### **Perspective on Lung Injury and Recruitment** A Skeptical Look at the Opening and Collapse Story

Rolf D. Hubmayr

Mayo Clinic, Rochester, Minnesota

The last two decades have brought new insights into mechanisms of lung injury. These insights have profoundly altered the ventilator management of patients with adult respiratory distress syndrome (ARDS). As recently as a few years ago, ventilator management focused on maintaining blood gas tensions. The recognition that airways and parenchyma can be injured by physical stress has redirected attention to lung mechanics and to the determinants of tissue damage, remodeling, and repair. Although it is difficult to assess the relative effects of ventilator-induced lung injury (VILI) compared with other disease mechanisms, a wealth of experimental and clinical data indicates that VILI indeed exists and that it contributes to the mortality of patients with ARDS (1-6). Some ventilator parameters, such as large tidal volumes, are firmly established as determinants of VILI. Others, such as low positive endexpiratory pressure (PEEP) or high inspiratory flow, remain controversial (7-12).

In this perspective, I will argue that many controversies about ventilation strategy can be traced to uncertainties in the interpretation of data on regional lung function. I will emphasize the remaining gaps in our understanding of lung deformation at the acinar scale. I will argue that the dependent lung may be derecruited because it is filled with fluid, not because it is collapsed. In particular, I will raise questions about the interpretation of pressure-volume (PV) curves and about the mechanisms by which PEEP may benefit lung function.

### CONVENTIONAL VIEW OF THE REGIONAL MECHANICS OF INJURED LUNGS

The effects of ventilator settings on regional lung function of patients with ARDS have been inferred from analyses of computer tomographic (CT) lung images, respiratory system PV curves, histologic analyses of lung tissue, and indices of pulmonary gas exchange. The pioneering studies by Gattinoni and colleagues (13–16) revealed a topographic heterogeneity in lung injury and reinforced the idea that large portions of an injured lung are derecruited (i.e., they do not get aerated during positive pressure breathing). This important insight formed the basis for the "baby lung" concept, which explains why the lungs of patients with ARDS are less compliant and appear to be particularly prone to injury from overdistension. The same

Am J Respir Crit Care Med Vol 165. pp 1647–1653, 2002 DOI: 10.1164/rccm.2001080-01CP Internet address: www.atsjournals.org group of investigators examined the effects of ventilator settings and posture on the regional distribution of thoracic gas (17, 18) and concluded that dependent portions of the injured lung are exposed to a compressive pressure and are collapsed (13-15). They attributed dependent atelectasis to the increased weight of edematous lung and argued that the goal of PEEP is to counterbalance this superimposed pressure (13, 14, 19). The proposed mechanism appears consistent with the interpretation of whole lung mechanics measurements in patients and in experimental models of ARDS when studied in the supine posture. The PV curve of injured lungs is characterized by a prominent lower inflection point (LIP), a nonlinearity marking a volume-dependent increase in lung inflation compliance (9, 20). The pressure near LIP has been regarded as the critical opening pressure above which most of the collapsed units open up and may be recruited (15, 21, 22).

This interpretation of CT images and PV curves seems to fit well with the experimental evidence, which suggests that the application of PEEP has beneficial effects on gas exchange, lung mechanics, edema formation, and markers of inflammation (23–28). On the basis of this evidence the hypothesis emerged that PEEP prevents the repeated opening and collapse of lung units and thereby protects lung tissue from mechanical injury. It was pointed out that the local stress associated with alveolar recruitment could exceed 100 cm H<sub>2</sub>O if there was heterogeneity in alveolar volumes on an acinar level (29). Interdependence arguments originally put forth by Mead and colleagues dictate that the tissue attachments between large aerated units and neighboring collapsed units carry a stress that is substantially greater than the average transpulmonary pressure (30).

The most direct test of the collapse and shear injury hypothesis was performed by Muscedere and coworkers (26). These investigators demonstrated epithelial lesions in small airways and alveolar ducts if *ex vivo* ventilated unperfused rat lungs were allowed to deflate to pressures below the LIP. The same model was subsequently used to study the consequences of PEEP on inflammatory gene expression and cytokine release (27, 31). The results of this work underscored the importance of preventing lung collapse and helped establish the concept of "biotrauma." Biotrauma is an expansive view of pulmonary mechano-transduction that emphasizes the delicate interplay between tissue deformation, edema, inflammation, and mechanical properties (32).

In summary, the conventional view of VILI is the following. The weight of the lung is increased by edema. As a result, dependent regions of the lung are compressed and collapse. Lung injury is caused by large stresses in the parenchyma surrounding atelectatic regions and the large shear stresses required to reopen collapsed airways and alveoli. This view of the mechanics of edematous lungs provides the rationale for the ventilator setting of PEEP in patients with ARDS.

<sup>(</sup>Received in original form August 23, 2001; accepted in final form March 28, 2002) Supported by National Institutes of Health grants HL 57364 and HL 63178.

Correspondence and requests for reprints should be addressed to Rolf D. Hubmayr, M.D., Room 8-62, Stabile Building, Mayo Clinic, Rochester, MN 55905. E-mail: rhubmayr@mayo.edu

### CRITIQUE AND ALTERNATIVE INTERPRETATION OF OBSERVATIONS ABOUT THE REGIONAL MECHANICS OF INJURED LUNGS

The conventional view of the mechanics of edematous lungs rests on assumptions and interpretations of observations, namely, that (1) lung weight is an important determinant of the topographic distribution of regional volume, (2) the gray scale of pixels in a CT scan reflects the dimensions of alveoli and acini in the region, and (3) alveolar collapse and reopening are the principal mechanisms responsible for abnormal PV curves in patients with ARDS. In the following paragraphs, I will raise questions about each of these assumptions.

## Is Lung Weight an Important Determinant of the Topographic Distribution of Regional Volume?

Research on normal animals conducted in the 1970s and 1980s established that lung weight accounts for no more than 20% of the vertical gradient in pleural pressure and alveolar volume (33–37). In other words, under normal conditions lung weight is only a minor determinant of the topographic distribution of parenchymal stress and strain. This can be appreciated intuitively by noting that gravitational gradients in pressure and volume vary considerably with posture (even though lung weight is more or less the same in all postures).

Before considering whether lung weight plays a greater role in injury states, it might be helpful to review some fundamental continuum mechanics concepts (37, 38). To an engineer, the *in situ* distribution of lung parenchymal pressure and volume is a shape-matching problem between two gravitationally deformed elastic solids: the lungs and the chest wall (including heart and mediastinum). The cartoon in Figure 1 shows a very simple, but nevertheless instructive, shape-matching problem (the fitting of an elastic cone into a rigid cylinder). As long as the elastic solid (the cone) resists a shape change (behaves like a solid rather than like a liquid), its stress distribution will be shape-dependent. Note that the vertical orientation of the stress and strain gradients need not imply a gravitational mechanism. For example, the experiment shown in Figure 1 might well have been conducted in a gravity-free environment.

The mechanics of lung-chest wall interactions are a bit more complex than the example of Figure 1 because both structures are deformable and because the unstressed reference shape of neither structure is known.\* Given the mass of the abdomen and its mechanical coupling to the lung through the diaphragm and rib cage, the weight of the abdomen is a major determinant of thoracic cavity shape and hence of the shape of the lung. Because the lung resists isovolumic deformations (it is not a liquid), its pressure and volume distributions depend on thoracic cavity shape. Similarly, the weight of the heart affects lung shape and the distribution of regional volume (39–41). Thus, in the normal lung, the weight of the boundary structures, i.e., chest wall and mediastinum, is more important than the weight of the lungs themselves (34).

Injured lungs are more likely to maintain their shape after removal from the thorax than normal lungs. This suggests that they are less likely deformed by gravity and are more likely to resist a shape change when they are constrained by a gravitationally deformed thorax (37). To be sure, if the weight of the lung increases, the pleural pressure gradient would be expected to increase, but the relation between lung weight and pleural pressure gradient and the relation between pleural pressure gradient and regional volume are not straightfor-



*Figure 1.* Cartoon of a shape-matching problem between an elastic solid (*cone*) and a rigid cylinder. The shape change (from *cone* to *cylinder*) imposes a nonuniform stress that is not gravitationally determined. Adapted with permission from Reference 62.

ward. Thus, it is worthwhile to examine the CT evidence that is cited in support of the hypothesis that the weight of the lung causes collapse of the dependent regions of the lung.

#### Does a CT Image of the Lung Contain Information About Alveolar Volume and Its Gravitational Distribution?

In the normal lung, the answer to this question is yes. The gray scale of CT scans of normal lungs at total lung capacity are quite uniform, and this is consistent with other evidence that the lung is uniformly expanded at total lung capacity (42, 43). At volumes below total lung capacity, vertical gradients in gray scale are consistent with other data on topographic gradients in regional lung expansion (16). CT data obtained in animals are consistent with data on pleural pressure gradients (44). These gradients are particularly pronounced in the supine posture (36).

In a series of papers, Gattinoni and colleagues showed that in supine patients with ARDS these vertical gradients in gray scale are steeper than they are in normal volunteers (15, 16). Gattinoni and colleagues interpreted this finding as evidence that patients with ARDS had steeper gradients in alveolar size. However, the correlation between gray scale and alveolar size (and hence local tissue stress) holds only if the amount of water per alveolus is uniform. Consider a lung with a vertical gradient in pulmonary edema. In such a lung a vertical gradient in gray scale would at least in part reflect a gradient in water per alveolus. This simple example shows that gradients in gray scale correspond to gradients in regional air but need not imply gradients in tissue expansion or alveolar size.

CT images of the thorax are density maps from which the topographic distribution of air per unit tissue volume may be estimated. However, the images do not define tissue state, and they give no information on tissue extension or strain. Therefore, it is not possible to measure the amplitudes of regional lung expansion during mechanical ventilation. In short, CT provides data on regional air content but not on regional volume or parenchymal strain.

Given the information content of pulmonary CT images, it should also be obvious that recruitment, defined as the aeration of previously airless regions, need not imply the reversal of collapse. Imagine that the region of interest contains a certain number of alveoli that are already expanded with edema fluid instead of air. Adding air may expand them further and lower their mean gray scale, but no inference can be drawn about their final state. Alternatively, adding air will have no effect on the fluid-filled alveoli but will further expand alveoli without fluid. At the scale of CT measurement this will increase

<sup>\*</sup> To do so would require measurements of *ex vivo* lung shape and thoracic cavity shape after lung removal in a gravity-free environment.

the air density but should also decrease the number of fluidfilled alveoli within the region of interest, assuming the area of the region of interest remains constant.

Notwithstanding the uncertainty in the interpretation of gravitational CT gray scale gradients, it should be noted that in some lung injury models, vertical gradients in extravascular lung water were found to be quite small (45). In this context, it has been suggested that the choice of injury model, PEEP, and tidal volume settings may determine the extent to which dependent alveolar edema is redistributed to more nondependent interstitial spaces (46).

## Does the PV Curve Provide Specific Answers About Regional Lung Mechanics and Injury Mechanisms?

Numerous mechanisms have been proposed to explain the change in lung mechanics in the presence of injury and edema. These include increased minimal surface tension caused by surfactant inactivation (47), airway block caused by air–liquid interfaces and bubble formation in small airways (48–50), bronchoconstriction (51, 52), pneumoconstriction (53), and peribronchial edema (49). In a series of classic papers, Hildebrandt emphasized the importance of surfactant film properties as the primary source of stress adaptation and viscoelastic lung behavior (54–57). In other words, recruitment, defined as the addition of previously derecruited or atelectatic lung units, is certainly not the principal mechanism that accounts for the volume and time history of the normal lung.

Because changes in the PV curve cannot a priori be attributed to recruitment as opposed to changes in surface tension of already recruited units, does the shape of the inflation curve with its prominent LIP imply a unique mechanism? The answer is probably no. It is certainly true that expanding a lung from a degassed state initially meets with a large impedance, but so is the case with inflation of an edematous lung in which all units are open (58–61). This can be easily demonstrated at the bench when one inflates a saline-filled lobe with air (Figure 2, reproduced from Reference 62). The very compliant part of the PV curve above the LIP is reminiscent of the behavior of lungs that were rinsed with fluids of fixed surface tension (63-65). That behavior has been modeled successfully (58). These properties are the result of a transition from fluid-filled alveoli to air-filled alveoli with constant surface tension. The alveolar tissue is fully opened during this transition. This explanation for the knee of the PV curve is quite different from



*Figure 2.* Pressure–volume curves of a canine caudal lobe containing air only, saline only, and a air-saline mixture. Note the high initial impedance when air is injected into a saline-filled lung. Adapted with permission from Reference 62.

the explanation that is based on the hypothesis that the alveoli or airways are collapsed and pop open at a critical pressure.

To summarize, the term recruitment, defined as the aeration of a previously airless gas exchange unit, should not be reserved for a single mechanism, and a change in the shape of the PV curve does not mean that recruitment must have occurred.

## What Inferences May Be Drawn from Histopathologic Studies of Lung Tissue?

Although the term "atelectasis" is used liberally in reports describing injured lungs, there is sparse morphometric evidence of alveolar collapse (as opposed to flooding) in the published literature (66). In part, this reflects the difficulties in preserving the *in situ* lung architecture during fixation and/or removal of the lungs from the chest (67). Muscedere and coworkers (26) studied isolated, nonperfused, saline-lavaged rat lungs that were ventilated with PEEP below or above the lower inflection point of their static PV curves. Lungs that were ventilated without PEEP showed a marked fall in compliance and severe histologic damage in the form of hyaline membranes, epithelial denudation, and necrotic debris in distal airways. The authors suggested that distal airway collapse with resulting shear stress on airway walls causes damage and mediator release and that the same mechanism may contribute to VILI in patients with ARDS. Although this hypothesis is appealing and has found broad support in the clinical community, certain limitations of the experimental model should be noted. Unlike the ex vivo preparation, injured (and flooded) lungs do not collapse in situ to residual volume at every breath. Furthermore, the absence of perfusion (and hence flooding) in the ex vivo model may have amplified an injury mechanism that may well be of limited importance in vivo (see below).

## What is the Probability That an Alveolus Will Collapse Without Flooding?

Two mechanisms dominate the pathobiology of ARDS: (1) surfactant dysfunction and (2) altered vascular barrier function (68, 69). As outlined previously, interdependence arguments predict that for an alveolus to collapse in the face of rising surface tension, local alveolar pressure must fall by many tens of cm  $H_2O$  (30). Given the micromechanics of alveolar corner vessels and extra-alveolar capillaries, such stress concentrations ought to promote flooding, particularly in the presence of increased microvascular permeability (69). Recall that much of the surfactant dysfunction in ARDS has been attributed to flooding and plasma protein-induced changes in surfactant physicochemical properties in the first place (47). Contrast this scenario with absorption atelectasis complicating inhalational anesthesia. The reduction in lung volume and the decrease in mucociliary clearance increase the probability of liquid bridge formation in dependent small airways. As the subtended lung unit collapses, there is also a local increase in vascular filtration pressure. However, in contrast to ARDS, the vascular barrier function of the lung is normal, so that the unit can collapse to a much smaller volume (and become atelectatic) before fluid is drawn into it. Once an alveolus is either flooded or atelectatic, the loss of surface tension near alveolar corner vessels causes blood flow to decrease (70).

### LESSONS FROM THE BEDSIDE

To date, five randomized clinical trials have addressed the efficacy of so-called lung protective mechanical ventilation strategies in patients (5, 6, 71–73). In general, in all five trials the conventional treatment arm employed higher tidal volumes and larger alveolar ventilation targets than the so-called lung protective or low volume arm. Three trials turned out to be negative; i.e., there was no difference in survival, length of mechanical ventilation, or hospital stay among the treatment groups. Two trials, a Brazilian single-center study and the ARDS Network trial (5, 6), attributed a statistically significant survival benefit to the lung protective treatment. A number of design features appear to distinguish positive from negative clinical trials. (1) In positive trials there was a greater difference in tidal volume settings among the treatment groups. The tidal volume target in the conventional treatment arm of the two positive trials approximated 12 ml/kg, whereas those of the three negative trials was only 10.3 (71), 10.8 (73), and 10.2 ml/kg (72). (2) Judged by the lung mechanics parameters, patients in the negative trials may have had lesser degrees of injury than did patients in the positive trials. For example, the respiratory system compliance (a measure of the size of the baby lung) of patients randomized to the low volume arms of the two positive trials averaged approximately 0.4 ml/cm H<sub>2</sub>O/kg, whereas it averaged approximately 0.5 ml/cm H<sub>2</sub>O/kg in the negative trials. All that can be concluded at this point is that tidal volumes approaching 12 ml/kg are injurious to the lungs of patients with ARDS.

More relevant to this perspective is that the five randomized trials have provided little information about "best PEEP." The arguments for and against PV curve-based PEEP management have been elegantly articulated (74). The hypothesis that the injured lung is fully recruited at pressures greater than LIP has been rejected (75). High degrees of PEEP and recruitment maneuvers are the centerpieces of the open lung approach. Yet, in the ARDS Network trial, recruitment maneuvers failed to show a sustained benefit on gas exchange in supine patients (8). Four of five trials (5, 71-73) used similar and relatively modest PEEP settings ( $\sim 10 \text{ cm H}_2\text{O}$ ), which differed little among the treatment arms. In contrast, patients in the lung protective treatment arm of the Brazilian trial were managed with high PEEP settings averaging 17 cm H<sub>2</sub>O. Because the two positive trials differed dramatically in their approach to PEEP but were quite similar with respect to tidal volume, it is hard to conclude anything about best PEEP from them. Patients in the ARDS network trial were more likely to receive bicarbonate buffers and respiratory rate adjustments with the aim of correcting acidemia. It has been argued that the higher rates might have produced auto-PEEP, but no measurements to support this are available.

### EVIDENCE IN SUPPORT OF EDEMA AS THE SOURCE OF REGIONAL IMPEDANCE IN ARDS

#### **Parenchymal Marker Studies**

Cognizant of CT's limitations as a measurement tool of regional lung mechanics, our group used the parenchymal marker technique to quantify both spatial and temporal heterogeneity in lung deformation in oleic acid–injured dogs (76, 77). The parenchymal marker technique describes the topographic distribution of regional volume and ventilation in laboratory animals. The transthoracic injection of metallic markers and their subsequent imaging with biplane fluoroscopy make it possible to track the same anatomic regions in space and time. As a result, the topographic distributions of volume, ventilation, and strain may be computed.

We were initially surprised to find that oleic acid injury did not produce the collapse of dependent lung units in this model of ARDS (77). However, in hindsight this finding is consistent with earlier observations by Slutsky and colleagues, who reported significant reductions in intrathoracic gas volume but found no changes in chest wall dimensions in oleic acid-injured dogs (78). We have simply extended this finding to a smaller scale, i.e., regions as small as 1 cm<sup>3</sup>. The other surprise was that it proved impossible to demonstrate opening and collapse on this scale no matter how hard we looked for it. For example, during sinusoidal oscillations of the respiratory system, 95% of the regions of the oleic acid injured caudal lobe expanded within 12° (phase angle) of each other. This means that during mechanical ventilation at a rate of 20 per minute, 95% of the regions reach their peak volume within the same 100-millisecond window. On the basis of these findings, we proposed an alternative mechanism for the topographic variability in regional impedances and lung expansion after injury, namely, liquid and foam in alveoli and/or conducting airways. Our inability to demonstrate temporal heterogeneity on a cubic centimeter volume scale does not establish airway liquid and foam as the prevailing mechanism. The fact that neither temporal nor spatial heterogeneity was organized along gravitational lines, however, was difficult to reconcile with the "weight of the lung hypothesis."

#### Alveolar Microscopy

Most of the evidence I have presented so far, be it pro or con recruitment and collapse, represents inferences about alveolar micromechanics from measurements that were made on a scale several orders of magnitude greater than that of the structures of interest. It therefore seems prudent to examine data about lung deformation that were derived from microscopic images. Current views on alveolar micromechanics and the interactions between surface tension and tissue stress can be traced to the classic morphometric studies by Bachofen, Weibel, and colleagues (79-82) and the consequent quantitative analysis by Wilson and Bachofen (83). Accordingly, tension is carried by a helical network of collagen and elastin fibers that surround and support alveolar ducts, whereas surface tension acting in parallel to alveolar walls counterbalances the hoop stress at the alveolar entrance ring. It is remarkable how little is known about alveolar deformation during breathing. Most believe that alveoli unfold in the tidal breathing range and only get stretched at high lung volumes (84, 85). Others believe that only the alveolar ducts expand during breathing, whereas alveolar volume and surface area remain more or less constant (86). These uncertainties place substantial constraints on analyses of alveolar mechanics in injury states.

Figure 3 shows subpleural alveoli of two isolated perfused rat lungs that were imaged with laser confocal microscopy. The image on the left is a three-dimensional representation of



Figure 3. Laser confocal images of subpleural alveoli of a normal (*left*) and an edematous (*right*) rat lung. The perfusate was labeled with fluorescein labeled dextran, i.e., edema fluid appears white, the alveolar walls gray, and air pockets are black. (Gajic and Lee; unpublished observations.)

a normal lung. The image on the right is a single optical slice approximately 30 µm below the pleural surface of an injured lung that had been perfused with a fluorescein labeled dextran containing solution. Therefore, edema fluid appears white, the alveolar walls gray, and trapped air black. Note that the alveoli of the edematous lung are not collapsed, that they are completely or partially flooded and that they contain air pockets of different sizes and shapes. Similar observations were made by Bachofen and colleagues describing electron micrographs of edematous rabbit lungs (87). The presence of different-sized air pockets with different radii of curvature implies a nonuniform alveolar gas pressure and/or nonuniform surface tension. Regional differences in alveolar protein concentrations or in their physicochemical properties (e.g., caused by differences in their state of nitrosylation) could well be the source of nonuniform surface tension. Nonuniform surface tension might promote the movement of molecules against concentration gradients and drive the heterogeneity in regional tissue expansion. Maintenance of a nonuniform alveolar gas pressure in turn raises the possibility that the airpockets are trapped by liquid and foam. The possibility that alveolar gas pressures could be nonuniform in injured lungs was not considered in the CT-based analyses that led to the dependent lung collapse hypothesis. However, nonuniform alveolar pressure and trapped gas explains why lung injury and edema need not raise the vertical gradient in regional lung volume (77). It also explains why changes in the gravitational distribution of pleural pressure cannot be interpreted as evidence that dependent lung is collapsed.

# IS THE DISTINCTION BETWEEN EDEMA AND COLLAPSE IMPORTANT?

I have reviewed the evidence that forms the basis for the more widely accepted hypothesis about the mechanics of edematous lungs, namely, that the increased weight of the edematous lung causes collapse and atelectasis in the dependent regions of the wet lung and that a high opening pressure is required to open airways that are collapsed. I have also reviewed the data that contradict this hypothesis and described an alternate hypothesis, namely, that edema fluid and foam fill dependent regions in the wet lung and that high pressures are required to drive foam through airways and inflate parenchyma in which surface tension is high and alveoli are fluid-filled.

To be sure, the two hypotheses have points in common. In both hypotheses, the regions that are collapsed, according to the first hypothesis, or fluid and foam-filled, according to the second hypothesis, are unventilated at lower peak airway pressures, and higher airway pressures are required to recruit these regions. However, the mechanisms of airway opening are different in the two, and these differences imply different mechanisms of VILI. In the case of a collapsed wet tube that is pried open by the sharp leading edge of a wedge of gas, the pressure at the air-liquid interface is dissipated over a small area, and the lining cells in the vicinity of the air-liquid interface experience a large stress. This process has been modeled quantitatively (88). However, if the branching network of open airways were occluded by liquid bridges interspersed with trapped gas, airway opening pressure would be dissipated over a series of curved menisci, the volume of tissue that is subjected to stress would be larger, and the local stresses on the lining cells would be smaller. In that case, VILI may occur through overdistension of aerated alveoli, rather than by shear stresses in airways as they open.

From the point of view of the scientist, the question which of these hypotheses gives a more accurate description of the mechanics of edematous lungs is central. Perhaps the scientist has faith that in the long run the question will be resolved. However, I am concerned that the question also has more immediate and practical consequences. If the first hypothesis is accepted wholeheartedly and uncritically, research time and effort may be misdirected. Also, admitting uncertainty about mechanisms may save the critical care community from the pitfalls of tunnel vision. Specifically, it may not be crucial to determine a patient's PV curve precisely. Also, maximizing oxygen tension through the use of aggressive recruitment may be gratifying in the short term, but at this point, who can say that it prevents lung injury and promotes alveolar repair? When a clinician asks "how should I ventilate this patient," the investigator should contemplate "how does an alveolus deform during a breath; what is the accompanying stress; how do cells sense and respond to this stress; and finally, can the cell and molecular responses to deformation be manipulated?"

**Acknowledgment:** The author wishes to thank Dr. Ted Wilson for his insights and the many stimulating discussions about this and related topics and Ms. Lori Oeltjenbruns for preparing the manuscript.

#### References

- Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 1998;157:294–323.
- International Consensus Conference in Intensive Care Medicine. Ventilator-associated lung injury in ARDS. Am J Respir Crit Care Med 1999;160:2118–2124.
- Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999;282:54–61.
- West JB. Pulmonary capillary stress failure (invited review). J Appl Physiol 2000;89:2483–2489.
- 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.
- Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Olivera R, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347–354.
- Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB. Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 1972;51:2315–2323.
- Brower RG, Clemmer T, Lanken P, MacIntyre N, Matthay M, Morris A, Schoenfeld D, Thompson T. Effects of recruitment maneuvers in acute lung injury patients ventilated with lower tidal volumes and higher positive end-expiratory pressures [abstract]. *Am J Respir Crit Care Med* 2001;163A.
- Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. *Am J Respir Crit Care Med* 2001;163:69–78.
- Hotchkiss JR, Blanch L, Murias G, Adams AB, Olson DA, Wagensteen OD, Leo PH, Marini JJ. Effects of decreased respiratory frequency on ventilator-induced lung injury. *Am J Respir Crit Care Med* 2000;161: 463–468.
- Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975; 292:284–289.
- Tobin MJ. Medical progress: advances in mechanical ventilation. N Engl J Med 2001;344:1986–1996.
- Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA* 1993;269:2122– 2127.
- Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:1807–1814.
- Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. *Am Rev Respir Dis* 1987;136:730–736.
- 16. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradi-

ent of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:8–13.

- Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991;74: 15–23.
- Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, Gattinoni L. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998;157:387–393.
- Crotti S, Mascheroni D, Caironi P, Pelosi P, Ronzoni G, Mondino M, Marini JJ, Gattinoni L. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 2001; 164:131–140.
- Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984;86:58–66.
- Falke KJ. Do changes in lung compliance allow determination of "optimal PEEP? Anaesthesist 1980;29:165–168.
- Lachmann B. Open up the lung and keep the lung open. *Intensive Care* Med 1992;18:319–321.
- Argiras EP, Blakeley CR, Dunnhill MS, Otremski S, Sykes MK. High PEEP decreases hyaline membrane formation in surfactant deficient lungs. *Br J Anaesth* 1987;59:1278–1285.
- Broccard AF, Hotchkiss JR, Kuwayama N, Olson DA, Jamal S, Wangensteen DO, Marini JJ. Consequences of vascular flow on lung injury induced by mechanical ventilation. *Am J Respir Crit Care Med* 1998;157:1935–1942.
- Corbridge TC, Wood LD, Crawford GP, Chudoba MJ, Yanos J, Sznajder JI. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990;142:311–315.
- Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994;149:1327–1334.
- Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997;99:944–952.
- Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974;110:556–565.
- Marini JJ. Ventilator-induced airway dysfunction? Am J Respir Crit Care Med 2001;163:806–807.
- Mead J, Takashima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970;28:596–603.
- Ranieri VM, Zhang HB, Mascia L, Aubin M, Lin CY, Mullen JB, Grasso S, Binnie M, Volgyesi GA, Slutsky AS. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology* 2000;93:1320–1328.
- 32. Slutsky AS. Basic science in ventilator-induced lung injury: implications for the bedside. *Am J Respir Crit Care Med* 2001;163:599–600.
- Agostoni E, D'Angelo E. Comparative features of the transpulmonary pressure. *Respir Physiol* 1970;11:76–83.
- Agostoni E, D'Angelo E, Bonanni MV. The effect of the abdomen on the vertical gradient of pleural surface pressure. *Respir Physiol* 1970; 8:332–346.
- D'Angelo E, Michelini S, Agostoni E. Partition of factor contributing to the vertical gradient of transpulmonary pressure. *Respir Physiol* 1971; 12:90–101.
- Hubmayr RD, Walters BJ, Chevalier PA, Rodarte JR, Olson LE. Topographical distribution of regional volume in anesthetized dogs. *J Appl Physiol* 1983;54:1048–1056.
- Wilson TA. Solid mechanics. In: Fishman AP, editor. Handbook of physiology. Baltimore, MD: The Williams and Wilkins Co.; 1986. p. 35–40.
- Rodarte JR, Fung YC. Distribution of stresses within the lung. In: Fishman AP, editor. Handbook of physiology. Baltimore, MD: The Williams and Wilkins Co.; 1986. p. 233–246.
- Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. Am J Respir Crit Care Med 2000;161:1660–1665.
- Bar-Yishay E, Hyatt RE, Rodarte JR. Effect of heart weight on distribution of lung surface pressures in vertical dogs. J Appl Physiol 1986; 61:712–718.
- Malbouisson LM, Busch CJ, Puybasset L, Lu Q, Cluzel P, Rouby JJ. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. *Am J Respir Crit Care Med* 2000;161:2005–2012.
- Chevalier PA, Rodarte JR, Harris LD. Regional lung expansion at total lung capacity in intact vs excised canine lungs. J Appl Physiol Respir Environ Exer Physiol 1978;45:363–369.

- Glazier JB, Hughes JM, Maloney JE, Pain MC, West JB. Vertical gradient of alveolar size in dog lungs frozen in situ. J Physiol 1966;186:114P–115P.
- Hoffman EA, Lai-Fook SJ, Wei J, Wood EH. Regional pleural surface expansile forces in intact dogs by wick catheters. *J Appl Physiol Respir Environ Exer Physiol* 1983;55:1523–1529.
- 45. Tsang JY, Baile EM, Hogg JC. Relationship between regional pulmonary edema and blood flow. *J Appl Physiol* 1986;60:449–457.
- Iancu DM, Zwikler MP, Michel RP. Distribution of alveolar edema in ventilated and unventilated canine lung lobes. *Invest Radiol* 1996;31: 423–432.
- Spragg RG, Lewis JF. Pathology of the surfactant system of the mature lung: Second San Diego Conference. Am J Resir Crit Care Med 2001; 163:280–282.
- Cook CD, Mead J, Schreiner GL, Frank NR, Craig JM. Pulmonary mechanics during induced pulmonary edema in anesthetized dogs. *J Appl Physiol* 1959;14:177–186.
- Delaunois L, Sergysels R, Martin RR. Acute effects on airways mechanics of pulmonary edema induced by intravenous oleic acid in dogs. *Bull Eur Physiopath Respir* 1980;16:47–55.
- Frazer DG, Stengel PW, Weber KC. The effect of pulmonary edema on gas trapping in excised rat lungs. *Respir Physiol* 1979;38:325–333.
- Chung KF, Keyes SJ, Morgan BM, Jones PW, Snashall PD. Mechanisms of airway narrowing in acute pulmonary edema in dogs: influence of the vagus and lung volume. *Clin Sci* 1983;65:289–296.
- Derks CM, O'Hollander AA, Jacobovitz-Derks D. Gas exchange and respiratory mechanics in moderate and severe pulmonary oedema in dogs. *Bull Eur Physiopath Respir* 1981;17:163–177.
- Esbenshade AM, Newman JH, Lams PM, Jolles H, Brigham KL. Respiratory failure after endotoxin infusion in sheep: lung mechanics and lung fluid balance. *J Appl Physiol* 1982;53:967–976.
- Bachofen H, Hildebrandt J, Bachofen M. Pressure-volume curves of airand liquid-filled excised lungs: surface tension in situ. J Appl Physiol 1970;29:422–431.
- Hildebrandt J. Pressure-volume data of cat lung interpreted by a plastoelastic, linear viscoelastic model. J Appl Physiol 1970;28:365–372.
- Horie T, Hildebrandt J. Dynamic compliance, limit cycles, and static equilibria of excised cat lung. J Appl Physiol 1971;31:423–430.
- Horie T, Hildebrandt J. Volume history, static equilibrium, and dynamic compliance of excised cat lung. J Appl Physiol 1972;33:105–112.
- Wilson TA, Anafi R, Hubmayr RD. Mechanics of edematous lungs. J Appl Physiol 2001;90:2088–2093.
- Avery ME. The aeration of the lung at birth. In: Schaffer AJ, editor. The lung and its disorders in the newborn infant. Philadelphia, PA: WB Saunders; 1968. p. 24–30.
- Suki B, Andrade JS Jr, Coughlin MF, Stamenovic D, Stanley HE, Sujeer M, Zapperi S. Mathematical modeling of the first inflation of degassed lungs. *Ann Biomed Eng* 1998;26:608–617.
- Martin-Lefèvre L, Ricard JD, Roupie E, Dreyfuss D, Saumon G. Significance of the changes in the respiratory system pressure-volume curve during acute lung injury in rats. *Am J Respir Crit Care Med* 2001; 164:627–632.
- Martynowicz MA, Hubmayr RD. Mechanisms of regional lung expansion in acute respiratory distress syndrome. In: Vincent J-L, editor. Yearbook of intensive care and emergency medicine. Berlin: Springer-Verlag; 1999. p. 252–268.
- Smith JC, Stamenovic D. Surface forces in lungs: I. alveolar surface tension-lung volume relationships. J Appl Physiol 1986;60:1341–1350.
- Stamenovic D, Smith JC. Surface forces in lungs: II. microstructural mechanics and lung stability. J Appl Physiol 1986;60:1351–1357.
- Stamenovic D, Smith JC. Surface forces in lungs: III. alveolar surface tension and elastic properties of lung parenchyma. J Appl Physiol 1986;60:1358– 1362.
- 66. Montaner JSG, Tsang J, Evans KG, Mullen JB, Burns AR, Walker DC, Wiggs B, Hogg JC. Alveolar epithelial damage: a critical difference between high pressure and oleic acid-induced low pressure pulmonary edema. J Clin Invest 1986;77:1786–1796.
- Bachofen H, Ammann A, Wangensteen D, Weibel ER. Perfusion fixation of lungs for structure-function analysis: credits and limitations. J Appl Physiol 1982;53:528–533.
- 68. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, Lamy M, Marini JJ, Matthay MA, Pinsky MR, et al. Ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling: acute respiratory distress syndrome. Am J Respir Crit Care Med 1998;157:1332–1347.
- Kollef MH, Schuster DP. The acute respiratory distress syndrome. N Engl J Med 1995;332:27–37.
- 70. Albert RK, Lamm WJ, Rickaby DA, al-Tinawi A, Dawson CA. Lung in-

#### **Critical Care Perspective**

flation distends small arteries (< 1 mm) in excised dog lungs. J Appl Physiol 1993;75:2595–2601.

- 71. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, CLementi E, Mancebo J, Factor P, Matamis D, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome: the Multicenter Trail Group on tidal volume reduction in ARDS. Am J Respir Crit Care Med 1998;158:1831–1838.
- 72. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dood-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999;27:1492–1498.
- 73. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 1998; 338:355–361.
- Dreyfuss D, Saumon G. Pressure-volume curves: searching for the Grail or laying patients with adult respiratory distress syndrome on Procrustes' bed? Am J Respir Crit Care Med 2001;163:2–3.
- Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire, Brochard L. Influence of tidal volume on alveolar recruitment. *Am J Respir Crit Care Med* 2001;163:1609–1613.
- Martynowicz MA, Walters BJ, Hubmayr RD. Mechanisms of recruitment in oleic acid-injured lungs. J Appl Physiol 2001;90:1744–1753.
- Martynowicz MA, Minor TA, Walters BJ, Hubmayr RD. Regional expansion of oleic acid-injured lungs. *Am J Respir Crit Care Med* 1999; 160:250–258.
- 78. Slutsky AS, Scharf SM, Brown R, Ingram RH Jr. The effect of oleic acid-

induced pulmonary edema on pulmonary and chest wall mechanics in dogs. *Am J Respir Crit Care Med* 1980;121:91–96.

- Bachofen H, Gehr P, Weibel ER. Alterations of mechanical properties and morphology in excised rabbit lungs rinsed with a detergent. J Appl Physiol 1979;47:1002–1010.
- Bachofen H, Hildebrandt J. Area analysis of pressure-volume hysteresis in mammalian lungs. J Appl Physiol 1971;30:493–497.
- Gil J, Bachofen H, Gehr P, Weibel ER. The alveolar volume to surface area relationship in air- and saline-filled lungs fixed by vascular perfusion. J Appl Physiol 1979;47:990–1001.
- Weibel ER. Functional morphology of lung parenchyma. In: Handbook of physiology. Bethesda, MD: The Williams and Wilkins Co.; 1986. p. 89–112.
- Wilson TA, Bachofen H. A model for mechanical structure of the alveolar duct. J Appl Physiol 1982;52:1064–1070.
- Bachofen H, Schürch S, Urbinelli M, Weibel ER. Relations among alveolar surface tension, surface area, volume, and recoil pressure. J Appl Physiol 1987;62:1878–1887.
- Tschumperlin DJ, Margulies SS. Alveolar epithelial surface area-volume relationship in isolated rat lungs. J Appl Physiol 1999;86:2026–2033.
- Carney DE, Bredenberg CE, Schiller HJ, Picone AL, McCann, Gatto LA, Bailey G, Fillinger M, Nieman GF. The mechanism of lung volume change during mechanical ventilation. *Am J Respir Crit Care Med* 1999;160:1697– 1702.
- Bachofen H, Schürch S, Michel RP, Weibel ER. Experimental hydrostatic pulmonary edema in rabbit lungs: morphology. *Am Rev Respir Dis* 1993;147:989–996.
- Gaver DP III, Kute SM. A theoretical model study of the influence of fluid stresses on a cell adhering to a microchannel wall. *Biophys J* 1998;75:721–733.