function. However, mechanical ventilation might lead to lung injury depending on the respiratory tract condition. In order to understand the effects of aging for patients undergoing mechanical ventilation, it is important to investigate the lung airways by considering the aging effects, as more than 50% of the patients on mechanical ventilation are over the age of 65.

Lung airways are composed of heterogeneous material with mucosa, submucosa, lamina propria, and adventitia layers (Tan *et al.*, 2008; Bai *et al.*, 1994; Alcaraz *et al.*, 2003). The mechanical properties such as stiffness in each airway layer also vary (Kamm, 1999; Wang *et al.*, 2011; Faffe and Zin, 2009), especially with aging. Several *in vitro* (Kalén *et al.*, 1989; Hayflick, 1965; Schneider and Mitsui, 1976) and *in vivo* (Sherratt, 2009; Kovacs and DiPietro, 1994; Petersen *et al.*, 2010) models have been developed to study the effects of mechanical force or pressure on the airways. Several researchers have previously measured the airway tissue strains responsible for stressing and rupturing the lung's fiber network experimentally. However, the strains on airway tissue due to aging have not been extensively studied. A review of the literature indicated that there were no studies relating the stress and strain environment in aged airways under mechanical ventilation conditions.

The purpose of this study is to investigate how aging affects the stresses and strains in each airway layer of the lung airway tissue during mechanical ventilation coupled mechanics. The boundary conditions for tissue analysis were obtained from the whole lung model under mechanical ventilation through fluid structure interaction (FSI) simulations. The results obtained from both FSI simulations and tissue analysis are presented and discussed.

2. PROPOSED MODELS, GOVERNING EQUATION, AND BOUNDARY CONDITION

2.1 WHOLE LUNG

Physiologically accurate, aging, whole lung airway models are necessary first steps to obtain reliable data in order to effectively employ the tissue model. We have developed a surface model (fig. 1a) of the respiratory tract for a TB whole lung model from G1 to G23 based on medical images, including a CT scan of a healthy non-smoking 53-year-old male. For the elderly model, the mean value for a mean segmental bronchus diameter bore no significant relationship to age (Niewoehner and Kleinerman, 1974; Janssens *et al.*, 1999; Weibel *et al.*, 2014) (Dennis 1974). However, considerably greater variation was found in the measurement of the mean bronchiolar diameter, which ranges in size from 0.5 to 1.048 mm. Based a review of the literature (Suki and Bartolák-Suki, 2015) (Dennis 1974), age-related changes in the size (20% reduction of airway diameter for 70 year-old,)of bronchioles (20% reduction of airway diameter for 70 year-old,) and the alveolar diameter (265 μm at age 50 and 453 μm at age of 70) were considered. From this data, the mean bronchiole and alveolar diameter were calculated for the computational model to generate the 70-year-old aging case using Gambit, ICEM CFD and DesignModuler in ANSYS Workbench. The results of pressure obtained from the whole lung simulation model were used for the tissue analysis model.

2.2 TISSUE MODEL

The airway tissue of bronchioles consists of three major layers (epithelium, lamina propria, and smooth muscle) as shown in fig. 1d. In this study, we considered the distinct composition of each layer with different properties making up the airway tissue.

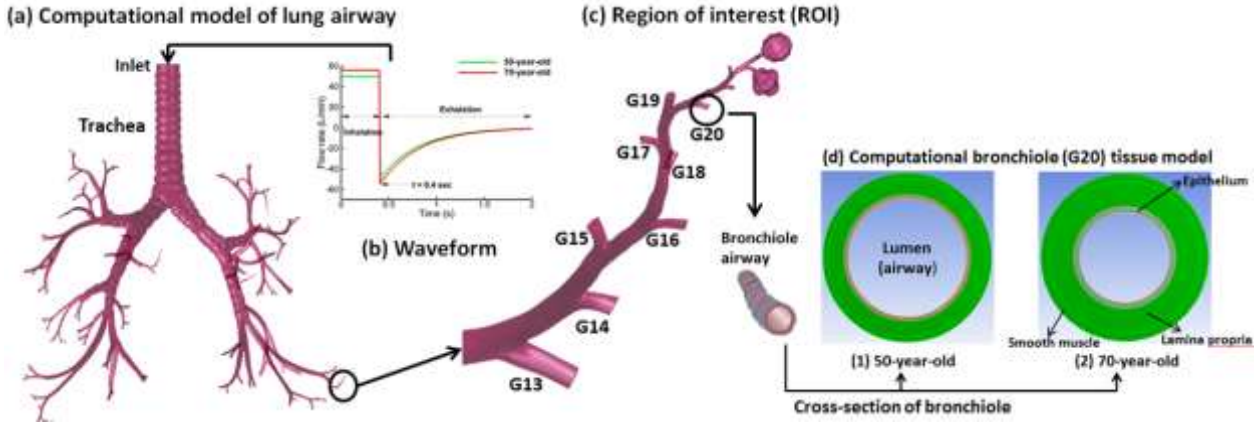


Fig. 1 Overview of human lung model: (a) computational trachea-bronchiole lung model, (c) enlargement of bronchiole parts where aging effect has occurred with region of interest (ROI), and tissue model with different ages, (d) 50-year-old (normal case) and 70-year-old tissue models

The tissue model as shown in fig. 1d was assumed to be circular in shape representing the airway. The airway lumen diameter and thickness of tissue layers for normal and aging case were determined based on the literature review (Politi *et al.*, 2010; Lai-Fook and Hyatt, 2000; Montaudon *et al.*, 2007) for the computational tissue model in this study.

2.3 GOVERNING EQUATIONS

The governing equations for airflow in the whole lung were Navier-Stokes equations on a moving mesh with the assumption of incompressible flow. The equations governing the principles of mass and momentum conservation were described using Einstein's repeated index convention (Reddy, 1993).

Conservation of mass

$$\frac{\rho}{\sqrt{g}}\frac{\partial}{\partial t}(\sqrt{g})+\rho\frac{\partial}{\partial x_j}(u_j-\frac{\partial \tilde{x}_j}{\partial t})=0\,. \qquad (1)$$

Conservation of momentum

$$\frac{\rho}{\sqrt{g}}\frac{\partial}{\partial t}(\sqrt{g}u_i)+\rho\frac{\partial}{\partial x_j}[(u_j-\frac{\partial \tilde{x}_j}{\partial t})u_i]=-\frac{\partial p}{\partial x_i}+\mu\frac{\partial^2 u_i}{\partial x_j^2}\,. \qquad (2)$$

Where $\tilde{x}$ represents the moving mesh location, $\sqrt{g}$ is the metric tensor determinate of the transformation, that is, the local computational control-volume size, ρ is fluid density, p is fluid pressure, μ is fluid viscosity, and u is fluid velocity.

The governing equations for movement of the airway's wall during mechanical ventilation were the time-dependent structural equations and were described below using Einstein's repeated index convention (Reddy, 1993).

Equation of motion

$$\frac{\partial \sigma_{ij}}{\partial x_j} + F_i = \rho \frac{\partial^2 u_j}{\partial t^2}. \qquad (3)$$

Constitutive relations

$$\sigma_{ij} = C_{ijkl}\varepsilon_{kl}. \qquad (4)$$

where σ is the stress in each direction, F is the body force, ρ is density, and u is the displacement, C is the elasticity tensor, and ε is the strain in each direction.

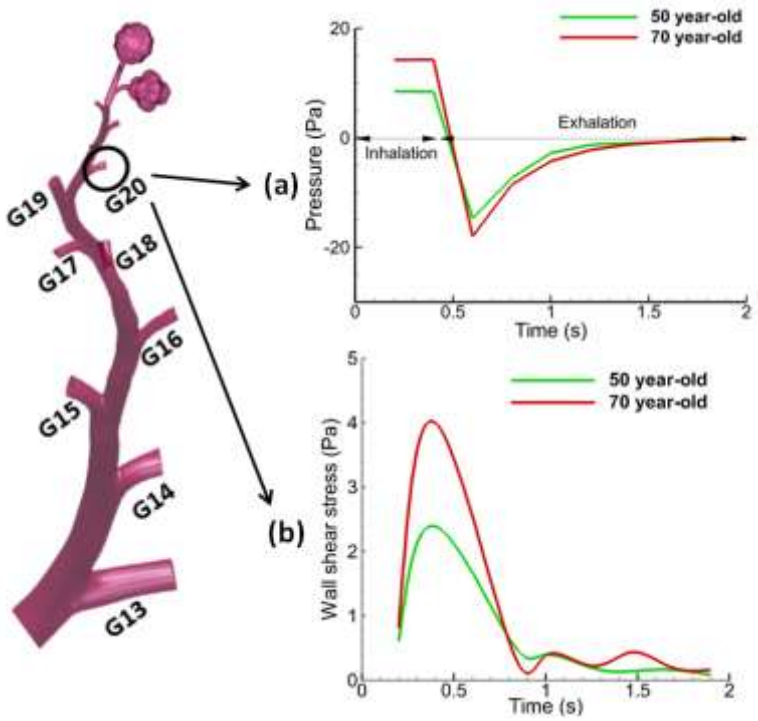


Fig. 2 (a) collected pressure and (b) wall shear stress in airway at G20 from whole lung simulation for ages 50 and 70). Inhalation period was from 0 to 0.4 seconds, and exhalation period was from 0.4 to 2 seconds.

2.4 BOUNDARY CONDTION FOR TISSUE MODEL:

The boundary conditions (pressure and material properties) of the heterogeneous tissue model at G20 were obtained from the simulation of the whole lung, before the simulation of the tissue model was performed. The transient (unsteady) breathing waveform of the normal and the elderly model was employed at the inlet of the whole lung respectively as shown in fig. 1b. The mechanical ventilation waveform for flow rate includes an inhalation period from 0 - 0.4 seconds, and exhalation period from 0.4 - 2 seconds.

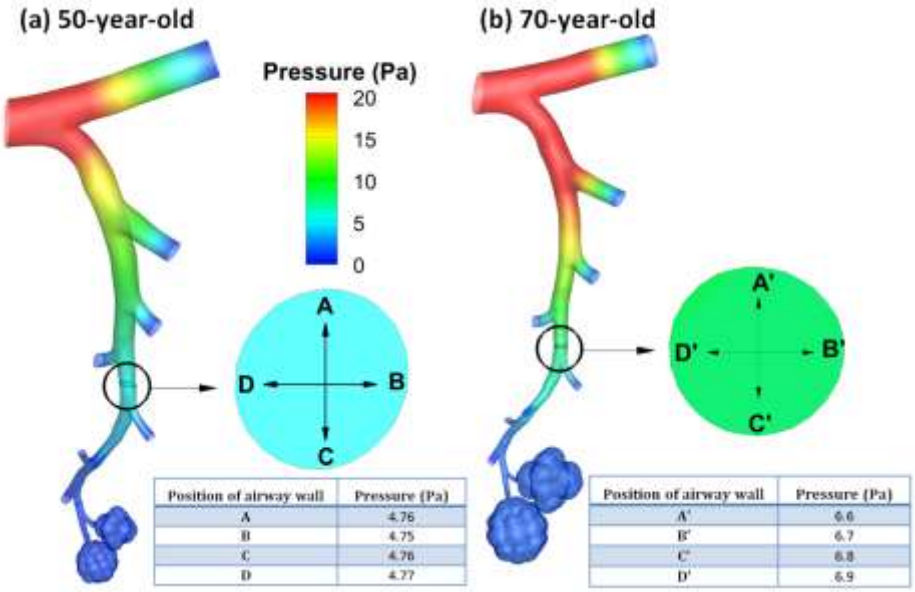
The stress-strain properties for tissue layers are assumed to be hyperelastic with non-linear Neo-hookean material properties given as below.

$$\sigma = \frac{\partial W}{\partial \varepsilon}(1-\alpha) \qquad (5)$$

$$W = \mu\frac{\mu}{2}(I_1 - 3) + \frac{1}{d}(J-1)^2, \qquad (6)$$

where W = strain energy per unit reference volume, I = first deviatoric strain invariant, μ = initial shear modulus of the material, d = material incompressibility parameter, J = determinant of the elastic deformation gradient pressure and α = aging effect coefficient.

Using the ANSYS software, it is estimated that the material properties for a 70-year-old are approximately 7% stiffer than the 50-year-old. In the whole lung FSI simulation, the results of pressure and material properties were used in tissue analysis to investigate the effect of aging on the tissue model.



Position of airway wall	Pressure (Pa)
A	4.76
B	4.75
C	4.76
D	4.77

Position of airway wall	Pressure (Pa)
A'	6.6
B'	6.7
C'	6.8
D'	6.9

Fig. 3 Pressure contours at where aging effect has occurred (G12~G23) and numerical value of pressure at region of interest (G20)

3. RESULTS AND DISCUSSION

The results of pressure variation from the whole lung simulation are shown in fig. 2a. The pressure during inhalation was constant and appeared to increase during the exhalation. The pressure for 70-year-olds was higher than normal (50-year-old) during inhalation and the opposite during exhalation. This is due to the presence of narrower airways for the 70-year-old case. Higher pressure introduces higher wall shear stress, as shown in fig. 2b. This wall shear stress may also influence strain levels on the tissue layers. The calculation of average pressure from fig. 2a was performed at each generation and is shown in fig. 3. The pressure of a 70-year-old is approximately 1.5 times higher than that of a 50-year-old for the bifurcation considered.

Figure 4 shows the normal and shear strain distributions in each layer for both 50 and 70-year-old cases. It can be seen from Fig. 4 that both the normal and shear strains in the 50-year-old case were higher than those in the 70-year-old case. The greatest normal and shear strain values occurred within the epithelium layer. The distribution of normal strain has a decreasing trend from epithelium to smooth muscle layer for both 50 and 70 year old cases. Maximum normal strain shows at the epithelium layer, and this is due to stiffer smooth muscle material properties in comparison to the epithelium.

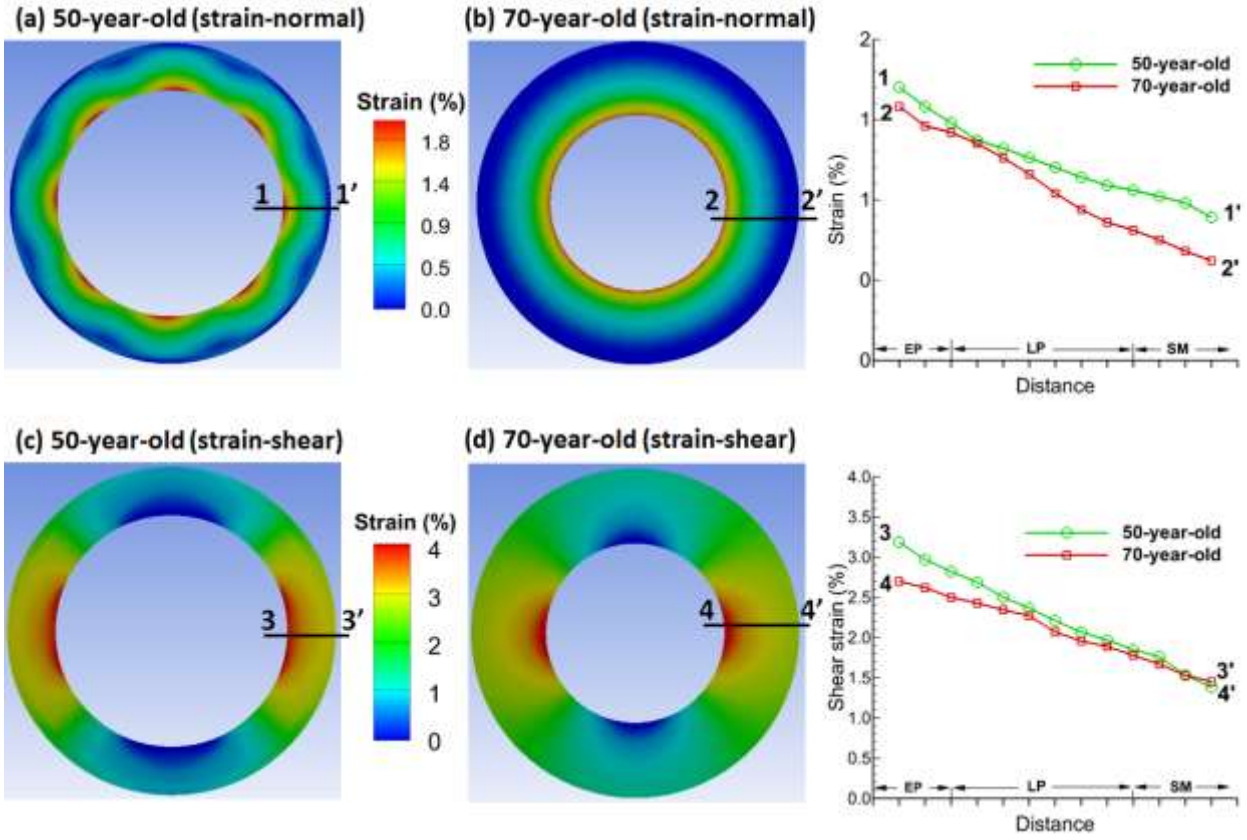


Fig. 4 Contours of strain (normal and shear) distribution of tissue layers: (a) and (c) are for 50-year-old, and (b) and (d) are for 70-year-old.

The contours of normal and shear stresses for the two cases (50 yrs old and 70 yrs old) are presented in Fig. 5. It can be seen from Fig. 5 that the largest shear stresses were present in the smooth muscle layer. The epithelium layer is the layer that had the greatest contact with the fluid and air; therefore, it would be more affected by the forces produced that result in the stresses and strains on the tissue. In comparison, the 70-year-old case produced lower strains than the 50-year-old case. However, the shear stresses obtained within the 70-year-old case were greater than those obtained in the 50-year-old case. Specifically, the maximum shear stresses (7 kPa) for the 70-year-old occurred within the smooth muscle layer whereas the maximum shear stress

(4.5 kPa) was obtained in the 50-year-old case (see Fig. 5c, d). Overall the results presented in Figs. 4-5 demonstrate that aging greatly affects both the normal and shear strains and that aging reduces their magnitude in comparison to the normal case.

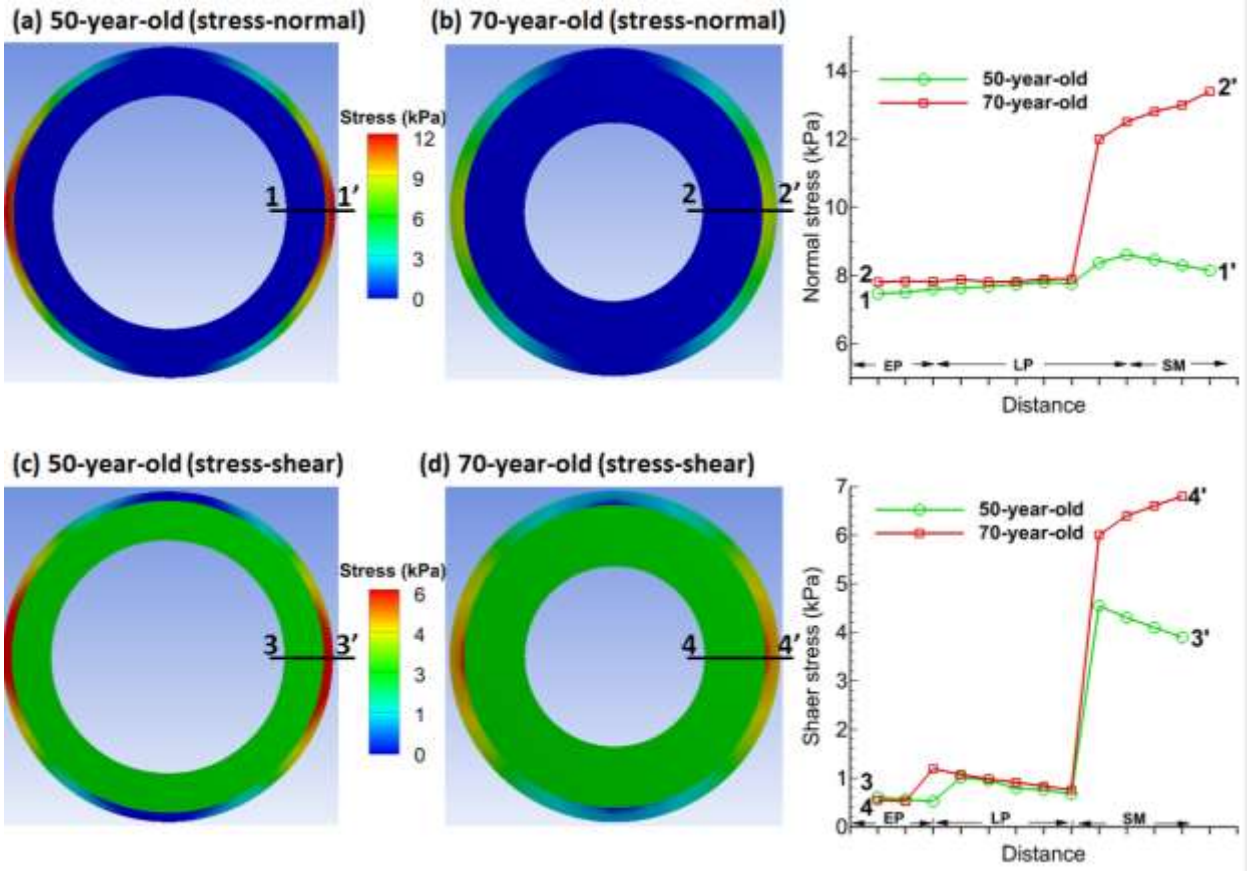


Fig. 5 Contours of stresses (normal and shear) distribution of tissue layers: (a) and (c) are for 50-year-old, and (b) and (d) are for 70-year-old.

4. CONCLUSIONS

This study investigated the effects of aging in an airway tissue model in order to estimate the stress and strain environment through coupled mechanics. The boundary conditions for tissue analysis were obtained from the whole lung model under mechanical ventilation through fluid structure interaction (FSI) simulations. For tissue analysis, first a normal (50-year-old) tissue model with multiple layers was studied. Then the aging effect was introduced (70-year-old), where geometrical changes (with changing lumen diameter and tissue layer thickness) as well as material properties changes was considered to investigate the stress/strain environment in airway tissue. The results of the distribution of normal strain had decreasing trends from the epithelium to the smooth muscle for both ages. Maximum normal strain was observed at the epithelium layer. All the tissue layers of the 50-year-old case had higher strain than the layers of the 70-year-old case. The simulation results showed that the aging model had significant effects on the pattern of strain and stress distributions in the

airway. These strains induced can greatly damage the airway tissue leading to shearing and swelling. Overall, the results of stress/strain environment obtained from the tissue analysis indicate that aging significantly affects the mechanical environment, and these strains may lead to tissue injury, which needs to be investigated in the future.

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