed by the right lower, right upper, left lower, and right middle lobes, which mirrors Jahani et al.’s results [48].

The pressure distributions of the lung in the three different simulation scenarios are visualized in Fig. 7. All pressure distribution results are shown at both maximum inspiration and maximum expiration. Qualitatively, it can be discerned from Fig. 7 that the subject had the highest magnitude of pressure during both inhalation and exhalation in the right middle lobe and left upper lobe. These results correlate with the percentage of healthy (air-filled) acini determined from the CT images (Table 3). As these two lobes had the lowest percentage of COVID-19 affliction, they were expected to have the most unrestricted airflow. It is also notable that the three more COVID-19 affected lobes, the right upper and right and left lower lobes, show very different pressure distributions and magnitudes when comparing the healthy case to the diseased simulations. Furthermore, the diseased simulation scenarios show much more heterogeneity in air pressure distribution throughout the lung. Table 5 shows the average pressure at the terminal bronchioles in the entire lung for each simulation. From these values, it can be seen that the healthy lung simulation produced the highest average pressure magnitude and the least heterogeneity, while progressive disease states caused an increase in standard deviation and a substantial decrease in mean pressure.

4. Discussion

Few computer modeling studies have been performed with the aim of better understanding ventilation dynamics changes in advanced cases of COVID-19. Three purely mathematical yet elegant and informative models of COVID-19 effects on pulmonary ventilation and perfusion were presented by Voutouri et al. [49], Busana et al. [50] and Herrmann et al. [51]. Another mathematical modeling study by Weaver et al. [52] simulated the effect of increased respiratory effort of patients with COVID-19 acute hypoxemic respiratory failure during spontaneous breathing on parameters associated with lung injury such as tidal swings in pleural pressure. Additionally, a computational fluid dynamics model of airflow in the upper airways of COVID-19 patients was also recently presented by Pan et al. [53]. In our simulation-based study, a virtual physics-based hypothesis-testing platform was developed and presented to study lobar ventilation dynamics of COVID-19-infected lungs. In particular, the mechanical changes in severely COVID-19-afflicted lungs compared to theoretically healthy lungs were modeled and examined in a multi-scale modeling framework. To the authors’ knowledge, this is the first in silico modeling approach to use 4D CT images of COVID-19-induced lung damage to simulate regional airflow and pressure distribution in the COVID-19-infected lung. We present this study as the first step towards patient-specific physics-based models of COVID-19-afflicted lung dynamics and to lay the foundation for more detailed and individualized in silico models currently in development by our group. The multi-scale approach presented here uses patient-specific lung geometry and injury patterns obtained from CT images of a patient with advanced COVID-19 and accounts for changes in flow rate into individual lobes as a consequence of COVID-19-induced lung injury and decreased tissue compliance. Heterogeneous damage in the parenchyma of the lung due to COVID-19 was represented through changing the surfactant levels and tissue compliance at the acinar level. In addition, our computational models enabled the visualization of acinar-level impacts of the infection on global lung dynamics. Images obtained through 4D CT were processed for efficient image segmentation and conversion.
to physics-based computer models. This methodology provides a solid foundation for future investigations of other potential mechanisms of COVID-19 damage to the lungs and the ensuing effects on global lung function through a computationally efficient approach.

Our disease scenario simulation results showing differences in the lobar distribution of tidal volume are in agreement with previous studies demonstrating that lung damage in advanced ARDS, which resembles Type H COVID-19 pneumonia as categorized byGattinoni et al. [54], can decrease the compliance of injured regions to a large extent, hence decreasing airflow [55]. As expected, the least damaged lobe (right middle, 29.6% damage at end-inhalation) showed a large increase (83%) in tidal volume share when comparing the healthy and the most severe simulated disease case, and the most damaged lobe (right lower, 78.2% damage measured at end-inhalation) experienced a significant decrease in ventilation share (−35%) in the same comparison. Meanwhile, the full lung (56.7% damage at end-inhalation) also showed a notable overall reduction in tidal volume when comparing the healthy and the most severe simulated disease state (−58%).

In this study, analysis of damaged regions from the segmented CT images showed that lower lobes contained higher amounts of damage (combined GGO and consolidated regions) than other lobes (Tables 2 and 3), in this patient. These findings correspond to those from previous studies of CT imaging of COVID-19 lungs [56]. In a study using ventilation/perfusion single-photon emission computed tomography combined with computed tomography (V/Q SPECT/CT) performed in COVID-19 patients, large ventilation defects in the subpleural areas were observed [57]. The researchers observed that ventilation defects were present in the GGO areas while perfusion was largely preserved. However, in more severely damaged areas of the lung where complete alveolar filling and parenchymal lesions and fibrosis were present, perfusion defects were additionally observed which can be a sign of involvement of capillary walls [57]. Furthermore, the researchers proposed a potential adaptive mechanism where redistribution of ventilation towards the healthy parenchyma occurs [57]. This is indeed what our multi-scale model demonstrates: as the severity of damage in the right lower, left lower, and to some extent in the right upper lobe was increased, ventilation was redistributed to the least injured right middle and left upper lobes (Table 4). While our computer model in its current version only includes ventilation, we are actively developing a perfusion model which will be coupled to our ventilation dynamics model and will enable us to simulate microangiopathy induced by COVID-19.

Our simulations reasonably predicted a decrease in overall tidal volume as the level of lung damage and surfactant loss was increased. Although preserved compliance has been reported in early CARDs, lungs

Fig. 4. Flowchart for running the tidal breathing simulation for healthy and diseased lungs. The airway tree model was coupled with the sigmoidal acinar model in CHASTE [33] to simulate tidal breathing. Different levels of surfactant reduction were applied to the acinar model to simulate lung function in disease states.
Fig. 5. Flow through the trachea (a) and each lung lobe (b–f) during tidal breathing over one breathing cycle, plotted by tracking the flow every 100 time steps.

Fig. 6. Time-dependent volume change of the entire lung, determined at the trachea (a), and individual lobes (b–f). Values for volume change obtained by integration of flow rates.

Table 2
Tidal volume of the different lobes during one breathing cycle based on the integration of simulation results.

| Lobes       | Tidal Volume under different conditions (L) | % change between healthy and 20-40 | Diseased 20-60 | % change between healthy and 20-60 |
|-------------|---------------------------------------------|-----------------------------------|----------------|-----------------------------------|
| Whole lung  | 0.592                                       | 0.392                             | 0.248          | 0.248                             |
| Right upper | 0.106                                       | 0.070                             | 0.040          | 0.040                             |
| Right middle| 0.079                                       | 0.071                             | 0.060          | 0.060                             |
| Right lower | 0.111                                       | 0.062                             | 0.030          | 0.030                             |
| Left upper  | 0.196                                       | 0.137                             | 0.091          | 0.091                             |
| Left lower  | 0.101                                       | 0.052                             | 0.026          | 0.026                             |
Table 3

| Lobar Share of Tidal Volume from Jahani et al. [48] study on lobar distribution of ventilation in healthy subjects (5th column). |
|---------------------------------------------------------------|
| Lobar Share of Tidal Volume of Healthy simulation | Lobar Share of Tidal Volume of Diseased 20–40 simulation | Lobar Share of Tidal Volume of Diseased 20–50 simulation | Lobar Share of Tidal Volume from CT | Mean Lobar Air Volume from Jahani et al. |
| Right upper | 17.9% | 17.9% | 16.3% | 23.5% | 20.9% |
| Right middle | 13.3% | 18.1% | 24.3% | 8.6% | 10.7% |
| Right lower | 18.7% | 15.8% | 12.2% | 13.2% | 22.8% |
| Left upper | 33.1% | 35.0% | 36.5% | 38.8% | 25.8% |
| Left lower | 17.1% | 13.2% | 10.6% | 13.7% | 20.6% |
the foundation for patient-specific investigations of pulmonary ventilation in COVID-19 patients and individualized treatment strategies.

Conflicts of interest

The authors declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

A.V., E.D., S.M., and A.P., performed the method development and simulations and wrote the manuscript. M.S.P and A.J. and K.Y. collected the CT data. S.M.G. and V.M.contributed to study conceptualization and protocol development. All authors reviewed the manuscript and contributed to the scientific discussion.

Declaration of competing interest

None Declared.
Acknowledgments

This material is based on the work supported by the National Science Foundation under 2034964. Furthermore, this material is based upon the work supported by the National Science Foundation Graduate Research Fellowship under Grant No. 2037785 (Shnea Middleton). Special thanks to nurses and respiratory therapists at Vidant Medical Center for their help with this study, and to Vidant Radiation Oncology (Greenville, North Carolina, USA) for the use of CT scanner in the facility. Special thanks to Rafel Bordas for insightful email correspondence on lung model generation.

References

[1] WHO coronavirus (COVID-19) dashboard. WHO coronavirus (COVID-19) dashboard with vaccination data. https://covid19who.int/
[2] Lopez-Leon, S. et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci. Rep. 11, 7661 (2021).
[3] WHO (2019) Weekly Epidemiological Update, 2021.
[4] H. M. Youssef, N. A. Alghamdi, M. A. Ezzat, A. A. Elbary, A. M. Shawky, A modified SEIR model applied to the data of COVID-19 spread in Saudi Arabia, AIP Adv. 10 (2020) 125210.
[5] Gattinoni, et al., COVID-19 does not lead to a “typical” acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 201 (2020) 1299–1300.
[6] S. Bayraktaroğlu, A. Çinkooğlu, N. Ceylan, R. Savas, The novel coronavirus pneumonia (COVID-19): a pictorial review of chest CT features, Diagn. Interv. Radiol. 27 (2021) 188–194.
[7] J. Herrmann, V. Mori, J. H. T. Bates, B. Suki, Modeling lung perfusion abnormalities: the contribution of structure-dependent airway pressure-volume curve, J. Appl. Physiol. 84 (1998) 389–395.
[8] S. B. Polak, I. C. Van Gool, D. Cohen, J. H. von der Thüsen, J. van Paassen, Pulmonary and systemic involvement in COVID-19 patients assessed with ultrasound-guided minimally invasive autopsy, Histopathology 77 (2020) 186–197.
[9] A. Çinkooglu, N. Ceylan, R. Savas, The novel coronavirus – chest CT infiltrates using lung CT analyzer and 3D slicer, Br. J. Radiol. 88 (2015), 20140624.
[10] L. Weaver, et al., High risk of patient self-inflicted lung injury in COVID-19 with frequent encounters of spontaneous breathing patterns: a computational modelling study, Ann. Intensive Care 11 (2021) 109.
[11] C. Van Ertbruggen, C. Hirsch, M. Paiva, Anatomically based three-dimensional model of airways to simulate flow and particle transport using computational fluid dynamics, J. Appl. Physiol. 98 (2000) 970–980. Bethesda, Md : 1985.
[12] S. Choi, et al., 1D network simulations for evaluating regional flow and pressure distributions of ventilation in healthy human lungs, J. Biomech. 46 (2013) 319–328.
[13] E. Barisione, et al., Fibrotic progression and radiologic correlation in matched lung samples from COVID-19, Front. Physiol. 11 (2020) .
[14] J. G. Venegas, R. S. Harris, B. A. Simon, A comprehensive equation for the pulmonary pressure-volume curve, J. Appl. Physiol. 84 (1998) 389–395.
[15] A. J. Swan, A. R. Clark, M. H. Tawhai, A comprehensive computational model of the topographic distribution of ventilation in healthy human lungs, J. Theor. Biol. 300 (2012) 222–231.
[16] M. Ismail, A. Comerford, W. A. Wall, A model of surfactant-induced surface tension effects on the parenchymal tethering of pulmonary airways, J. Biomech. 46 (2013) 319–328.
[17] A. Fedorov, et al., 3D slicer as an image computing platform for the quantitative analysis of cardiac functional imaging network, Magn. Reson. Imag. 30 (2012) 1323–1341.
[60] A.J. Swan, A.R. Clark, M.H. Tawhai, A computational model of the topographic distribution of ventilation in healthy human lungs, J. Theor. Biol. 300 (2012) 222–231.

[61] M. Ismail, A. Comerford, W.A. Wall, Coupled and reduced dimensional modeling of respiratory mechanics during spontaneous breathing, Int. J. Numer. Methods Biomed. Eng. 29 (2013) 1285–1305.

[62] J. Matuszak, A. Tabuchi, W.M. Kuebler, Ventilation and perfusion at the alveolar level: insights from lung intravital microscopy, Front. Physiol. 11 (2020).

[63] A.R. Clark, M.H. Tawhai, Temporal and spatial heterogeneity in pulmonary perfusion: a mathematical model to predict interactions between macro- and microvessels in health and disease, ANZIAM J. 59 (2018) 562–580.

[64] N. Jahani, Y. Yin, E.A. Hoffman, C.L. Lin, Assessment of regional non-linear tissue deformation and air volume change of human lungs via image registration, J. Biomech. 47 (2014) 1626–1633.

[65] Y. Yin, E.A. Hoffman, C.-L. Lin, Local Tissue-Weight-Based Nonrigid Registration of Lung Images with Application to Regional Ventilation Spiromics View Project Cardiopulmonary Mechanisms Affecting Cognition in COPD View Project Local Tissue-Weight-Based Nonrigid Registration of Lung Images with Application to Regional Ventilation, 2009, https://doi.org/10.1117/12.811715.

[66] M.H. Tawhai, C.-L. Lin, Image-based modeling of lung structure and function, J. Magn. Reson. Imag. 32 (2010) 1421–1431.