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A computational model of the topographic distribution of ventilation in healthy human lungs

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ABSTRACT

The topographic distribution of ventilation in the lungs is determined by the interaction of several factors, including lung shape, airway tree geometry, posture, and tissue deformation. Inter-species differences in lung structure-function and technical difficulty in obtaining high resolution imaging of the upright human lung means that it is not straightforward to experimentally determine the contribution of each of these factors to ventilation distribution. We present a mathematical model for predicting the topological distribution of inhaled air in the upright healthy human lung, based on anatomically structured model geometries and biophysical equations for model function. Gravitational deformation of the lung tissue is predicted using a continuum model. Airflow is simulated in anatomically based conducting airways coupled to geometrically simplified terminal acinar units with varying volume-dependent compliances. The predicted ventilation distribution is hence governed by local tissue density and elastic recoil pressure, airway resistance and acinar compliance. Results suggest that there is significant spatial variation in intrinsic tissue properties in the lungs. The model confirms experimental evidence that in the healthy lungs tissue compliance has a far greater effect than airway resistance on the spatial distribution of ventilation, and hence a realistic description of tissue deformation is essential in models of ventilation.

1. Introduction

The human lung typically operates in the upright posture, yet imaging modalities that are used to study lung function are usually restricted to acquiring data in horizontal positions (Hopkins et al., 2007b; van Beek and Hoffman, 2008; Sá et al., 2010), or use relatively low resolution methods to measure function in the upright lung (Amis et al., 1984). A recent study has tried to address this limitation by administering contrast when upright and then imaging when supine (Petersson et al., 2009). However, this is still not a precise image of the upright ventilation distribution. The alternative option of studying animals is confounded by species differences in airway and lung geometry which will impact on resistance and on functional differences between normal postures. A mathematical model that is predictive of ventilation distribution in the human in the upright posture would therefore have obvious application in relating experimental or clinical imaging-based measurements of lung function (supine or prone) to upright lung function, and additionally in providing a framework for *in silico* experiments.

Heterogeneity that is present in the distribution of inhaled air to different regions of healthy human lungs impacts on the function of the organ. Specifically, heterogeneous ventilation in the presence of heterogeneous and poorly correlated perfusion reduces gas exchange efficiency. Large scale effects lead to preferential ventilation of lung tissue (parenchyma) in gravitationally dependent regions compared with non-dependent regions during tidal breathing (Glenny, 2009). Due to the combined effects of the asymmetrically branching structure of the lung airways and regionally varying tissue compliance, a large degree of variability is superimposed on this dependent to non-dependent ventilation distribution. Although ventilation is heterogeneous, it exhibits an important spatial correlation as a result of the structure of the lung: low-ventilation regions neighbour other low-ventilation regions and vice versa (Altemeier et al., 2000). In addition, the complex interaction of the shape of the lungs and chest wall and motion of the lobes could be important in determining the ventilation distribution (Glenny et al., 2000). A mathematical model that is predictive of the ventilation distribution in the lung must therefore include a description of airway anatomy and its relationship to airflow resistance, as well as tissue deformation and local elasticity in response to gravity. Ultimately it should also include interaction with the chest wall and diaphragm.

Early computational modelling studies of ventilation distribution attributed regional differences in ventilation to a pleural pressure gradient in the lungs and hence to the effects of the non-linear pressure–volume relationship of the tissue, but did not

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attempt to incorporate airway or lung structure (Milic-Emili et al., 1966). More recently, Tawhai et al. (2006) proposed a model that couples tissue deformation and flow, however this model was limited to using the local tissue deformation as a flow boundary condition, which negates its use in studies where resistance is important. Models have been developed that incorporate airway resistance in idealised symmetric airway geometries, which neglect ventilation heterogeneity due to airway structure (Lambert et al., 1982; Wiggs et al., 1990; Venegas et al., 2005). Campana et al. (2009) presented a model in an anatomically based asymmetric airway tree (Tawhai et al., 2004), but assumed uniform compliance and hence did not introduce the effect of gravity acting on the tissue. This inherently assumes that airway resistance is dominant in determining the distribution of ventilation, which is a reasonable assumption in the context of that study where major bronchoconstriction was simulated. However, experimental and theoretical studies have shown that in the normal lung, compliance dominates over airway resistance in determining ventilation distributions (Milic-Emili et al., 1966; Otis et al., 1956). Therefore, a representation of tissue mechanics must be included in theoretical models of ventilation to capture the balance between resistance and compliance.

The current study presents a theoretical model of ventilation that integrates each of (1) an anatomically based structure, (2) tissue deformation due to gravity (and hence the effect on local tissue compliance) and (3) airway resistance. It is the first theoretical model to concurrently describe each of these important contributing features and so is the only existing model that can explain how these factors interact to influence the function of the airways. Model results support experimental findings that the effect of airway resistance on ventilation distribution in normal breathing is likely to be minor in comparison to the gradient of transpulmonary pressure, and hence compliance (Milic-Emili et al., 1966). In addition, this integrated model suggests that conventional estimates for acinar compliance that are used in mathematical models (i.e. constant or linear compliance distributions) are insufficient to give rise to the significant heterogeneity in the distribution of ventilation that has been observed experimentally (Altemeier et al., 2000; Robertson et al., 2005; Musch et al., 2002).

2. Methods

The ventilation model presented here combines the results of previously published models of the structure of the lungs and conducting airways (Tawhai and Burrowes, 2003; Tawhai et al., 2004) and lung tissue mechanics (Tawhai et al., 2009) with a model of airflow. The airflow model couples flow in the conducting airways (based on measurements made by Pedley et al., 1970) and an equation of motion which drives flow into the acinus via a temporally changing pleural pressure. The model of the acinus is similar in its translation of physical processes to the classic single compartment model (Ben-Tal, 2006); however, each acinus is now represented by an individual compartment, resulting in $\sim 32,000$ individual expanding and contracting compartments plus $\sim 64,000$ airways that comprise the conducting airway tree. The model is implemented in CMISS (www.cmiss.org—an in-house mathematical modelling environment.

2.1. Structural model

Subject-specific structural models for the lungs and conducting airways as described in detail in previous studies (Tawhai and Burrowes, 2003; Tawhai et al., 2004) were used to define geometries which solve functional models of tissue mechanics and airflow. In brief, finite element models of the lungs and central airways were geometry fitted to MDCT (multidetector-row computed tomography) imaging of the lungs of a healthy volunteer male. Imaging was acquired supine at 90% of vital capacity, which is assumed close to TLC (total lung capacity). Imaging data were provided by the University of Iowa Comprehensive Lung Imaging Center (I-Clic) under the Human Lung Atlas project. Imaging of subjects in this study has been approved by the University of Iowa Institutional Review Board and Radiation Safety Committees. The subject and model used in the current study was also used in a prior study of lung soft tissue mechanics (Tawhai et al., 2009).

Airways additional to the segmented central airways were generated using a volume-filling branching algorithm, to fill the lung-shaped volumetric mesh. The algorithm uses the central airways as initial conditions and the lung shape as a boundary condition for "growth" of a space-filling tree geometry. The supine TLC models were scaled to the subject's upright FRC (functional residual capacity) volume obtained from pulmonary function tests (PFTs) whilst seated (4.47 L). This assumed no change in shape of the chest wall or diaphragm with the change in posture between supine and upright lungs, but allowed for lung volume differences between the supine and upright postures.

To construct models of airway function, the proportion of the measured lung volume that resides in the conducting airways and the respiratory airways must be calculated. Conducting airway radii were assigned using the subject's FRC tracheal radius (7.26 mm, calculated from the mean tracheal cross-sectional area from FRC imaging and assuming a circular cross-section) and a Horsfield diameter ratio (R_dH) of 1.152. The Horsfield diameter ratio was selected such that the model's mean length to diameter ratio was close to 2.8 (Horsfield et al., 1976). Using this conducting airway geometry the volume of the conducting airways including and distal to the trachea was 102 mL. An additional 80 mL was included to account for the volume of the upper airways (proximal to the trachea), based on the predictive equation from Hart et al. (1963) for total anatomical dead space as a function of body height. Alveolar volume at FRC was then 4.29 L (the PFT measured volume minus the volume of all conducting airways). To obtain the volume of a single acinus this value was divided by the number of acinar units in the model (31,800) resulting in a mean acinar volume, defined as V_{FRC}, of 135 mm^3. Fig. 1 shows the model geometry: the right lung is shown with spheres representing acinar units and the left lung is shown with the conducting airways only.

2.2. Tissue deformation and compliance

The pre-inspiratory (FRC) model geometry and regional distribution of compliance were estimated using finite deformation elasticity, using the methods previously presented by Tawhai et al. (2009) for the left lung of two supine human subjects including the subject considered here. As this component of the functional model has been reported previously, details are provided as an appendix. In brief, the lungs and air were assumed to comprise a compressible, homogeneous, isotropic material, with the non-linear relationship between tissue stress and strain defined by a strain energy density function (W):

$$W = \frac{\xi}{2}\exp(aJ_1^2 + bJ_2), \quad (1)$$

where J_1 and J_2 are the first and second invariants of the Green–Lagrangian finite strain tensor, and ξ, a, and b are constant coefficients.[1] The lungs were assumed free to slide within a rigid pleural cavity during introduction of gravity loading, and enforced to remain in contact with the cavity surface. Tissue deformation in this

[1] Note that the strain energy density function in Tawhai et al. (2009) is written incorrectly; the correct version – as used here – appears in Burrowes and Tawhai (2010).