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Biomechanics of liquid–epithelium interactions in pulmonary airways

Samir N. Ghadiali[a,*], Donald P. Gaver[b]

[a] Department of Mechanical Engineering and Mechanics, Bioengineering Program, Lehigh University, Bethlehem, PA 18015, USA
[b] Department of Biomedical Engineering, Tulane University, New Orleans, LA, USA

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ABSTRACT

The delicate structure of the lung epithelium makes it susceptible to surface tension induced injury. For example, the cyclic reopening of collapsed and/or fluid-filled airways during the ventilation of injured lungs generates hydrodynamic forces that further damage the epithelium and exacerbate lung injury. The interactions responsible for epithelial injury during airway reopening are fundamentally multiscale, since air–liquid interfacial dynamics affect global lung mechanics, while surface tension forces operate at the molecular and cellular scales. This article will review the current state-of-knowledge regarding the effect of surface tension forces on (a) the mechanics of airway reopening and (b) epithelial cell injury. Due to the complex nature of the liquid–epithelium system, a combination of computational and experimental techniques are being used to elucidate the mechanisms of surface-tension induced lung injury. Continued research is leading to an integrated understanding of the biomechanical and biological interactions responsible for cellular injury during airway reopening. This information may lead to novel therapies that minimize ventilation induced lung injury.

1. Introduction

The lung is a highly complex and dynamic structure which contains an intricate network of bifurcating airways that allow for efficient gas transport from the environment to alveoli, which are the functional units of gas exchange (Levitzky, 2007). These airways can be separated into conducting and respiratory zones. Conducting airways are approximately the first 15 generations proximal to the mouth and nose, and are primarily responsible for providing a conduit between the upper airways and the periphery of the lung. These airways also environmentally condition the inhaled air as it reaches the respiratory zone.

The main function of the respiratory zone, which is composed of smaller bronchioles and terminal bronchioles, is to provide a site for gas exchange. The airways in the respiratory zone (generations 20–27) are significantly more compliant than the conducting airways and give rise to pulmonary alveoli which emerge along the airways and have a hexagonal structure (Hubmayr, 2002; Levitzky, 2007). The walls of small pulmonary airways and alveoli are lined with epithelial cells (EpC), which are an important component of the alveolar-capillary barrier that separates the air-space within the alveoli with interstitial and blood fluids. The alveolar-capillary barrier also consists of a layer of pulmonary endothelial cells that line the walls of the alveolo-capillary network

It has long been established that the surface tension forces within the thin layer of fluid that lines pulmonary airways/alveoli play a major role in the global mechanics of lung inflation. As shown by the schematic pressure–volume curves in Fig. 1, von Neergaard (1929) demonstrated that the pressures required to inflate an air-filled lung were significantly larger than those required to inflate a fluid-filled lung. In addition, the saline-filled lung exhibited a larger slope (dV/dP) indicating a more compliant lung. This indicates that surface tension forces at the air liquid interface oppose lung inflation, and it has been well-established that the reduction of these surface tension forces is critical for normal lung inflation (Pison et al., 1996). Furthermore, as shown in Fig. 1 the hysteresis between inflation and deflation curves in an air-filled lung indicates that the surface tension forces are different during inflation and deflation. This change in surface tension can be directly attributed to the presence of surface-active compounds, i.e. pulmonary surfactants, which are released by alveolar type II EpC into the thin layer of fluid that coats the walls of pulmonary alveoli and respiratory airways.

To reduce surface tension forces, the alveoli secrete pulmonary surfactant, which decreases the surface tension of the lining fluid. Surfactant insufficiency is a major contributor to pulmonary disease. For instance, infant respiratory distress syndrome (IRDS), which results from lung immaturity at birth and causes a high lining-fluid surface tension and a propensity for airway closure, results in atelectasis of compliant airways and inhomogeneous

* Corresponding author. Tel.: +1 610 758 5168; fax: +1 610 758 6224.
E-mail addresses: sag3@lehigh.edu (S.N. Ghadiali), donald.gaver@tulane.edu (D.P. Gaver).

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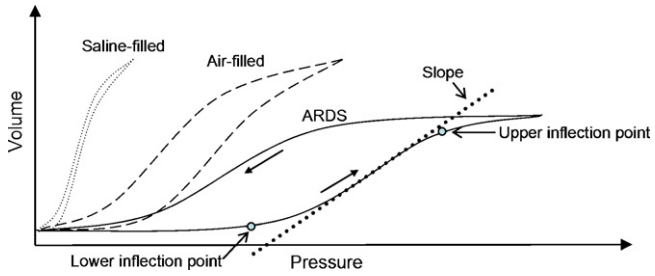

Fig. 1. Schematic diagram of pressure–volume loops in saline-filled, normal air-filled and injured lungs (ARDS).

ventilation (Avery and Mead, 1959). While surfactant replacement therapy (SRT) and protective mechanical ventilation is effective in the short-term treatment of IRDS (Notter and Finkelstein, 1984; Patton and Schulman, 1992), RDS remains the fourth leading cause of death of premature infants in the United States (Guyer et al., 1999). Additionally, acute respiratory distress syndrome (ARDS) can result in surfactant insufficiency due to plasma proteins leaking into the airspaces (Haitsma et al., 2004). Though recent attempts to treat ARDS with SRT did not significantly improve survival (Lewis and Veldhuizen, 2003; Spragg et al., 2004), there is still great interest in this treatment modality (Baudouin, 2004). Finally, there are indications that surfactant deficiency can play a role in asthma (Liu et al., 1995; Cheng et al., 2001), though the evidence for this is inconclusive.

Pulmonary surfactant is a lipid-protein complex formed in the type II alveolar epithelial cells. While predominantly comprised of lipids (~90%), the surfactant proteins (~10%) are necessary for normal functioning (Hall et al., 1992; Yu and Possmayer, 1993). Approximately 80% of the phospholipid content is dipalmitoylphospatidylcholine (DPPC) that is responsible for attaining ultra-low surface tensions (<5 dyn/cm) (Klaus et al., 1961; Hawco et al., 1981; Tchoreloff et al., 1991). Also, phosphatidylglycerol (DPPG) aids in spreading the surfactant (Klaus et al., 1961; Bangham et al., 1979; Bélorgey et al., 1991; Tchoreloff et al., 1991). The surfactant-associated proteins (SP-A, B, C, and D) influence physicochemical properties. The hydrophobic proteins, SP-B and SP-C, aid adsorption and respreading of the surfactant monolayer that has been compressed to ultra-low surface tensions (Yu and Possmayer, 1990, 1992; Wang et al., 1995, 1996).

Recent investigations show that surfactant proteins SP-B and SP-C can dramatically influence surfactant interfacial properties. Studies by Zasadzinski, Waring and colleagues (Zasadzinski, 1996; Lipp et al., 1998; Zasadzinski et al., 2001) demonstrate that SP-B and SP-C can induce monolayers of pulmonary surfactant adsorbed to an air–liquid interface to collapse under compression to form subsurface multilayers (Lipp et al., 1998; Diamant et al., 2000; Crane and Hall, 2001; Takamoto et al., 2001; Lu et al., 2002) that will respread to the primary interface when the interfacial surface area expands (Ding et al., 2001).

The delicate structure of the lung makes it particularly susceptible to mechanical injury (West and Mathieu-Costello, 1997, 1999). As we will describe below, the interactions between tissue, liquid and surfactant are critical to the normal function of the lung, but may also lead to damage under patho-physiological conditions. These interactions are fundamentally multiscale, since air–liquid interfacial dynamics are known to effect global lung mechanics, while surface tension forces at the alveolar/small-airway scale operate at the molecular and airway scales. Aberrant behavior of the surface lining fluid may cause significant damage and/or injury to the pulmonary epithelium that, in turn, can influence whole organ function. The goal of this article is to review the state-of-knowledge regarding the effect of surface tension forces on airway and alveolar mechanics as well as the effect of surface tension forces on epithelial cell function and injury.

2. Clinical Significance of air–liquid flows in the pulmonary system

2.1. Infant respiratory distress syndrome

Upon birth, the alveolar space as well as the respiratory and several of the conducting airways are completely filled with amniotic fluid. In order to initiate respiration, the infant must generate sufficient inflation pressures in order to "open" these fluid-filled structures. Specifically, the opening of fluid-filled airways and alveoli involves the propagation of air–liquid interfaces and microbubbles of air that displace the surrounding liquid and thus aerate the lung. Premature infants born prior to approximately 25 weeks of gestation are likely to have an immature surfactant system, resulting in elevated interfacial surface tension. While a mature surfactant system decreases lung inflation pressures by reducing surface tension forces at the air–liquid interface, a premature neonate with an immature surfactant system can not initiate respiration on their own since they are unable to generate the large inflation pressures required to overcome elevated surface tension forces. As a result, large regions of the lung may remain occluded with liquid (atelectasis). In addition, mechanical instability and subsequent lung collapse after inflation can occur in surfactant deficient neonates. As a result, airway/alveolar closure in premature infants causes severe hypoxia and death if not treated quickly in an intensive care environment.

One possible method to treat infant respiratory distress syndrome (IRDS) involves mechanical ventilation. However, the large mechanical forces generated by these ventilators, i.e. large inflation pressures, can damage the airway and alveolar epithelium. As a result, the epithelium may become highly permeable to proteins from the microvasculature that can, in turn, inactivate surfactant (Robertson, 1989). This inactivation further elevates reopening pressures and establishes a positive feedback cycle in which significant airway wall damage can occur. Note that in IRDS, surfactant inactivation is secondary to the original problem of surfactant insufficiency. The primary goal in the prevention or treatment of IRDS is to minimize the use or damaging effects of mechanical ventilators by reducing surface tension forces through the development of a functional surfactant system. Specifically, the standard of care for the prevention of IRDS includes the antenatal administration of corticosteroids before an anticipated premature delivery, which serves to accelerate lung maturation and stimulate surfactant production (Patton and Schulman, 1992). However, this treatment strategy is only effective if one can determine which fetuses are at risk of developing IRDS prior to birth.

After delivery, the standard of care includes the postnatal administration of exogenous surfactant (surfactant replacement therapy (SRT)). The postnatal delivery of exogenous surfactant can significantly reduce surface tension forces in the lung, allowing the infant to initiate respiration with lower lung inflation pressures. The lower lung inflation pressures also help reduce epithelial cell damage and protein leakage and therefore reduce the subsequent surfactant inactivation. Delivery of pulmonary surfactant to atelectic regions of the lung is accomplished through direct administration *via* the conducting airways followed by gravitational draining and surface-tension-induced spreading (Halpern et al., 1998). Methods for enhanced delivery of exogenous surfactant or uptake of endogenous surfactant remain an active area of research (Williams and Jensen, 2000; Anderson et al., 2004; Gaver et al., 2005; Zimmer et al., 2005).