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The influence of tethering and gravity on the stability of compliant liquid-lined airways

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ABSTRACT

This study revolves around two simple questions: 1) how does pulmonary airway recruitment/de-recruitment (RecDer) depend on the tethering support provided by surrounding airways and alveoli, and 2) does airway angle of inclination (θ) influence airway stability? These two questions are critical to understanding the existence and prevention of atelectrauma, which may contribute to ventilator-induced lung injury (VILI). To address these questions, we develop PDMS 2 mm ID compliant tubes that mimic pulmonary airways. Airway obstruction is modeled using silicone oil, and recruitment occurs through insufflation with a constant flow of air at $Q = 0.25$ ml/s. Parenchymal tethering is modeled through the use of a pressure chamber through which we independently establish the external pressure (P_{ext}). Repetitive RecDer oscillation is observed as a function of P_{ext} and θ. We find that airway collapse significantly increases the rate of instability, and this rate correlates strongly with the dimensionless film thickness ($\varepsilon = h/R$), where h is the film thickness and R is the transmural pressure dependent vessel radius. Furthermore, the angle of orientation influences RecDer oscillation, with stability decreased when airflow is directed in the upward direction. These results may provide insight into protective mechanical ventilation processes that can reduce the existence or severity of VILI.

1. Introduction

Respiratory distress syndrome (RDS), acute respiratory distress syndrome (ARDS), asthma and cystic fibrosis are examples of lung diseases where lining fluid abnormalities play a key role in disease etiology. For example, ARDS afflicts nearly 200,000 individuals annually in the US alone, with a mortality rate of 40%. ARDS is not a 'life-style' condition – instead it arises from insults such as bacterial infection (sepsis), liquid aspiration or noxious gas inhalation. A hallmark of ARDS is the existence of fluid filled lungs with high surface tension interfaces. ARDS afflicts individuals in the prime of their life, and survivors may suffer from long-term neurological deficits, depression and decreased quality of life (Hopkins et al., 2005). Furthermore, the ICU length of stay is significantly correlated with decreased quality of life, suggesting that a reduction of ARDS severity through improved treatment can have a long-term impact on patients and their families (Hopkins et al., 2004).

Mechanical ventilation may cause ventilator-induced lung injury (VILI) because it can introduce large mechanical stresses on sensitive pulmonary tissues. The damaging effects and the potential for improvement is demonstrated by the benefits associated with reducing ventilation tidal volumes from the prior standard of 12–6 ml/kg (2004). This change in ventilation standards significantly reduced mortality of ARDS from 75% to 40%, and is attributed to the reduction of lung over-distension (volutrauma). VILI damage can also be caused by atelectrauma that arises due to the repeated recruitment and de-recruitment (RecDer) of airways and alveoli, resulting in epithelial cell damage due to mechanical stresses associated with interfacial flows and fluid-structure interactions (Bilek et al., 2003; Glindmeyer et al., 2012; Huh et al., 2007; Jacob and Gaver, 2012; Kay et al., 2004).

Aligning mechanical ventilation processes with the physical capacity of the lung could impart benefits to patient survival. Accurate patient-centered alignment may require computational models that couple multi-phase flows with multi-scale models of the lung (Howatson Tawhai, 2000; Mullally et al., 2009; Ryans et al., 2016; Suki et al., 1994; Tawhai and Burrowes, 2008). To be tractable, such models will need to rely on robust reduced-dimension rules that can be used to provide estimates of micro-scale phenomena that interact with macro-scale behavior.

In the present study, we are focused on elucidating events associated with (de)recruitment of compliant tubes that model compliant pulmonary airways. We are specifically interested in how the transmural pressure, defined as the difference between the internal and external pressure ($P_{tm} = P_{Int} - P_{ext}$), affects existence of repeated recruitment/de-recruitment events (RecDer oscillation) due to

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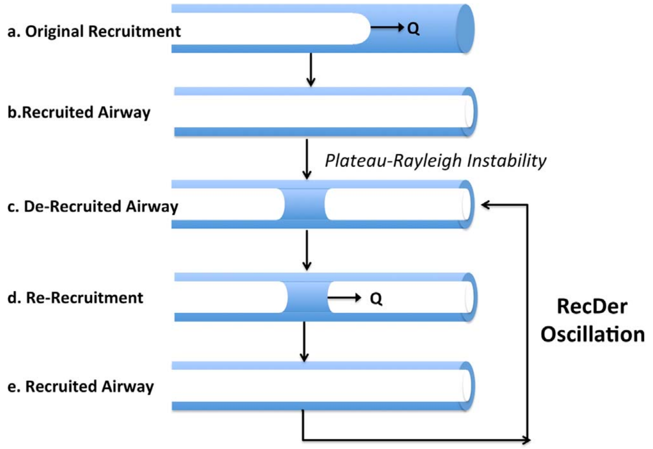

Fig. 1. Schematic of the Recruitment/De-recruitment (RecDer) dynamics that are investigated in this model. Note that although not illustrated, the tube is compliant and may undergo cross-sectional buckling as a result of a negative transmural pressure.

fluid-structure instabilities. We also investigate whether the angle of inclination affects RecDer events.

We have developed model compliant tubes that are intended to mimic the properties of pulmonary airways. We evaluate the compliance to establish the 'tube-law,' and then investigate the stability to fluid-structure instabilities within a pressure chamber to independently set P_{Ext}. Below we describe the basic RecDer dynamics that we investigate. This process is described in Fig. 1 and explained in detail below.

1.1. Airway compliance

Pulmonary airways are liquid-lined compliant vessels that convey air to and from the alveoli for gas-exchange with the environment. A general description of the compliance is provided by the 'tube law' that represents the relationship between the dimensionless cross-sectional area (A/A_0) and the transmural pressure (P_{tm}), where A_0 represents the area of the fully inflated airway. Lambert et al. (1982) mathematically described the sigmoidal behavior for central and peripheral airways. That analysis quantified the variable compliance behavior in the lung, with peripheral airways being highly compliant $\left(\frac{1}{A}\frac{dA}{dP_{tm}}\right)$ especially near $P_{tm}=0$. Fig. 2 provides representative tube-laws that qualitatively describe pulmonary airway compliance based upon the analysis of Lambert *et al.*; this illustrates the highly compliant nature of peripheral airways in comparison to central airways. We note that any given airway has a strong P_{tm} dependence to the compliance – pulmonary airways are much less compliant when fully inflated ($P_{tm} > 17\ \text{cmH}_2\text{O}$) or when fully collapsed ($P_{tm} < -5\ \text{cmH}_2\text{O}$). Collapsed buckle radially, with the primary mode of instability creating a dumbbell form in untethered tubes; however other modes may dominate if tethering exists (Flaherty et al., 1972). In the present study we will develop in vitro models of untethered compliant airways that can be used to investigate these collapse mechanisms.

1.2. Recruitment

Airway recruitment occurs when a fluid obstructed airway is reopened by the penetration of a finger of air that displaces the liquid and obstruction (Fig. 1). Many experimental and theoretical investigations have explored the behavior of recruitment in rigid and flexible models, and an array of phenomena exists based upon the volume of the obstruction, the airway wall flexibility, the

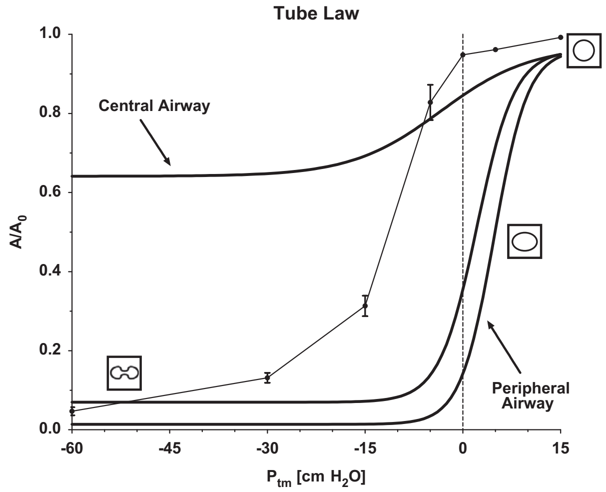

Fig. 2. Representative compliance representation (tube-law) representing a change in cross-sectional area (A/A_0) as a function of transmural pressure, $P_{tm.}$ Bold lines represent pulmonary airways, and data and narrow line represents the PDMS tube used in this study.

surface tension, the existence of surfactant, the viscosity of the fluid and the recruitment velocity (Gaver et al., 1990, 1996; Ghadiali and Gaver, 2000, 2003; Halpern and Gaver, 2012; Yap and Gaver, 1998). A key dimensionless parameter that describes the flow field is the capillary number,

$$Ca = \frac{\mu U}{\gamma}, \tag{1}$$

which represents the relationship between viscous and surface tension interactions. Here μ is the viscosity, U is the reopening viscosity and γ is the surface tension. The volume of fluid retained in the vessel is of critical importance to RecDer phenomena. In a rigid tube, the foundational work of Taylor (1961) empirically established the dimensionless film thickness that is accurate over the range $10^{-4} < Ca < 10^{-1}$:

$$\varepsilon = \frac{h}{R} = 0.5Ca^{1/2}, \tag{2}$$

where h, is the residual film thickness and R is the tube radius. This behavior is modified by the nature of closure, but it provides a framework by which one can develop a basic understanding of recruitment/de-recruitment stability.

1.3. Plateau-Rayleigh Instability

The Plateau-Rayleigh instability is hypothesized to be responsible for the occlusion of liquid-lined pulmonary airways (Campana and Saita, 2006; Cassidy et al., 1999; Heil et al., 2008; Kamm and Schroter, 1989). Briefly, this surface-tension-induced instability relates to the interfacial pressure drop on the air-liquid interface that coats the interior surface of the airway, which is a function of the local curvature. Statically, Laplace's law is

$$\Delta P = \gamma\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \tag{3}$$

where ΔP is the interfacial pressure drop, and R_1 and R_2 are radii of curvature in orthogonal directions (for example, $R_1 \sim$ the local radius of the interface in the radial direction and R_2 is related to the wavelength of the interfacial perturbation in the axial direction). In gravity-free systems, theory and experiments have demonstrated that a liquid-lined vessel will obstruct due to interfacial instabilities if the dimensionless film thickness $\varepsilon \equiv \frac{h}{R} > \varepsilon_{crit}$, where h is the local film thickness and R is the radius of the tube. These studies show that $0.09 < \varepsilon_{crit} < 0.12$, and that

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