

Do airway secretions play an underappreciated role in acute respiratory distress syndrome?

Jerónimo Graf and John J. Marini

University of Minnesota, Minneapolis/St Paul, Minnesota, USA

Correspondence to John J. Marini, MD, Professor of Medicine, Regions Hospital, Pulmonary/Critical Care, MS-11203B, 640 Jackson Street, St Paul, MN 55101, USA
Tel: +1 651 254 3411; fax: +1 651 254 3098;
e-mail: john.j.marini@healthpartners.com

Current Opinion in Critical Care 2008, 14:44–49

Purpose of review

We review the evidence that airway secretions may have an underappreciated role in acute respiratory distress syndrome, contributing to physiologic disarrangements, ventilator dependence and perhaps to injury generation. As common manipulations of ventilator settings, position and fluid status have the potential to influence these problems, explorations into the secretion dynamics of acute lung injury may be fertile ground for developing therapeutic advances.

Recent findings

Principles that govern the interaction of airflow and airway fluids suggest that mobile fluids and secretions are pumped by well-selected ventilatory patterns toward the airway opening. Conversely, other selections may inhibit these fluids from clearance or encourage their translocation between lung regions. Recent laboratory work demonstrates that choices for tidal volume and positive end-expiratory pressure may localize or disperse proteinaceous lung edema or bacteria. Gravitational factors may interact with ventilatory pattern for benefit or harm.

Summary

Capability of ventilation and positioning to mobilize secretions implies the potential for clearance or containment of inflammatory mediators and infection. Ventilatory and positional prescriptions could be designed to meet one of either conflicting targets. Additional experimental and clinical investigations are required before adopting these proposed therapeutic principles into practice.

Keywords

acute respiratory distress syndrome, clearance of airway secretions, lung protective ventilation, mechanical ventilation, pneumonia

Curr Opin Crit Care 14:44–49
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1070-5295

Introduction

Retention of airway secretions is generally viewed as a problem that assumes primary importance in those with overt clearance problems due to underlying airway disorders (such as cystic fibrosis or chronic obstructive pulmonary disease) and those with profound neuromuscular weakness. Yet, airway secretions may have more fundamental importance than recognized in acute respiratory distress syndrome (ARDS) as well by contributing to physiologic disarrangements, ventilator dependence and perhaps to injury generation.

ARDS is fundamentally a parenchymal disorder, initiated by lung edema that forms as a consequence of inflammation-induced permeability at the alveolar endothelial and epithelial levels. Resulting alveolar flooding and collapse manifests as hypoxemia, radiographic opacities and reduced respiratory system compliance [1]. The key disease recognition features of hypoxemia, infiltrates and

lung volume loss are not necessarily tied to alveolar pathology, but may be generated or perpetuated by hidden problems of the airways, especially when secretion-related occlusion or narrowing of the airways encourages secondary resorption atelectasis [2].

Airspaces within the acutely injured lung contain proteinaceous edema fluids and inflammatory debris. During mechanical ventilation these materials will be subjected to the pressure differences that determine how airflow and lung volume shift during the respiratory cycle. Theoretically, such forces can move these materials towards the airway opening or toward the alveoli. These forces cycle tidally in both directions, with the potential to transport inflammatory products from one region of the lung to another. Other factors, specifically gravity, airway geometry, fluid rheological properties and quantities, as well as regional lung mechanics (local airway resistance and compliance) interact to influence the net movement of secretions.

Relatively little attention has been accorded this topic in the literature or in daily practice. Our purpose is to review how such mechanisms could contribute to either containment or propagation of lung injury as well as influence clearance of mucus in mechanically ventilated patients with ARDS. Although hardly conclusive, these theoretical and experimental observations provide sufficient basis for concern to suggest avenues for research with potential clinical applications for prevention and treatment of this syndrome.

Theory and experimental base

Pathological descriptions of ARDS often address events within the alveoli and preterminal bronchioles, but rarely consider more proximal airways. Yet, bronchiolar overdistention in areas of consolidation [3] and diffuse epithelial desquamative injury, with local release of inflammatory mediators in intrapulmonary bronchi and terminal bronchioles [4], has been noted in animal models of bronchopneumonia or surfactant depletion subjected to injurious mechanical ventilation.

Pneumonia and aspiration are among the most common precipitants for ARDS [5], suggesting that the inflammatory insult initially affects the lung from its epithelial side, with alveolar exposure to noxious products gaining access via the airways. As opposed to this 'primary' injury, indirect or secondary ARDS develops as inflammatory mediators are carried through the bloodstream to the lungs, causing alveolar endothelial damage [6]. It is conceivable that airways exposed to the mediator-rich bloodstream could be affected in a similar fashion, although this has not been proven. Whether primary or secondary, there is little reason to think that the bronchial tree is spared the inflammation that afflicts the gas-exchanging membrane. Once formed, airway secretions may be difficult to clear.

Even in centers highly experienced with noninvasive respiratory support, more than 83% of the patients with ARDS ultimately require endotracheal intubation and invasive mechanical ventilation [7]. Both interventions favor the retention of airway secretions, as mucociliary transport is depressed [8] and cough effectiveness is impaired. Seepage of oropharyngeal [9] contents through the imperfect cuff seal of the endotracheal tube seeds the bronchial tree with infective inoculums and may eventually lead to ventilator-associated pneumonia [10].

Two-phase gas-liquid flow mechanism

The interaction of airflow with liquid-lined surfaces has been studied in an engineering context under the topic heading of 'two-phase gas-liquid flow'. Key principles from this field were first applied to an airway model by

Clarke *et al.* [11]. Air flowing over a liquid layer develops a shear force on its surface proportional to the square of airflow velocity [12]. If this velocity is high enough, the resulting shear force can overcome viscous, frictional or gravitational resistance, so that the liquid layer will be propelled in the direction of airflow. Initially, it was thought that such a mechanism would operate only during coughing, where extremely high airflow velocities are generated in the central airways. Nevertheless, Blake [13] theoretically suggested, and then Kim *et al.* [14] experimentally demonstrated in a vertical airway model lined by viscous fluids with continuous upward airflow, that this mechanism might also be responsible for mucus transport during tidal breathing (even up to the 10th generation of airways) if sufficient liquid thickness (3–15% of the tube diameter) is present. Airflow-driven liquid transport may be possible even in peripheral airways because critical Reynolds number and threshold liquid layer thickness for linear movement of liquid decrease with smaller airway diameter [14]. Factors such as tube dimensions, depth of the liquid layer and its rheologic properties interact with airflow velocity to generate movement by the two-phase gas-liquid flow mechanism [11,12,14].

Airflow in the airways is, however, not continuous but bidirectional – it periodically and repetitively reverses. Warwick [15] postulated that an appropriate differential airflow velocity would encourage a net mucus flow towards the throat and that during mechanical ventilation airflows could be manipulated to pump mucus out of the lungs. Kim *et al.* [16•] studied the movement of viscous fluids subjected to periodic asymmetric reversible airflow on an airway model. They found that, when inspiratory and expiratory airflows differed by more than 10%, the liquid layer transport speed was governed by the absolute value of the higher airflow rather than by the difference between opposite airflow rates.

Applying these principles in mechanically ventilated sheep, the same group documented that an inverse inspiratory to expiratory time ratio that generated higher expiratory than inspiratory airflows promoted outward transport of a mucus simulant injected onto the main stem bronchi. Using an inspiratory to expiratory ratio of 1:2.7, however, none of the injected mucus was externally collectable [17•]. A similar effect was achieved when the expiratory airflow bias was generated by asymmetric high-frequency oscillation applied to the airway opening in mechanically ventilated sheep [18].

Among the several important rheologic properties of airway fluids, viscosity is perhaps the most germane to two-phase gas-liquid flow transport. In the aforementioned tube model of the airway, Kim *et al.* [14,19] showed that smaller amounts of low viscosity fluids will

move more easily than highly viscous ones if provided a sufficiently high airflow. On the other hand, if there is a sufficient amount of high-viscosity fluid, relatively *slower* airflows will move it, albeit at a low rate [14,19]. In other words, movement of low-viscosity fluids along a horizontal plane depends primarily on airflow velocity, while movement of highly viscous fluids is more dependent on their depth or amount. In the later instance, even relatively slow airflows may succeed in mobilizing the mucus if the depth and quantity are great enough in relation to tube diameter.

Effect of gravity

Depending on the spatial orientation of the airways, gravity may act in conjunction with or against a tidally cyclical airflow bias in moving secretions through the bronchial tree. At the lobar level, the spiraling array of segmental openings ensures that at any given position some feeder channels are less gravitationally dependent than others, whatever the orientation of the lung might be [20]. Even in the horizontally positioned lung, some airways will have opposing orientations. If we consider that a patient can be positioned with the head up or down at different inclinations or laterally with different angles, and either supine or prone, the best orientation for clearance may be difficult to specify.

The in-vitro experiments of two-phase gas–liquid transport by Kim *et al.* [14,16,19] were done in vertical tubes with an upward airflow. As already mentioned, they were able to show movement of viscous fluids against gravity with airflows within the tidal ventilation range, provided a critical depth was maintained by continuous infusion of the liquid. Directional migration also occurred in the asymmetric periodic flow model when the upward (expiratory) flow exceeded the downward (inspiratory) flow by 10% or more. It seems possible then that airflow-driven movement may overcome gravitationally dependant distribution of liquids in the airways. Airflow can also act synergistically with gravitation in terms of airway liquid displacement. When mucus simulant was injected in the main bronchi of mechanically ventilated sheep, the amount of mucus collected at the airway opening was more than doubled when an expiratory airflow bias (by asymmetric high frequency oscillation) and positioning (with a 15° head-down tilt) were used together, as compared to each intervention by itself [18].

The importance of position-aided clearance of secretions is illustrated by the findings of Panigada *et al.* [21]. In healthy sheep mechanically ventilated for up to 72 h, they showed that when the trachea was horizontally positioned secretions drained spontaneously without the need for airway suctioning. Moreover, the bacterial colonization of the tracheobronchial tree and lung parenchyma was

not different from nonintubated healthy sheep. In contrast, sheep ventilated with a 30° upward orientation of the trachea developed heavy airway colonization and impairment of gas exchange [21].

In ARDS, gravity may have additional indirect effects on airway secretions through its modifications of regional mechanics. As dependent regions collapse or flood, tidal volume redistributes to the nondependent regions of the lung [1,4]. These regions then become more susceptible to airflow driven retention or elimination of secretions.

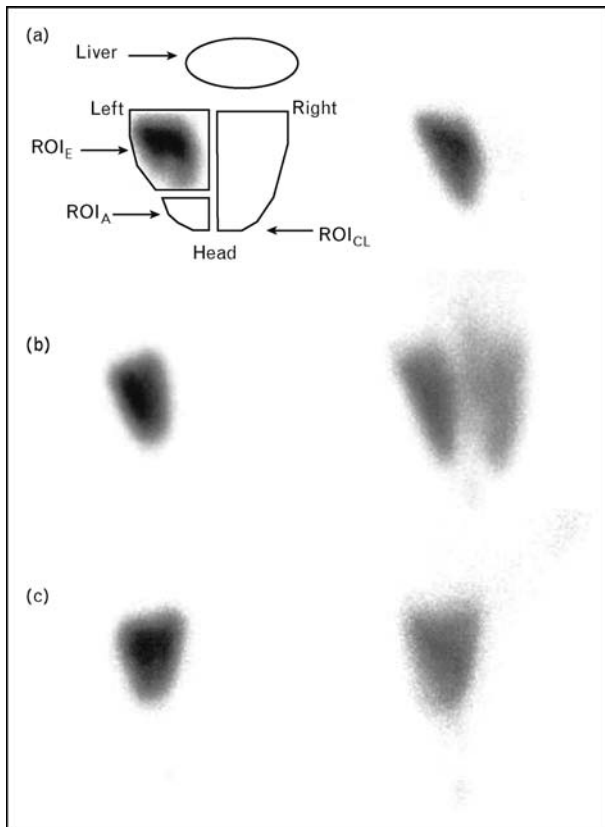
Airway dissemination of fluid

The lung injury of ARDS, although widely distributed, is currently accepted to be heterogeneous. These injured lungs are comprised of some morphologically and functionally affected alveolar units alongside other units with better preserved structure and function, as assessed by compliance and gas-exchange properties. This aeratable volume is known as the ‘baby lung’ [22]. Although also nonhomogeneous and function-impairing, lobar pneumonia is by definition a pathological entity that can be geographically identified along anatomical boundaries [3,23].

If airflow and gravity can propel fluids within the airways, it should be possible for noxious biofluids, formed peripherally and rich with inflammatory mediators or bacteria, to migrate from injured to healthy lung sectors through the airways, as the lung is a segmented structure, organized as parallel compartments connected by a branching common corridor. The potential for such propagation to occur has been strongly suggested by a growing body of experimental work. For example, using a two-compartment test lung system, Volpe *et al.* [24] demonstrated transfer of mucus simulant across a carinal division from the low-compliant (‘diseased’) to the high-compliant (‘healthy’) chamber, propelled by regional airflow biases.

Very recently the potential for adverse ventilatory patterns to transfer localized radiolabeled proteinaceous alveolar edema to the opposite lung was elegantly shown in a rat model by de Prost *et al.* [25]. As shown in Fig. 1, labeled albumin dispersed within the injected lung and into the opposite lung shortly after large tidal volumes were administered without positive end-expiratory pressure (PEEP). In contrast, the tracer remained confined to the injected lung without detectable spreading during spontaneous breathing and when PEEP was used with a range of different tidal volumes during passive inflation [25]. In a prior study, these investigators showed that when ventilating from zero end-expiratory pressure (ZEEP), dispersion of the tracer could be observed when tidal volume was large enough to produce a plateau pressure above 20–25 cmH₂O [26].

Figure 1 Effect of mechanical ventilator settings on intrapulmonary dispersion of proteinaceous edema fluid



The left panels are examples of scintigraphy images integrating the 15 min following instillation of ^{99m}Tc -labeled albumin solution into one lung while rats were ventilated with a tidal volume of 8 ml/kg and positive end-expiratory pressure (PEEP) of 2 cmH₂O. The right panels are examples of scintigraphy images integrating the last 15 min of the experiment, after 165 min of ventilation with one of three different settings. In (a) the rat continued to be ventilated with a tidal volume of 8 ml/kg and PEEP of 2 cmH₂O; the tracer remained confined to the initial zone. In (b) after ventilation with a tidal volume of 29 ml/kg and zero end-expiratory pressure, homo- and contralateral dispersion of the tracer is evident. In (c) ventilation with a tidal volume of 24 ml/kg and PEEP of 6 cmH₂O averted dispersion of the tracer. ROI, region of interest. Reproduced from [25**].

The same group was able to demonstrate the influence of different ventilatory strategies on contralateral contamination with bacteria from a well developed unilateral pneumonia in rats [27**]. None of the spontaneously breathing control animals developed contralateral contamination. Among the mechanically ventilated rats, those ventilated with low tidal volumes and PEEP were less likely to experience cross-contamination. Interestingly, when the same 'protective' ventilatory strategy (with PEEP and low tidal volume) was applied in the lateral decubitus position with the 'good' (noninoculated) lung down, cross-contamination rates were comparable to those of rats ventilated from ZEEP [27**].

The explanation for high tidal volume-mediated dissemination of airway contents is likely to relate to the

associated high inspiratory and expiratory flows. Faster *inspiratory* peak flows favor secretion transport toward the alveoli; faster *expiratory* peak flows – produced by passive end-inspiratory recoil forces and muscular effort – favor clearance. When regional compliances are different, such as in pneumonia or ARDS, inspiratory gas will flow more quickly into the more compliant regions, propelling airway fluids towards these healthy compartments. On the other hand, although the proportion of the tidal volume distributed in the diseased regions will be less, lower compliance could contribute to increase local peak expiratory flows [28] with an associated higher tendency to translocate airway fluids mouthward.

While larger tidal volume should favor expulsion, the protective effect of PEEP on limiting airway dissemination appears to be even more important than tidal volume limitation. Although the mechanism for its benefit is less straightforward, a likely possibility is that PEEP expands the local reservoir capacity and favors interstitial storage of sieved alveolar liquid. PEEP thereby helps to maintain proteinaceous and surfactant-inhibiting fluid marginalized [29] and out of the conduits that link airspaces. Whatever the mechanism, it is worth noting that the protective effects of low tidal volume and higher PEEP may not be sufficient to contain bacteria in the infected side when a gravitationally disadvantageous lateral position is assumed [27**].

In both aforementioned rat experiments [25**,27**] spontaneous breathing helped prevent airway propagation. This observation is in agreement with the work by Charles *et al.* [30], who demonstrated more widespread distribution of pathogens in mechanically ventilated rabbits challenged endobronchially with bacterial inoculums identical to their spontaneously breathing counterparts. The extent to which these findings can be attributed to tracheal instrumentation or to differences in size or distribution of tidal volume is unknown.

Implications for mechanical ventilation settings and positioning

Considering these arguments concerning liquid movement in the airways, it is possible to design a rational, but clearly hypothetical, ventilating and positioning strategy that would depend on the stage of ARDS or pneumonia; the ability of mechanical ventilation to drive secretions mouthwards or towards the alveolar level may have different implications over time.

Vigorous fluid repletion, an almost universal therapy of hypotensive conditions such as sepsis and pneumonia [31], aids in forming secretions even when alveolar capillary pressures remain normal [32]. Relatively high tidal volumes may aid in translocating these thin, mobile fluids

to previously unaffected areas where infectious colonies may seed healthy tissue.

In the initial stages of ARDS, when low-viscosity edema fluid is present, the objective may be to avoid spreading of proteinaceous fluid with the potential to inactivate preformed surfactant [33] rendering the affected airspaces more prone to collapse. Preventing such transfer of noxious fluids to healthy lung units should help to preserve gas exchange and to limit the injury process. Such containment is consistent with the current protective ventilation strategies involving low tidal volumes and adequate PEEP. The use of decelerating flow patterns, inherent to pressure control ventilation, may also help to sustain higher peak inspiratory than expiratory flows that keep fluids from proximal displacement. Such a mechanism provides a complementary explanation for the positive results of trials involving important reductions of tidal volumes and the use of PEEP in ARDS [34,35].

When pneumonia is the cause of respiratory failure that requires invasive ventilatory support the same rationale may be applied, but the gravitational factor should be considered. There is credible evidence that from a gas-exchange perspective the most affected lung should be nondependently placed [36]. Nonetheless, from an infectious containment point of view, the opposite may be true [27^{••}]. If intra-airway propagation is a genuine hazard, timing of the ventilatory prescription and positioning may be of under-recognized importance; ARDS progresses from an edematous to an organizing phase, or in the case of pneumonia, leukocyte influx and fibrinaceous exudates congeal airway fluids over a few days.

Once the lung injury is stabilized by resolution of the precipitating factor, clearance of viscous airway secretions (rather than containment) may become the priority. In this context, a strategy involving the use of higher tidal volumes, longer inspiratory times (lower inspiratory flow), lower PEEP and placing the most affected lung region in nondependent orientation may be tolerated to aid unlogging the airways and clearing inflammatory debris.

Conclusion

Existing experimental data suggest that choices for mechanical ventilation settings and positioning may drive airway contents towards the airway opening, towards the alveoli or between different lung regions. This capability implies a largely untapped potential for aiding secretion clearance, as well as for containing rather than dispersing inflammatory mediators and infection. Depending on the stage of ARDS or pneumonia, ventilatory and positional prescriptions could be designed to meet one of these targets. Additional experimental and clinical investigations are clearly required before adopting these

therapeutic principles into daily practice, however intriguing and plausible they may appear to be.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 106–107).

- 1 Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. *Lancet* 2007; 369:1553–1564.
- 2 Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology* 2005; 102:838–854.
- 3 Goldstein I, Bughalo MT, Marquette CH, *et al.* Mechanical ventilation-induced air-space enlargement during experimental pneumonia in piglets. *Am J Respir Crit Care Med* 2001; 163:958–964.
- 4 Tsuchida S, Engelberts D, Peltekova V, *et al.* Atelectasis causes alveolar injury in nonatelectatic lung regions. *Am J Respir Crit Care Med* 2006; 174:279–289.
- 5 Rubenfeld GD, Caldwell E, Peabody E, *et al.* Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353:1685–1693.
- 6 Pelosi P, D'Onofrio D, Chiumello D, *et al.* Pulmonary and extrapulmonary acute respiratory distress syndrome are different. *Eur Respir J Suppl* 2003; 42:48s–56s.
- 7 Antonelli M, Conti G, Esquinas A, *et al.* A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med* 2007; 35:18–25.
- 8 Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M. Mucociliary transport in ICU patients. *Chest* 1994; 105:237–241.
- 9 Van Uffelen R, Van Saene HK, Fidler V, Lowenberg A. Oropharyngeal flora as a source of bacteria colonizing the lower airways in patients on artificial ventilation. *Intensive Care Med* 1984; 10:233–237.
- 10 Markowicz P, Wolff M, Djedaini K, *et al.* Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. *Am J Respir Crit Care Med* 2000; 161:1942–1948.
- 11 Clarke SW, Jones JG, Oliver DR. Resistance to two-phase gas–liquid flow in airways. *J Appl Physiol* 1970; 29:464–471.
- 12 Wallis GB. One-dimensional two-phase flow. New York: McGraw-Hill; 1969.
- 13 Blake J. On the movement of mucus in the lung. *J Biomech* 1975; 8:179–190.
- 14 Kim CS, Rodriguez CR, Eldridge MA, Sackner MA. Criteria for mucus transport in the airways by two-phase gas–liquid flow mechanism. *J Appl Physiol* 1986; 60:901–907.
- 15 Warwick WJ. Mechanisms of mucus transport. *Eur J Respir Dis* 1983; 64:162–167.
- 16 Kim CS, Iglesias AJ, Sackner MA. Mucus clearance by two-phase gas–liquid flow mechanism: asymmetric periodic flow model. *J Appl Physiol* 1987; 62:959–971.
- This classic experimental study establishes the physical requirements for displacement of viscous fluids in a tube model driven by airflow simulating tidal ventilation.
- 17 Benjamin RG, Chapman GA, Kim CS, Sackner MA. Removal of bronchial secretions by two-phase gas–liquid transport. *Chest* 1989; 95:658–663.
- This in-vivo study confirms previous in-vitro observations suggesting that airflows generated during tidal ventilation can drive the bulk movement of fluid in the airways.
- 18 Freitag L, Long WM, Kim CS, Wanner A. Removal of excessive bronchial secretions by asymmetric high-frequency oscillations. *J Appl Physiol* 1989; 67:614–619.
- 19 Kim CS, Greene MA, Sankaran S, Sackner MA. Mucus transport in the airways by two-phase gas–liquid flow mechanism: continuous flow model. *J Appl Physiol* 1986; 60:908–917.
- 20 Weibel ER, Sapoval B, Filoche M. Design of peripheral airways for efficient gas exchange. *Respir Physiol Neurobiol* 2005; 148:3–21.
- 21 Panigada M, Berra L, Greco G, *et al.* Bacterial colonization of the respiratory tract following tracheal intubation-effect of gravity: an experimental study. *Crit Care Med* 2003; 31:729–737.
- This provocative animal study explores the effect of airway orientation on airway clearance and bacterial colonization. Results call into question current positioning recommendations for mechanically ventilated patients.

- 22** Gattinoni L, Pesenti A. The concept of 'baby lung'. *Intensive Care Med* 2005; 31:776–784.
- 23** Dreyfuss D, Ricard JD. Acute lung injury and bacterial infection. *Clin Chest Med* 2005; 26:105–112.
- 24** Volpe M, Adams A, Marini J. Mucus shifts according to expiratory/inspiratory flow ratio. *Respir Care* 2006; 51:1316.
- 25** De Prost N, Roux D, Dreyfuss D, *et al.* Alveolar edema dispersion and alveolar protein permeability during high volume ventilation: effect of positive end-expiratory pressure. *Intensive Care Med* 2007; 33:711–717.
 •• A pioneering animal study that convincingly demonstrates the effects of mechanical ventilator settings on edema fluid dispersion within the lung, without exploring on its mechanisms. It also addresses the effects of tidal volume and PEEP on lung permeability to albumin.
- 26** De Prost N, Dreyfuss D, Saumon G. Evaluation of two-way protein fluxes across the alveolo-capillary membrane by scintigraphy in rats: effect of lung inflation. *J Appl Physiol* 2007; 102:794–802.
- 27** Schortgen F, Bouadma L, Joly-Guillou ML, *et al.* Infectious and inflammatory dissemination are affected by ventilation strategy in rats with unilateral pneumonia. *Intensive Care Med* 2004; 30:693–701.
 •• A unique study which suggests that ventilatory strategies and position can modify bacterial cross-contamination rates, as well as systemic dissemination and inflammatory response, in unilateral pneumonia.
- 28** Bergman NA. Properties of passive exhalations in anesthetized subjects. *Anesthesiology* 1969; 30:378–387.
- 29** Malo J, Ali J, Wood LD. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol* 1984; 57:1002–1010.
- 30** Charles PE, Piroth L, Desbiolles N, *et al.* New model of ventilator-associated pneumonia in immunocompetent rabbits. *Crit Care Med* 2002; 30:2278–2283.
- 31** Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377.
- 32** Hanly P, Light RB. Plasma volume expansion and PEEP in a canine model of acute *Pseudomonas* pneumonia. *Lung* 1989; 167:285–299.
- 33** Seeger W, Stöhr G, Wolf HR, Neuhof H. Alteration of surfactant function due to protein leakage: special interaction with fibrin monomer. *J Appl Physiol* 1985; 58:326–338.
- 34** The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308.
- 35** Amato MB, Barbas CS, Medeiros DM, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354.
- 36** Hasan FM, Beller TA, Sobonya RE, *et al.* Effect of positive end-expiratory pressure and body position in unilateral lung injury. *J Appl Physiol* 1982; 52:147–154.