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Computational Models of Ventilator Induced Lung Injury and Surfactant Dysfunction

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Abstract

Managing acute respiratory distress syndrome (ARDS) invariably involves the administration of mechanical ventilation, the challenge being to avoid the iatrogenic sequellum known as ventilator-induced lung injury (VILI). Devising individualized ventilation strategies in ARDS requires that patient-specific lung physiology be taken into account, and this is greatly aided by the use of computational models of lung mechanical function that can be matched to physiological measurements made in a given patient. In this review, we discuss recent models that have the potential to serve as the basis for devising minimally injurious modes of mechanical ventilation in ARDS patients.

Introduction

Ventilator-induced lung injury (VILI) refers to the damage that is often imposed upon the lung tissues during mechanical ventilation [1]. VILI is almost always associated with a lung that is already injured, and is most often encountered in the medical condition known as acute respiratory distress syndrome (ARDS), a severe form of pulmonary edema caused by factors other than elevated pulmonary venous pressures imposed by congestive heart failure [2]. Unfortunately, there are no treatments for ARDS other than supportive care aimed at allowing the body's own reparative processes to manifest. The primary basis of this support is mechanical ventilation, but herein lies the problem. Mechanical ventilation itself can be highly damaging to an already injured lung, so it must be applied in a manner that minimizes VILI. Minimizing VILI requires that knowledge of the stresses and strains induced by a given regimen of mechanical ventilation be used to predict subsequent injury to the lung tissues, an objective that can be facilitated with computational models. We are still some distance away from being able to achieve this prediction in the clinical arena, but recent

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Conflict of Interest

The authors have no conflicts of interest to declare.

research on the computational modeling of lung mechanical function in animal models of ARDS and VILI is beginning to show how it might eventually be achieved.

Pathophysiology of VILI

The most common causes of ARDS are pneumonia, sepsis, massive hemorrhage, and aspiration of stomach contents, all of which can lead to a condition in which mortality may reach 45–60% [3]. The damaging effects of mechanical ventilation in ARDS arise because the ARDS lung is much stiffer than normal [1, 2]. This generates damaging stresses and strain in the delicate distal regions of the lung, causing serous fluid and proteins to leak into the airspaces by passing through impaired endothelial and epithelial barriers [1, 4–6]. Here, the fluid and proteins interfere with the normal functioning of pulmonary surfactant, leading to a dramatic increase in surface tension [7–9] and hence in overall lung stiffness [1, 4]. VILI and surfactant dysfunction are thus inextricably linked, each affecting and often exacerbating the other.

Although the mortality from ARDS is high, it is not as high as it was just one decade ago thanks to advances that have been made in ventilatory management. Probably most important of these advances is the finding that tidal volume (V_t) needs to be substantially lower in ARDS than would normally be considered sufficient to maintain adequate minute ventilation and oxygenation [10]. The currently accepted goal for V_t in ARDS is 6 ml/kg ideal body weight [11], a level that often leads to alveolar partial pressures of carbon dioxide that are significantly higher than what is considered physiologically normal. This highlights the preeminence of reducing the stresses applied to the lung tissues during ventilation, even at the expense of derangements in gas exchange. It also highlights the importance of basing evidence for medical practice on the results of randomized clinical trials; until the results of the ARDSnet trial became known in 2000 [11], few would have guessed that gas exchange would ever play a role of secondary importance to that of the lung's mechanical environment.

However, we are now beginning to face a new problem. The seminal ARDSnet trial [11] demonstrated simply that 6 ml/kg was significantly safer than 12 ml/kg for ARDS patients. While the importance of this finding is difficult to overestimate, it leaves open many obvious follow up questions, such as whether a V_t of 5 or even 3 ml/kg might be better than 6 ml/kg [12], or what other parameters of mechanical ventilation are best combined with a V_t of 6 ml/kg. The size and cost of the ARDSnet trial make it clear that refining our evidence-based practice further for the ARDS population as a whole, now recognized as being highly heterogeneous, would require too many subjects to be feasible. It would seem, therefore, that our only way of moving forward to more optimal methods of ventilator management of ARDS would be to develop personalized approaches that can be tailored to individual patients based on their particular lung mechanics.

VILI is thought to occur via two distinct processes, termed *volutrauma* and *atelectrauma* [1, 13, 14]. Volutrauma refers to the damage caused by over-distending the lung tissues. In ARDS this is exacerbated because some regions of the injured lung invariably collapse completely and remain recalcitrant to re-inflation [15, 16]. This means that a tidal volume

that would typically be safe for a normal lung may dangerously over-inflate the limited volume of expandable tissue in an injured lung. Atelectrauma refers to the damage caused by the repetitive re-opening during inspiration of airways and/or alveoli that become closed during each prior exhalation [1, 17]. Recent work on the passage of air bubbles over epithelial monolayers indicates that most damage is produced by the gradient of forces directed perpendicularly to the epithelial surface that occur as the interface between air and liquid passes over the cells [18, 19].

Volutrauma is a phenomenon that manifests when tissue distension is high, so it presents a particular risk at the peak of inspiration. Conversely, most derecruitment and recruitment events in the lung occur at the lower volumes seen at the end of exhalation and start of inspiration, respectively. Ventilating the injured lung is thus generally seen as a balancing act between delivering a V_t sufficient to oxygenate the patient, limiting V_t and positive end-expiratory pressure (PEEP) to avoid over-distension, and having enough PEEP to limit the amount of derecruitment that occurs at the end of each exhaled breath [20]. Aside from not ventilating the lungs at all, however, it may not be possible to eliminate volutrauma and atelectrauma entirely, so VILI may progress to some degree even with optimal management. When this happens, there is a danger that the inflammatory cytokines and other mediators produced locally in the lung by the ongoing tissue damage will pass into the circulation and travel to more distant regions of the body, eliciting inflammatory damage to other organs [21]. This kind of disseminated injury is known as *biotrauma*, and is suspected to be behind the multi-organ failure that is the most frequent cause of death in ARDS [22].

Surfactant Biophysics

Pulmonary surfactant is produced by type II alveolar epithelial cells and is comprised of a mixture of phospholipids and proteins [23] which form a thin film (monolayer) atop the liquid that lines the distal regions of the lung. Healthy pulmonary surfactant reduces the surface tension of the liquid lining layer from approximately $\gamma = 72 \text{ mN.m}^{-1}$ (pure water) to near zero during dynamic compression of the air-liquid interface [24]. This reduction in γ is a function of the surfactant monolayer density (Γ), and reduces the Laplace pressure drop in the small airways and alveoli to prevent derecruitment at end-exhalation, thereby reducing breathing effort and promoting alveolar stability. These alterations in γ vary substantially during the respiratory cycle as surfactant molecules move between the surface of the fluid, subsurface surfactant multilayers, and the bulk fluid due to changes in surface area as modeled using molecular dynamics simulations [25, 26]. The relationship between γ and Γ may be modified in ARDS and VILI because increases in pulmonary epithelial barrier permeability allow plasma proteins to enter the airspaces [27]. These proteins interfere with surfactant structures and the surface film resulting in impaired surfactant function [7–9].

Surfactant function plays a critical role in the macro-scale behavior of the lung due to its effect on lung compliance. γ also affects the microscale fluid-mechanical forces which are a dominant factor in the recruitment and derecruitment of small airways and alveoli, and involves complex interactions between surface tension forces, surfactant transport, fluid flow, and the solid mechanics of the compliant airway. This problem has been approached using experimental techniques to quantify the effects of lung surfactant on macro-scale

quantities such as the pressure drop across the air-liquid interface [28–30] and microscale measures such as cellular damage [18, 19, 31] and flow-field alterations [32]. However, phenomena such as the fluid-mechanical stress profile at the airway wall, which may damage the epithelial lining and lead to atelectrauma [18], have yet to be investigated experimentally.

The reopening of a collapsed, fluid-occluded airway has been computationally modeled as the progression of a semi-infinite bubble moving at a constant velocity through a rigid, fluid-occluded channel or tube [33, 34]. These systems are characterized by the dimensionless capillary number $Ca = \mu U / \gamma$ which describes the ratio of surface tension and viscous forces, where μ is the fluid viscosity and U is the bubble tip velocity. The pressure required to push a finger of air through the occluding fluid is proportional to Ca , and the migrating bubble leaves a thin film of liquid along the walls, which is thicker at higher Ca . Using physiologically relevant parameter values, the magnitude of the pressure gradient is calculated to be inversely proportional to Ca , so cellular damage is increased at low velocities or high surface tensions.

The surface tension at any point on the air-liquid interface is proportional to Γ so that the bulk, subsurface, and surface concentrations of surfactant both modify and are altered by the flow field. This coupling makes solving surfactant transport in models of airway reopening challenging, particularly in time-dependent flows or with flexible airway walls. Simulations of steady reopening in rigid [35] and compliant [36, 37] domains suggest that the slow adsorption rate of pulmonary surfactant may, in some cases, increase the pressure required to reopen an airway compared to constant surface tension at the equilibrium value. This occurs because variations in surface tension along the interface result in tangential Marangoni stresses which rigidify the interface [38]. In order to side-step the limitations of slow surfactant adsorption, Gaver *et al* have proposed adding a sinusoidal component to the driving flow so that the bubble retracts periodically instead of progressing steadily forward [32, 39, 40]. This approach is intended to distribute surfactant from the bulk across the air-liquid interface and has demonstrated a 50% improvement in surfactant function in *in vitro* experiments [31]. These findings suggest that ventilation waveforms may be designed to maximize the efficacy of pulmonary surfactant and thus to minimize VILI [41].

Modeling the Mechanics of the Injured Lung

Most attempts to guide the setting of mechanical ventilation have focused on the pressure-volume behavior of the lungs, taking a purely static view of the situation [20]. Recruitment and derecruitment (R/D) of lung units tends to be markedly increased above normal levels in ARDS, which can have a dramatic effect on the lung's pressure-volume (PV) behavior [42]. The classic notion about the shapes of these curves is that the lower inflection point on the inspiratory limb marks the end of most recruitment as lung volume increases, while the upper inflection point represents the point at which strain stiffening of the lung tissue starts to dominate. Accordingly, it was reasoned that PEEP and V_t should be chosen to keep volume between these two inspiratory inflection points. However, it is known that recruitment in the injured lung continues progressively throughout the breath even up to pressures corresponding to total lung capacity [43], and a simple computational model of the

lung incorporating both nonlinear tissue elastance and progressive recruitment clearly demonstrates that these two phenomena together conspire to produce inflection points having little physiological relevance for mechanical ventilation [44]. Recently, we fit a combined inflation-recruitment model to PV curves from mice with VILI and were again able to recover evidence from these fits indicating that R/D takes place over an extended range of V that may encompass the entire vital capacity range in severe injury [42]. Chiew et al. [45] formalized this notion in a simple model of the lung that assumes a Gaussian distribution of R/D pressures, and demonstrated that these distributions change as ARDS develops in pigs in a way that could be useful for directing patient-specific approaches to mechanical ventilation.

A key dimension missing from most modeling studies of the PV curve in ARDS is the fact that R/D depends on time as well as pressure. The importance of time in R/D is clearly evident from the progressive increases in lung elastance occurring over periods of minutes that can be observed following a recruitment maneuver [6, 15, 16, 46]. These increases are even observed in a normal lung, albeit to a modest level, but in the injured lung these transient changes in elastance can far exceed its baseline value, indicative of a progressive derecruitment of most of the lung tissue [6, 46]. Taking the temporal dynamics of R/D into account is crucial when considering how to ventilate the injured lung because it offers the possibility that the optimal strategy may not be a fixed ventilation pattern, but rather may be a pattern that varies in time. The rapidity with which the lung derecruits after a recruitment maneuver is also strongly influenced by the nature and degree of lung injury [15]. In cases where derecruitment is relatively slow, an occasional recruitment maneuver may well be efficacious, but if derecruitment occurs rapidly then it may be necessary to apply recruitment maneuvers so frequently that they themselves become injurious [47].

At the scale of the whole lung, Bates and Irvin [48] offered a semi-empirical computational model of the lung to account for the dynamics of recruitment and derecruitment in which the lung is composed of a large collection of parallel lung alveolar units (Fig. 1A). Each unit is served by an airway capable of transitioning between two states, either open or closed. The dynamics of this transition are governed by a virtual trajectory parameterized by a variable, x , having a value between 0 and 1 (Fig. 1B). If the pressure applied to the airway is greater than some designated critical opening pressure, P_o , then x increases. Conversely, x decreases if pressure falls below a critical closing pressure P_c . The rate at which x either increases or decreases is proportional to the amount by which pressure either exceeds P_o or is less than P_c , respectively, with constants of proportionality s_o and s_c , respectively (Fig. 1B). Finally, if an airway is closed and its value of x reaches 1, then the airway will open immediately, and conversely the airway will close if it is open and x reaches 0. The dynamic behavior of the entire model is thus determined by the distribution functions used to assign values of P_o , P_c , s_o and s_c to the various airways in the model. This model can be fit to the changes in lung elastance that occur over time following a recruitment maneuver performed at various levels of PEEP (Fig. 2) [49]. Distributions of P_o , P_c , s_o and s_c recovered in this way have suggested that the primary biophysical abnormality responsible for the increased derecruitability of the lungs following injury with hydrochloric acid is an increase in surface tension, presumably due to a derangement in the function of pulmonary surfactant caused by

leakage of plasma fluid and proteins in the airspaces. The model has also shown that the distributions of P_o , P_c , s_o and s_c change systematically as injury worsens [49], and that saline lavage injury leads to different distributions when compared to those of acid injury [46, 49].

Modeling the Development of VILI

Volutrauma arises from ventilation at high lung volumes, while atelectrauma is associated with events that occur at low lung volumes, so VILI can be produced experimentally in animals by ventilating them for extended periods of time using large V_t and low PEEP [17, 42]. This produces the kinds of severe alveolar plasma protein leak and deranged lung mechanics typical of that seen in human patients, and can be studied using invasive methodologies, such as *in vivo* microscopy, in which the sub-pleural alveoli are visualized while an animal is being ventilated. Alveoli become mechanically unstable in experimental VILI, readily collapsing or filling with fluid at the end of exhalation [46, 50].

Volutrauma and atelectrauma may also act synergistically, producing a gradual worsening of lung derecruitability [17]. The rate at which VILI develops is titratable in mice through choice of tidal volume, and has been modeled computationally using the method of virtual trajectories coupled with the assumption that alveolar leak is related to the magnitude of the strains applied to the lung tissues, predicting the accelerating increases in VILI seen experimentally [51].

Conclusions

Computational models of the biophysical events involved in the development of VILI and its physiological phenotype have been developed by a relatively small number of groups over the past couple of decades. So far, these models have remained at the level of purely scientific investigation, encapsulating our growing quantitative understanding of the how the stresses and strains of mechanical ventilation produce damage to the lung tissues. We predict a change in practice, however, that may be rapidly approaching, in which such models will form the basis for approaches to clinical management seeking to minimize the injurious effects of mechanical ventilation. The advent of computer-controlled closed-loop mechanical ventilators that can readily adapt to changing patient mechanics make this development all the more clinically feasible today. Such approaches have the potential to be targeted specifically to individual patients on the basis of their unique and often changing physiological characteristics, thereby allowing evidence-based medicine to move into the domain of personalized therapy.

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References

1. Matthay MA, et al. Ventilator-induced lung injury: in vivo and in vitro mechanisms. *Am J Physiol Lung Cell Mol Physiol*. 2002; 283(4):L678–L682. [PubMed: 12225942]

2. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000; 342(18): 1334–1349. [PubMed: 10793167]
3. Rubenfeld GD, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005; 353(16): 1685–1693. [PubMed: 16236739]
4. Pavone LA, et al. Injurious mechanical ventilation in the normal lung causes a progressive pathologic change in dynamic alveolar mechanics. *Crit Care*. 2007; 11(3):R64. [PubMed: 17565688]
5. Allen GB, et al. Neither fibrin nor plasminogen activator inhibitor-1 deficiency protects lung function in a mouse model of acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2009; 296(3):L277–L285. [PubMed: 19060228]
6. Allen GB, et al. The response to recruitment worsens with progression of lung injury and fibrin accumulation in a mouse model of acid aspiration. *Am J Physiol Lung Cell Mol Physiol*. 2007; 292(6):L1580–L1589. [PubMed: 17351059]
7. Seeger W, et al. Alteration of surfactant function due to protein leakage: special interaction with fibrin monomer. *J. Appl. Physiol*. 1985; 58:326–338. [PubMed: 3838543]
8. Warriner HE, et al. A concentration-dependent mechanism by which serum albumin inactivates replacement lung surfactants. *Biophys J*. 2002; 82(2):835–842. [PubMed: 11806925]
9. Holm BA, Wang Z, Notter RH. Multiple mechanisms of lung surfactant inhibition. *Pediatr Res*. 1999; 46(1):85–93. [PubMed: 10400140]
10. Amato MB, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998; 338(6):347–354. [PubMed: 9449727]
11. ARDS-Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000; 342(18):1301–1308. [PubMed: 10793162]
12. Frank JA, et al. Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs. *Am J Respir Crit Care Med*. 2002; 165(2):242–249. [PubMed: 11790662]
13. Dos Santos CC, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol*. 2000; 89(4):1645–1655. [PubMed: 11007607]
14. Meade MO, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *Jama*. 2008; 299(6):637–645. [PubMed: 18270352]
15. Allen G, Bates JH. Dynamic mechanical consequences of deep inflation in mice depend on type and degree of lung injury. *J Appl Physiol*. 2004; 96(1):293–300. [PubMed: 12949024]
16. Allen G, et al. Transient mechanical benefits of a deep inflation in the injured mouse lung. *J Appl Physiol*. 2002; 93(5):1709–1715. [PubMed: 12381758]
17. Seah AS, et al. Quantifying the roles of tidal volume and PEEP in the pathogenesis of ventilator-induced lung injury. *Ann Biomed Eng*. 2011; 39(5):1505–1516. [PubMed: 21203845]
18. Bilek AM, Dee KC, Gaver DP III. Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. *J. Appl. Physiol*. 2003; 94:770–783. [PubMed: 12433851]
19. Kay SS, et al. Pressure gradient, not exposure duration, determines the extent of epithelial cell damage in a model of pulmonary airway reopening. *J. Appl. Physiol*. 2004; 97:269–276. [PubMed: 15004001]
20. Ranieri VM, et al. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology*. 2000; 93(5):1320–1328. [PubMed: 11046222]
21. Imai Y, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA : the journal of the American Medical Association*. 2003; 289(16):2104–2112. [PubMed: 12709468]
22. Tremblay LN, Slutsky AS. Ventilator-induced injury: from barotrauma to biotrauma. *Proc Assoc Am Physicians*. 1998; 110(6):482–488. [PubMed: 9824530]
23. Goerke J. Pulmonary surfactant: functions and molecular composition. *Biochim. Biophys. Acta*. 1998; 1408:79–89. [PubMed: 9813251]

24. Bachofen H, Schurch S. Alveolar surface forces and lung architecture. *Comp. Biochem. Physiol.* 2001; 129(1):183–193.
25. Baoukina S, et al. The molecular mechanism of monolayer-bilayer transformations of lung surfactant from molecular dynamics simulations. *Biophys J.* 2007; 93(11):3775–3782. [PubMed: 17704166]
26. Duncan SL, Larson RG. Folding of lipid monolayers containing lung surfactant proteins SP-B(1–25) and SP-C studied via coarse-grained molecular dynamics simulations. *Biochim Biophys Acta.* 2010; 1798(9):1632–1650. [PubMed: 20435014]
27. Taesch HW, Keough KMW. Inactivation of pulmonary surfactant and the treatment of acute lung injuries. *Pediatr. Pathol. Mol. Med.* 2001; 20:519–536. [PubMed: 11699577]
28. Gaver DP III, Samsel RW, Solway J. Effects of surface tension and viscosity on airway reopening. *J. Appl. Physiol.* 1990; 69:74–85. [PubMed: 2394665]
29. Ghadiali SN, Gaver DP III. An Investigation of Pulmonary Surfactant Physicochemical Behavior under Airway Reopening Conditions. *J. Appl. Physiol.* 2000; 88:493–506. [PubMed: 10658016]
30. Pillert JE, Gaver DP III. Physicochemical Effects Enhance Surfactant Transport in Pulsatile Motion of a Semi-Infinite Bubble. *Biophysical Journal.* 2009; 96:312–327. [PubMed: 18849416]
31. Glindmeyer HW IV, Smith BJ, Gaver DP III. In Situ Enhancement of Pulmonary Surfactant Function Using Temporary Flow Reversal. *J. Appl. Physiol.* 2012; 112(1):149–158. [PubMed: 21998268]
32. Smith BJ, et al. Lagrangian transport properties of pulmonary interfacial flows. *J Fluid Mech.* 2011; 705:234–257. [PubMed: 23049141]
33. Reinelt DA, Saffman PG. The penetration of a finger into a viscous fluid in a channel and tube. *SIAM J. Sci. Stat. Comput.* 1985; 6(3):542.
34. Shen EI, Udell KS. A Finite Element study of low Reynolds number two-phase flow in cylindrical tubes. *ASME J. Appl. Mech.* 1985; 52:253–256.
35. Ghadiali SN, Gaver DP III. The influence of non-equilibrium surfactant dynamics on the flow of a semi-infinite bubble in a rigid cylindrical capillary tube. *J. Fluid Mech.* 2003; 478:165–196.
36. Naire S, Jensen OE. Epithelial cell deformation during surfactant-mediated airway reopening: a theoretical model. *J. Appl. Physiol.* 2005; 99(2):458–471. [PubMed: 15802368]
37. Halpern D, Gaver DP. The influence of surfactant on the propagation of a semi-infinite bubble through a liquid-filled compliant channel. *Journal of Fluid Mechanics.* 2012; 698:125–159. [PubMed: 22997476]
38. Stebe KJ, Barthes-Biesel D. Marangoni Effects of Adsorption-Desorption Controlled Surfactants on the Leading Edge of an Infinitely Long Bubble in a Capillary. *J. Fluid Mech.* 1995; 286(25–48)
39. Zimmer ME, Williams HAR, Gaver DP III. The pulsatile motion of a semi-infinite bubble in a channel: flow fields, and transport of an inactive surface-associated contaminant. *J. Fluid Mech.* 2005; 537:1–33.
40. Smith BJ, Gaver DP III. The pulsatile propagation of a finger of air within a fluid-occluded cylindrical tube. *J. Fluid Mech.* 2008; 601:1–23. [PubMed: 19081756]
41. Amin SD, Suki B. Could dynamic ventilation waveforms bring about a paradigm shift in mechanical ventilation? *Journal of Applied Physiology.* 2012; 112(3):333–334. [PubMed: 22134688]
42. Smith B, Bates JHT. Assessing the Progression of Ventilator-Induced Lung Injury in Mice. *IEEE transactions on bio-medical engineering.* 2013
43. Albaiceta GM, et al. Tomographic study of the inflection points of the pressure-volume curve in acute lung injury. *Am J Respir Crit Care Med.* 2004; 170(10):1066–1072. [PubMed: 15317670]
44. Hickling KG. The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med.* 1998; 158(1):194–202. [PubMed: 9655729]
45. Chiew YS, et al. Physiological relevance and performance of a minimal lung model: an experimental study in healthy and acute respiratory distress syndrome model piglets. *BMC pulmonary medicine.* 2012; 12:59. [PubMed: 22999004]
46. Albert SP, et al. The Role of Time and Pressure on Alveolar Recruitment. *J Appl Physiol.* 2008; 106:757–765. [PubMed: 19074576]

47. Allen GB, et al. Choosing the frequency of deep inflation in mice: balancing recruitment against ventilator-induced lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2006; 291(4):L710–L717. [PubMed: 16698851]
48. Bates JH, Irvin CG. Time dependence of recruitment and derecruitment in the lung: a theoretical model. *J Appl Physiol*. 2002; 93(2):705–713. [PubMed: 12133882]
49. Massa CB, Allen GB, Bates JH. Modeling the dynamics of recruitment and derecruitment in mice with acute lung injury. *J Appl Physiol*. 2008; 105(6):1813–1821. [PubMed: 18948446]
50. Allen GB, et al. Pulmonary impedance and alveolar instability during injurious ventilation in rats. *J Appl Physiol*. 2005; 99(2):723–730. [PubMed: 15831795]
51. Smith BJ, Grant KA, Bates JH. Linking the development of ventilator-induced injury to mechanical function in the lung. *Ann Biomed Eng*. 2013; 41(3):527–536. [PubMed: 23161164]

Figure 2.

Fit of computational model shown in Fig. 1 to derecruitability data of lung Elastance versus time obtained in both normal (saline treated) and injured (acid treated) mice. Injured worsened with duration after administration of acid. Reproduced with permission from [49].

Figure 3.

Time courses of lung lung stiffness (Elastance) during sequences of derecruitability tests in mice ventilated at PEEP = 0 with tidal volumes (V_t) varying from 1.0 to 1.3 ml. As injury develops, the starting level of Elastance and its rate of subsequent increase both increase in an accelerating manner. Reproduced with permission from [51].