

FIFTY YEARS OF RESEARCH IN ARDS

Respiratory Mechanics in Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome is a multifactorial lung injury that continues to be associated with high levels of morbidity and mortality. Mechanical ventilation, although lifesaving, is associated with new iatrogenic injury. Current best practice involves the use of small V_T, low plateau and driving pressures, and high levels of positive end-expiratory pressure. Collectively, these interventions are termed “lung-protective ventilation.” Recent investigations suggest that individualized measurements of pulmonary mechanical variables rather than population-based ventilation prescriptions may

be used to set the ventilator with the potential to improve outcomes beyond those achieved with standard lung protective ventilation. This review outlines the measurement and application of clinically applicable pulmonary mechanical concepts, such as plateau pressures, driving pressure, transpulmonary pressures, stress index, and measurement of strain. In addition, the concept of the “baby lung” and the utility of dynamic in addition to static measures of pulmonary mechanical variables are discussed.

Keywords: mechanical ventilation; resistance; elastance; esophageal pressure; transpulmonary pressure

The acute respiratory distress syndrome (ARDS) is characterized by the rapid onset of severe hypoxic respiratory failure and alterations in pulmonary mechanics. Three main physiological abnormalities characterize ARDS: hypoxemia; reduced capacity to eliminate CO₂; and reduced lung volumes and compliance. LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure), a recent multinational observational study, found current intensive care unit and hospital mortality rates from ARDS of 35–46% (1). Whether all forms of ARDS share a common pathophysiologic course characterized by diffuse alveolar damage and neutrophil recruitment to

the lungs is unclear (2–6), but alterations of lung mechanics are ubiquitous and expose the remaining aerated lung to excessive ventilation. The subsequent local release of toxic mediators damages the capillary endothelium and alveolar epithelium. Once a patient with ARDS is placed under mechanical ventilation (MV), the most common abnormality is one of increased elastance secondary to this small lung size.

After the initial description of ARDS, clinical management historically focused on the oxygenation abnormalities. In an attempt to reverse hypoxemia, large V_T values of 12–14 ml/kg, and occasionally as large as 24 ml/kg of body weight, were prescribed (7–9). Similarly,

the use of positive end-expiratory pressure (PEEP) levels as high as 44 cm H₂O were proposed to reverse atelectasis and hypoxemia, as indicated by calculated shunt (10). Concerns were raised about the fear of oxygen toxicity (11), but, for a long period, there was little recognition of the possibility that this level of lung distension might be injurious (8).

Ventilator-induced Lung Injury

MV, although often lifesaving in ARDS, may aggravate or initiate lung injury through

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several mechanisms, collectively termed ventilator-induced lung injury (VILI) (12). Separating VILI into injuries that occur at high lung volumes and at low lung volumes provides a useful schema for potential treatment methods for these injuries (13). VILI occurring at high lung volume is due to regional alveolar overdistension (so called “volutrauma”), associated with high end-inspiratory transpulmonary pressure (P_L), but not with high airway pressure (P_{aw}) *per se*. VILI at low lung volume is due to high local tissue stress and parenchymal shear injury, supposedly caused by repetitive opening and closing of alveoli and distal small airways (“atelectrauma”), occurring when P_L suddenly increases at early inspiration (14, 15). VILI is associated with increases in pulmonary and systemic inflammatory mediators that may precipitate multiple organ dysfunction syndrome—a process that has been termed “biotrauma” (16, 17).

To mitigate alveolar distension and VILI at high lung volume, limitation of V_T and ventilating pressures are applied (18–22). The use of PEEP is believed to be useful in preventing VILI at low lung volumes associated with atelectrauma (14, 23–28). The combined application of low V_T and plateau pressure (P_{plat}) and high PEEP is collectively termed lung-protective ventilation. The exact V_T and PEEP combination best suited to each patient needs to be individualized. A management approach that accounts for unique patient characteristics through the measurement of respiratory mechanics, such as driving pressure (ΔP) and P_L , or the calculation of strain holds the promise of individualized ventilation and improved outcomes. Recent observational studies and *post hoc* analysis of randomized controlled trials show that markers of distension, lung deformation, or strain (such as ΔP) are strongly correlated with outcome in ARDS (29). Data also show an underutilization of the simplest measurements assessing respiratory mechanics at the bedside (1). These measurements have limitations, such as the inability to account for regional heterogeneity, chest wall stiffness, patient position, and the effects of spontaneous efforts. Despite these shortcomings, global measures, as described in this review, still form the basis of many of the major advances made in the ventilator management of ARDS, and underpin novel approaches. In this review, we introduce

both the theoretical principles and the technical considerations useful for performing and interpreting these measurements. For interpretation of respiratory mechanics during spontaneous breathing, we refer the reader to recent reviews (30, 31).

Respiratory Mechanics during Passive Ventilation

Static Measurements for the Respiratory System: Rationale and Practice

The equation of motion for the respiratory system, first proposed by Rohrer (32) and based on Newton’s third law (33), constitutes the fundamental theory of respiratory mechanics. It characterizes mechanical forces and provides the mathematical foundation for static measurements in clinical practice. During MV, both ventilator and respiratory muscles can apply pressures to the respiratory system. The sum of applied pressures is equal to the sum of opposing pressures, namely, elastic recoil pressure (P_{el}), flow-resistive pressure (P_{res}), and inertial pressure (P_{in}) as follows:

$$P_{vent} + P_{mus} = P_{el} + P_{res} + P_{in} = f_1(V) + f_2(\dot{V}) + f_3(\ddot{V}), \quad (1)$$

where P_{vent} is ventilator pressure; P_{mus} is muscle pressure; f_1 , f_2 , and f_3 are functions describing the relationships between P_{el} and volume (V), P_{res} and the rate of change in volume (flow, \dot{V}), and P_{in} and the rate of change in flow (acceleration, \ddot{V}), respectively. This equation applies during both inspiration and expiration, where inspiratory flow is usually defined as positive and expiratory flow as negative. Ventilator pressure is identical to P_{aw} . By assuming linear relationships in these functions, the motion of the system can be described:

$$P_{aw} + P_{mus} = E_{rs} \cdot \Delta V + R_{rs} \cdot \dot{V} + I_{rs} \cdot \ddot{V}, \quad (2)$$

where E_{rs} represents respiratory system elastance (the inverse of compliance), ΔV is the volume difference from the resting volume, R_{rs} represents respiratory system resistance, and I_{rs} represents inertance. Other than in situations such as high-frequency ventilation or coughing, inertance is negligible.

During passive ventilation, the respiratory muscles are relaxed and the P_{mus} is nil. ΔV is the sum of inspired volume (V_{insp}) above end-expiratory lung volume (EELV) and EELV above FRC. The product of E_{rs} and EELV above FRC is equivalent to the total P_{el} at the end of expiration (total positive end-expiratory pressure [$PEEP_{tot}$], namely, the sum of PEEP and intrinsic PEEP). Equation 2 can then be presented as:

$$P_{aw} = E_{rs} \cdot V_{insp} + R_{rs} \cdot \dot{V} + PEEP_{tot}. \quad (3)$$

P_{aw} , V_{insp} , and \dot{V} are directly monitored or set by the ventilator, whereas E_{rs} , R_{rs} , and $PEEP_{tot}$ need to be calculated. The use of a constant flow on the ventilator greatly facilitates this calculation. An end-expiratory occlusion (EEO), when V_{insp} and \dot{V} are nil, allows measuring $PEEP_{tot}$. An end-inspiratory occlusion (EIO) after delivering V_T allows calculating $P_{aw,EIO}$, defined as P_{plat} , and calculating Equations 4 and 5:

$$P_{aw,EIO} = E_{rs} \cdot V_T + PEEP_{tot} \quad (4)$$

$$E_{rs} = (P_{plat} - PEEP_{tot})/V_T. \quad (5)$$

When \dot{V} is constant, P_{res} will remain approximately constant throughout inspiration. The peak P_{aw} (P_{peak}) occurs at the end of inspiration:

$$P_{peak} = E_{rs} \cdot V_T + R_{rs} \cdot \dot{V} + PEEP_{tot}. \quad (6)$$

Subtracting Equation 4 from Equation 6 allows the calculation of R_{rs} :

$$P_{peak} - P_{aw,EIO} = R_{rs} \cdot \dot{V} \quad (7)$$

$$R_{rs} = (P_{peak} - P_{plat})/\dot{V}. \quad (8)$$

Of note, the calculated R_{rs} in Equations 3–8 is inspiratory resistance, which can differ from expiratory resistance. The latter can be higher in the absence of PEEP and depends on lung volume (34).

Measuring mechanical properties of the respiratory system requires only limited assumptions and the performance of EEO and EIO maneuvers (Figure 1). As there is no change in V_T or \dot{V} during these maneuvers (by using volume-controlled mode), they are called static measures. P_{aw} under static conditions is equal to alveolar pressure (P_{alv}), but may not reflect P_{alv} in regions with airway closure (frequent in morbidly obese patients [35] or during low PEEP ventilation in supine patients [36–39]). In general, compliance calculated

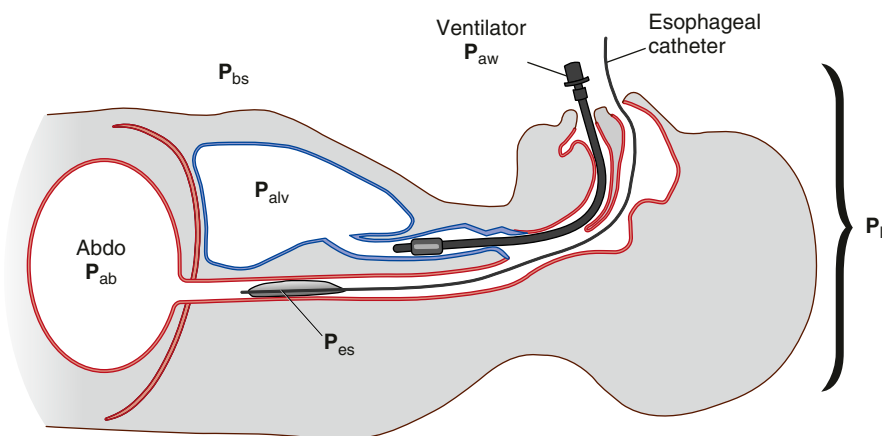


Figure 2. The clinician can directly measure the pressure from the ventilator at the airway opening (airway pressure [Paw]) and reference it to body surface pressure (Pbs). Esophageal pressure (Pes) may also be directly measured with a balloon manometer. Transpulmonary pressure (PL) = Paw – Pes. The alveolar pressure (Palv) can be measured from Paw during end-inspiratory (plateau) and end-expiratory (total positive end-expiratory pressure) holds. Abdominal pressure (Pab) can be measured in the stomach or the bladder. Abdo = abdomen. Artwork by Vicky Earle.

nondependent and dependent parts of the pleural space is enlarged in ARDS. Therefore, even if the Pes accurately measures an intrathoracic pressure, it only reflects the distending pressure at one level of the lung, adjacent to the position of the esophagus (45).

“Static” or “Quasistatic” Measures

The magnitude of elastic pressures generated during tidal ventilation relates to the risk of VILI (29). The resistive pressure component, dissipated across artificial airways and main bronchi, does not seem to cause significant bronchiolar and alveolar wall stress. Thus, when VT is kept constant, the influence of slower or faster inspiratory flow rates, generating higher or lower peak pressures, is expected to be negligible, not changing the effective stress on alveolar walls. Nevertheless, because the lung behavior in mammals is not elastic and linear, as assumed by Equation 3, but instead, *viscoelastic* (46–48), the influence of flow and inspiratory time might be relevant in certain conditions. As described in classical studies (41, 49, 50), a slower inflation, for instance, setting inspiratory flow less than 20 L/min, or the use of long inspiratory pauses (EIO > 0.5 s), would typically promote stress relaxation/adaptation of lung tissues, substantially decreasing the EIO pressure for a given VT (51). The longer the inspiratory pause, the higher the pressure

decay (typically amounting to 2–3 cm H₂O). Multiple phenomena participate in this decay, including surfactant spreading in the liquid lining layer, lung scaffold accommodation, pendelluft between alveolar units, or slow tidal recruitment (50, 52). As a consequence, the recommendation of long inspiratory pauses (2–5 s) may cause marked underestimation of the effective peak pressures reaching alveoli (Palv), even after discounting pressure losses through airways (53, 54). This peak Palv, however, has been directly linked to VILI (55), representing the effective pressure imposed by the ventilator against the respiratory system, being opposed by the elastic tension generated across the alveolar walls and thoracic structures.

It thus makes sense to use a shorter EIO (≤0.5 s) for measuring peak Palv or Pplat, especially to estimate the actual stress applied by the ventilator on lung tissues. This short occlusion would provide estimates of compliance similar to the so-called “dynamic compliance” in classical physiology (56, 57). The term is ambiguous, however (“dynamic compliance” has often referred to calculations using peak Paw, instead of peak Palv), and we prefer to name such estimate as “quasistatic compliance.” In brief, whereas an EIO maneuver that is too long may underestimate the risk of VILI, the use of peak proximal Paw would overestimate it, and we propose, instead, the use of short

inspiratory pauses and quasistatic compliance to better define these risks.

Other reasons favor shorter EIO maneuvers: (1) longer occlusions are more affected by imperceptible leaks, increasing errors; (2) when using low VT and inspiratory flows of 50–60 L/min, a 0.3-second EIO can be continuously applied, allowing ventilators to display Pplat; and (3) such short, continuously applied inspiratory pauses were shown to increase CO₂ elimination in patients with ARDS (58). Quasistatic or static measurements are relatively similar for the chest wall, an important issue to consider when partitioning the stress across the respiratory system (*see* subsequent discussion). A long inspiratory pause (2–5 s) may facilitate the calculation of chest wall mechanics by filtering artifacts caused by cardiac oscillation. For equivalent reasons, EEO maneuvers can be applied with a short duration (≤1 s), better estimating the effective swings in Palv.

Other methods can estimate compliance and resistance. The “multiple linear regression method” (40, 41) simultaneously finds the values for Ers, Rrs, and PEEPtot that best “explain” the observed tracings of Paw during inspiration and expiration, using fast sampling of flow, volume, and pressure signals (typically ≥100 Hz). The method assumes a linear model for the respiratory system (Equation 3). This method works for any controlled ventilatory mode, without the need for any specific maneuver, and matches the quasistatic values obtained during short occlusions, realistically representing the maximum swings in Palv (i.e., the ΔP), or the average values for Ers and Rrs during the whole respiratory cycle (Figure 3) (40, 41).

Airway Resistance and Expiratory Flow Limitation

Small airway (<2 mm in diameter) resistance plays a minimal role in terms of patient–ventilator interaction in ARDS. The values for airway resistance during inspiration have been found to be slightly higher than in normal subjects (59–61), probably secondary to decreased lung size, but the presence of significant resistance or intrinsic PEEP should alert the clinician to the possibility of coincident airway diseases and/or airway closure.

Airflow limitation during expiration, rather than inspiration, has been observed in

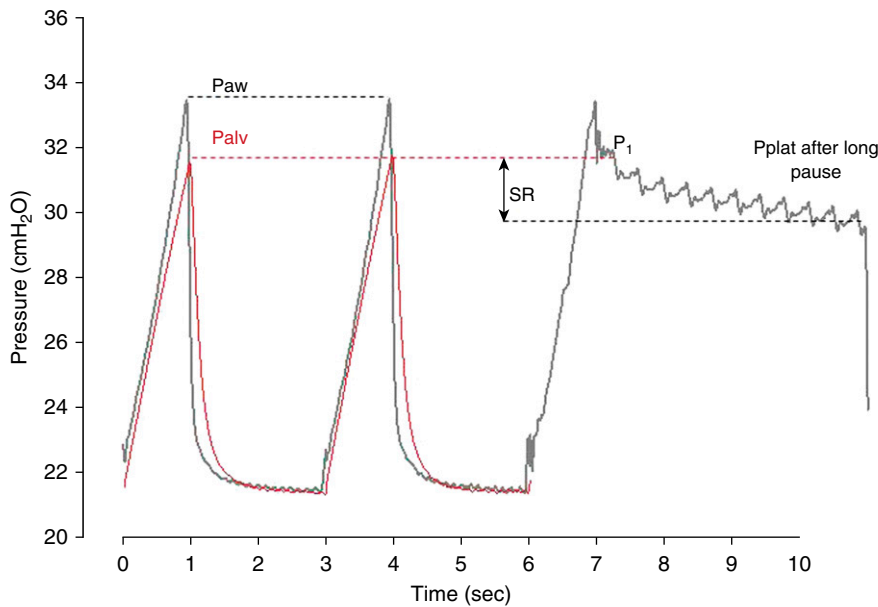


Figure 3. Tracings of airway pressure (P_{aw}) in a pig model of acute respiratory distress syndrome (gray lines), superimposed with estimated values for alveolar pressure (P_{alv} ; red lines; P_{alv} was obtained by multiple linear regression technique [MLR] according to the motion equation described in Equation 3). Note that the traditional plateau pressure (P_{plat}) estimated after a long inspiratory pause causes a slow decay in airway (and alveolar) pressures, due to stress relaxation/adaptation of lung tissues (SR), underestimating peak P_{alv} achieved in previous cycles (under dynamic conditions). Recent studies have suggested that such dynamic swings in P_{alv} (peak minus valley of P_{alv}), representing the effective driving pressure (ΔP), better predict the risk of ventilator-induced lung injury (VILI) than traditional measures. Thus, the traditional P_{plat} after a long inspiratory pause may underestimate the risk for VILI, justifying the preferential use of short inspiratory pauses (≤ 0.5 s) during measurements of P_{plat} or ΔP . By using this short procedure, the estimates of P_{plat} would be closer to P_{aw} immediately after occlusion (P_1) described in classic physiology, and closer to peak P_{alv} estimated by MLR.

patients with ARDS without a history of airway disease (62, 63), particularly under conditions of zero PEEP (34). This may contribute to the development of intrinsic PEEP. Similarly, a negative pressure applied to the expiratory circuit during exhalation failed to augment expiratory flow, suggesting flow limitation and small airway closure probably related to low lung volumes, increased lung weight (superimposed pressures) over the airways, and surfactant deficiency. This was not improved by bronchodilators, but was abolished by a PEEP of 10 cm H_2O . Other authors found intrinsic PEEP slowly increasing after a prolonged EEO, suggesting slow compartments favored by flow limitation (64). The clinical significance of these findings needs further investigation.

Clinical Reference Ranges of Respiratory Mechanics

Interpreting the measured variables of respiratory mechanics requires an

understanding of their physiological meanings as well as reference ranges and/or safe limits. However, the description of respiratory mechanics (particularly for lung and chest wall properties) in large cohorts is lacking.

To provide some reference ranges for clinicians, we derived data from the study by D’Angelo and colleagues (65) of patients undergoing surgery in the supine position (Table 1). Compliances in normal, awake subjects are higher than these ranges (66), but patients undergoing general anesthesia may be more comparable to intensive care unit patients.

The Baby Lung Concept

ARDS was initially conceived of as diffuse homogenous increases in elastance throughout the lung parenchyma. Computer tomography (CT) studies demonstrated that abnormalities in ARDS

are mostly regional, with areas of dense consolidation or atelectasis and other areas with normal, or near normal, aeration. This loss of aerated lung is reflected in reduced FRC, which may be as low as 20–30% of theoretical values expected for healthy subjects (67, 68). Gattinoni and colleagues (69), using quantitative CT scan analysis, found that the reduction in global compliance was mostly explained by the loss in aerated volume. This finding was made popular by the concept of “baby lung” (70).

Key insights derived from these observations are that the aerated lung in ARDS has nearly normal regional mechanics and that the ventilated lungs are not stiff, but small (69). Despite normal mechanical properties, the aerated lung in patients with ARDS can have abnormal increases in water permeability and metabolic rate when examined with positron emission tomography (71–73). This suggests that the “normal” lung areas are subject to increased inflammation, potentially in part because they are over-ventilated to compensate for the great loss of alveolar units. In experimental positron emission tomography/CT studies, simulating long-term MV with low V_T and low PEEP, the normal areas, receiving the highest regional ventilation—as compared with collapsed or hyperdistended areas—were the ones presenting greater progression of inflammation (74).

Use of Respiratory Mechanics to Guide Ventilation in ARDS and Minimize VILI at High Lung Volume

Webb and Tierney (24) and, later, the experimental studies of Dreyfuss and colleagues (25) on VILI demonstrated the potential complications associated with high-volume, high-pressure ventilation associated with large swings in PL. To mitigate alveolar distension and volutrauma, rigorous limitation of V_T and pressures are recommended (18–22).

V_T , P_{plat}

In the landmark ARDS Network trial, long-term mortality improved when V_T was limited to an average of 6 ml/kg of predicted body weight (a surrogate of predicted lung size in normal subjects) and P_{plat} to less than 30 cm H_2O (18). The Express study

Table 1. Clinical References for Calculation of Respiratory Mechanics

Derived Calculations	Average Value in ARDS*	Estimated Normal Values†	Explanation of Reference Range
Cr _s , ml/cm H ₂ O	38	1.6% of VC ml/cm H ₂ O	An average VC in normal subjects is around 4,000 ml; the predicted Cr _s would be 1.6% × 4,000 = 64 ml/cm H ₂ O
Cl _L , ml/cm H ₂ O	55	2.9% of VC ml/cm H ₂ O	Roughly predicted range: 90–140 ml/cm H ₂ O
Ccw, ml/cm H ₂ O	125	3.6% of VC ml/cm H ₂ O	Roughly predicted range: 100–200 ml/cm H ₂ O
Ers, cm H ₂ O/L	26	0.62 cm H ₂ O/1% VC (L)	An average VC in normal subjects is 4 L; this gives a predicted Ers as 0.62 ÷ 4% = 16 cm H ₂ O
EL, cm H ₂ O/L	18	0.34 cm H ₂ O/1% VC (L)	An average predicted value would be around 9 cm H ₂ O/L
Ecw, cm H ₂ O/L	8	0.28 cm H ₂ O/1% VC (L)	An average predicted value would be around 7 cm H ₂ O/L
EL/Ers	0.70	0.55	Estimated from predicted values of EL and Ers
Rrs, cm H ₂ O/L/s	—	8–12 at 60 L/min of square-wave inspiratory flow	This reference value is valid for inspiration only and depends on flow rate and the size of endotracheal tube

Definition of abbreviations: ARDS = acute respiratory distress syndrome; Ccw = chest wall compliance; Cl_L = lung compliance; Cr_s = respiratory system compliance; Ecw = chest wall elastance; EL = lung elastance; EL/Ers = the ratio of lung elastance to respiratory system elastance; Ers = respiratory system elastance; Rrs = respiratory system resistance at inspiration; VC = vital capacity.

*Mean values reported in or derived from Chiumello and colleagues (83), in which 6 ml/kg V_T and 5 cm H₂O of positive end-expiratory pressure were used in 24 patients with moderate or severe ARDS.

†Mean values reported in or derived from D'Angelo and colleagues (65) on 18 anesthetized paralyzed patients for minor surgery in the supine position. Predicted VC for men (L) = 5.76 × height (m) – 0.026 × age (yr) – 4.34; for women (L) = 4.43 × height (m) – 0.026 × age (yr) – 2.89.

titrated PEEP to reach a P_{plat} between 28 and 30 cm H₂O at Day 1, increasing PEEP-induced recruitment and limiting overdistension at the same time (26). Compared to a lower PEEP, this strategy reduced the days on ventilator and the days with organ failures, but not mortality. Although the use of small V_T and low P_{plat} has improved mortality in ARDS, there is no clear limit to these variables below which further decreases will not improve outcomes (75).

P_{plat} is the sum of PEEP or PEEP_{tot} and ΔP. A high P_{plat}, close to 30 cm H₂O, is an important alarm for the clinician. The incidence of complications, such as pneumothoraces, have markedly decreased since the use of lower P_{plat} (76). Excessive ΔP, and therefore excessive P_{plat}, increases the risk of V_T-induced strain, and is associated with higher mortality (1, 29). The mechanical effects of high PEEP depends on lung recruitability (77) and can be beneficial (recruitment of previously closed alveoli) or harmful (hyperinflation of previously opened alveoli). Therefore, increase in P_{plat} resulting from increased PEEP may be associated with different effects on ΔP, making clinical interpretation difficult; when ΔP was stratified, P_{plat} between around 22–34 cm H₂O was not associated with mortality (1).

ΔP

Amato and colleagues (19) proposed that VILI might be due to the swings in pressure

during ventilation rather than an absolute maximum level. This value, known as ΔP, corresponds to the elastic pressure swing, ΔP_{el,rs} = ΔV × Ers. ΔP equals V_T/Cr_s, and Cr_s is proportional to FRC (69, 78). ΔP thus describes the relationship between V_T and the lung volume available to receive the breath. Using a statistical tool known as multilevel mediation analysis to analyze individual data from 3,562 patients with ARDS enrolled in nine randomized trials, it was demonstrated that ΔP was the pulmonary mechanical variable most predictive of 60-day survival in ARDS (1, 29). Another study showed that ΔP and lung stress were closely related (79): a ΔP of 15 predicted a lung stress of 24 cm H₂O, a level that has been associated with VILI (80–83).

Limiting ΔP—possibly keeping it below 14 cm H₂O (1, 29)—can be achieved either by decreasing V_T or increasing Cr_s. V_T reduction may require volumes that do not support adequate oxygenation or sufficient CO₂ elimination. Increasing Cr_s by altering PEEP may not always be achievable. Clinical trials to prospectively test the use of ΔP for optimizing ventilatory management are needed.

PL

Talmor and coworkers (84–86) tested the principle of titrating PEEP to obtain a positive end-expiratory P_L (Figure 1) in a pilot study and in an ongoing multicenter trial. Gattinoni and colleagues (77, 80, 87) used end-inspiratory P_L values to guide the

upper limit of ventilating pressures and volumes. Gattinoni's calculations were not based on direct measurements of P_{pl,EIO}, but used the lung elastance-to-Ers ratio, which ignores the value of P_{pl} at end-expiration at zero PEEP. The estimates for end-inspiratory P_L are therefore lower when calculated by the direct measurement of P_{L,EIO} using P_{es}. Absolute values of P_{es} are reliable (42, 88), especially after proper correction for esophageal wall compliance and esophageal balloon volume (88), but there is a pressure gradient from the vertebral to the sternal part in the pleural space. So the two methods give different indexes that may reflect different local pressures (45).

Recent studies have also suggested a possibly important role of ΔP for general patients under MV (1), neurological patients (89), patients under extracorporeal membrane oxygenation (90), and patients under general anesthesia (91). The relatively constant value of E_{CW} across patients, even in morbid obesity (92–94), makes ΔP_{el,rs} a reasonable surrogate of ΔP_{el,L} in many circumstances. Sometimes, it makes sense to better estimate the cyclic alveolar wall stress through a direct measurement of ΔP_{el,L} (95) (instead of ΔP_{el,rs}), especially in situations of clearly impaired chest wall compliance, abdominal hypertension, or severe scoliosis. The lung ΔP alone (i.e., ΔP_L in Figure 1) is the component relevant to VILI (13), and might better surrogate lung strain than ΔP (which includes the elastance of the chest wall and

linked by the specific elastance of the lung (E_{Lspec}) such that:

$$\text{strain} = \text{stress}/E_{Lspec}. \quad (15)$$

Thus, if the net distending pressure, P_L , is known, strain may be estimated:

$$\text{strain} = P_L/E_{Lspec}. \quad (16)$$

The value of E_{Lspec} is approximately 13 cm H_2O , a value that varies moderately during disease in the range of tidal ventilation (8, 107). Thus, by measuring transpulmonary stress, strain may be inferred (i.e., $\sim 1/13$ of transpulmonary stress). Recent studies on tissue mechanics, however, have challenged the assumption of a linear relationship between stress and strain, suggesting that bedside estimates of strain are potentially problematic when estimating stresses near the limits of tissue rupture (108).

Use of Respiratory Mechanics to Minimize VILI at Low Lung Volumes

It is supposed that cyclic recruitment–derecruitment of alveoli may occur at low pressures (109–111). VILI at low lung volume is due to high local tissue stress and parenchymal shear injury supposedly caused by repetitive opening and closing of alveoli and distal small airways (atelectrauma) (14, 15).

In patients with recruitable lung, PEEP increases the amount of aerated lung at end expiration, increasing the number of functional lung units compared with zero end-expiratory pressure, and therefore potentially minimizing strain. Because the concept of strain assumes that there is a resting lung volume (equal to FRC) in which the stresses on alveolar walls are zero, the occurrence of recruitment with PEEP creates a conceptual problem. PEEP has two main effects: (1) unfolding of alveolar walls in previously collapsed alveoli (newly recruited), which become functional, but not necessarily strained; and (2) strain of previously functional and newly functional alveoli. Thus, PEEP will increase the end-expiratory lung volume, generating the so-called PEEP-induced increase in lung volume (V_{PEEP}), but at the same time will increase the “functional FRC” (i.e., the FRC that would be observed if the lung did not recollapse at zero end-expiratory pressure). Part of this V_{PEEP} is an unstressed component that should be subtracted from the true strain. In practice, it

is difficult to estimate this newly added (unstressed) lung size, and some simplifications have been proposed (106). Some investigators have added V_{PEEP} (“static strain”) to V_T (“dynamic strain”), and therefore calculate strain as $(V_T + V_{PEEP})/FRC$ (112). Others have calculated strain as $V_T/EELV$, where EELV includes both FRC and V_{PEEP} (113–115). Thus, the latter definition removed the “static” component from the numerator, in accordance with more recent studies showing that static strain forces (from PEEP) may be less injurious than dynamic strain forces (from V_T), and may be protective (116, 117).

PEEP-induced lung recruitment has a strong impact on strain calculation: the recruited volume and the new functional FRC generated by PEEP will increase the denominator in strain definitions. Thus, the ability to identify patients with recruitable lung has significant implications with respect to PEEP titration in ARDS. Both CT imaging and pressure–volume curves have

demonstrated an acceptable ability to differentiate patients with recruitable lung from those with unrecruitable lung (77, 118–120). Dellamonica and colleagues (106) have recently demonstrated that the comparison of EELV at two different PEEP levels allows the bedside assessment of PEEP-associated lung recruitment. This technique may help guide PEEP titration and strain management in patients with ARDS. For the different methods proposed to titrate PEEP, we refer the reader to another article of the same series (121).

Stress Raisers

The lung parenchyma in ARDS displays apparent heterogeneity in the distribution of consolidation and atelectasis. High regional strain may be exacerbated by the presence of “stress raisers”—interfaces of aerated and nonaerated lung that amplify regional tissue forces.

Mead and coworkers (122, 123) demonstrated that this led to an uneven

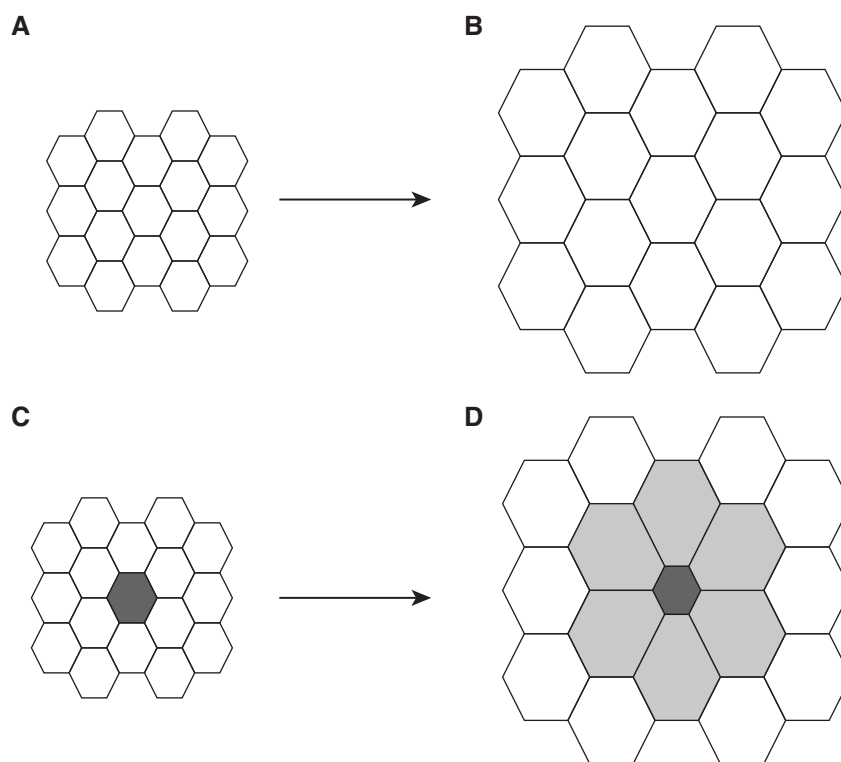


Figure 5. A stress raiser is a local area of inhomogeneous tissue that multiplies local stress and strain in the tissues around it when a given stress is directed through it. An equivalent volume of gas is ventilated into normal lung (A) and into a region of lung with a stress raiser—a collapsed or consolidated portion that does not participate in ventilation (the *dark gray lung unit* in C). An equivalent volume is applied to both lung units in A and C; however, the portions of lung around the stress raiser (*light gray regions* in D) are subjected to greater stress than those around the normally aerated central alveolus in B, whereas the size of the collapsed or consolidated portion (the *dark gray lung unit* in C and D) does not change size with ventilation. Adapted from Reference 126.

28. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–336.
29. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
30. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017;195:438–442.
31. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty Years of Research in ARDS. Spontaneous breathing during mechanical ventilation: risks, mechanisms, and management. *Am J Respir Crit Care Med* 2017;195:985–992.
32. Rohrer J. Der Zusammenhang der Atemkräfte und ihre Abhängigkeit vom Dehnungszustand der Atmungsorgane. *Pflugers Arch Gesamte Physiol Menschen Tiere* 1916;165:419–444.
33. Mead J. Mechanical properties of lungs. *Physiol Rev* 1961;41:281–330.
34. Kondili E, Prinianakis G, Athanasakis H, Georgopoulos D. Lung emptying in patients with acute respiratory distress syndrome: effects of positive end-expiratory pressure. *Eur Respir J* 2002;19:811–819.
35. Loring SH, O'Donnell CR, Behazin N, Malhotra A, Sarge T, Ritz R, Novack V, Talmor D. Esophageal pressures in acute lung injury: do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? *J Appl Physiol (1985)* 2010;108:515–522.
36. Hedenstierna G, Bindslev L, Santesson J, Norlander OP. Airway closure in each lung of anesthetized human subjects. *J Appl Physiol* 1981;50:55–64.
37. Hedenstierna G, McCarthy G, Bergström M. Airway closure during mechanical ventilation. *Anesthesiology* 1976;44:114–123.
38. Schonfeld SA, Ploysongsang Y. Airway closure and trapped gas during low volume breathing. *Respir Physiol* 1983;51:63–77.
39. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Airway closure, atelectasis and gas exchange during general anaesthesia. *Br J Anaesth* 1998;81:681–686.
40. Mancebo J, Calaf N, Benito S. Pulmonary compliance measurement in acute respiratory failure. *Crit Care Med* 1985;13:589–591.
41. Brusasco V, Warner DO, Beck KC, Rodarte JR, Rehder K. Partitioning of pulmonary resistance in dogs: effect of tidal volume and frequency. *J Appl Physiol (1985)* 1989;66:1190–1196.
42. Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. *Am J Respir Crit Care Med* 2016;194:1452–1457.
43. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, et al.; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014;189:520–531.
44. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, et al.; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med* 2016;42:1360–1373.
45. Yoshida T, Lima C, Roldan R, Morais CCA, Gomes S, Grieco DL, Richard J-CM, Brochard LJ, Kavanagh BP, Amato MBP. Validation of esophageal pressure by direct measurement of pleural pressure in normal and injured lungs [abstract]. *Am J Respir Crit Care Med* 2017; 195:A7528.
46. Similowski T, Levy P, Corbeil C, Albala M, Pariente R, Derenne JP, Bates JH, Jonson B, Milic-Emili J. Viscoelastic behavior of lung and chest wall in dogs determined by flow interruption. *J Appl Physiol (1985)* 1989;67:2219–2229.
47. Suki B, Barabási AL, Lutchen KR. Lung tissue viscoelasticity: a mathematical framework and its molecular basis. *J Appl Physiol (1985)* 1994;76:2749–2759.
48. Suki B, Bates JH. A nonlinear viscoelastic model of lung tissue mechanics. *J Appl Physiol (1985)* 1991;71:826–833.
49. Bachofen H. Lung tissue resistance and pulmonary hysteresis. *J Appl Physiol* 1968;24:296–301.
50. Fredberg JJ, Stamenovic D. On the imperfect elasticity of lung tissue. *J Appl Physiol (1985)* 1989;67:2408–2419.
51. Barberis L, Manno E, Guérin C. Effect of end-inspiratory pause duration on plateau pressure in mechanically ventilated patients. *Intensive Care Med* 2003;29:130–134.
52. Hildebrandt J. Pressure–volume data of cat lung interpreted by a plastoelastic, linear viscoelastic model. *J Appl Physiol* 1970;28:365–372.
53. Santini A, Milesi M, Maraffi T, Pugni P, Andreis D, Cavenago M, Gattinoni M, Protti A. Role of static and dynamic driving airway pressure in the development of ventilator-induced lung injury. *Intensive Care Med Exp* 2016;4:A677.
54. Mezidi M, Yonis H, Aublanc M, Lissonde F, Louf-Durier A, Perinel S, Taponnier R, Richard JC, Guérin C. Effect of end-inspiratory plateau pressure duration on driving pressure. *Intensive Care Med* 2016;4:A1040.
55. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugni P, Andreis DT, Nicosia F, Zannin E, Gatti S, et al. Role of strain rate in the pathogenesis of ventilator-induced lung edema. *Crit Care Med* 2016; 44:e838–e845.
56. D'Angelo E, Calderini E, Torri G, Robatto FM, Bono D, Milic-Emili J. Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time. *J Appl Physiol (1985)* 1989;67:2556–2564.
57. Sullivan KJ, Mortola JP. Dynamic lung compliance in newborn and adult cats. *J Appl Physiol (1985)* 1986;60:743–750.
58. Devaquet J, Jonson B, Niklason L, Si Larbi A-G, Uttman L, Aboab J, Brochard L. Effects of inspiratory pause on CO₂ elimination and arterial Pco₂ in acute lung injury. *J Appl Physiol (1985)* 2008;105: 1944–1949.
59. Pesenti A, Pelosi P, Foti G, D'Andrea L, Rossi N. An interrupter technique for measuring respiratory mechanics and the pressure generated by respiratory muscles during partial ventilatory support. *Chest* 1992;102:918–923.
60. Wright PE, Bernard GR. The role of airflow resistance in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1989; 139:1169–1174.
61. Pesenti A, Pelosi P, Rossi N, Virtuani A, Brazzi L, Rossi A. The effects of positive end-expiratory pressure on respiratory resistance in patients with the adult respiratory distress syndrome and in normal anesthetized subjects. *Am Rev Respir Dis* 1991;144:101–107.
62. Koutsoukou A, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, Milic-Emili J. Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000;161:1590–1596.
63. Koutsoukou A, Bekos B, Sotiropoulou C, Koulouris NG, Roussos C, Milic-Emili J. Effects of positive end-expiratory pressure on gas exchange and expiratory flow limitation in adult respiratory distress syndrome. *Crit Care Med* 2002;30:1941–1949.
64. Vieillard-Baron A, Prin S, Schmitt J-M, Augarde R, Page B, Beauchet A, Jardin F. Pressure–volume curves in acute respiratory distress syndrome: clinical demonstration of the influence of expiratory flow limitation on the initial slope. *Am J Respir Crit Care Med* 2002;165: 1107–1112.
65. D'Angelo E, Robatto FM, Calderini E, Tavola M, Bono D, Torri G, Milic-Emili J. Pulmonary and chest wall mechanics in anesthetized paralyzed humans. *J Appl Physiol (1985)* 1991;70:2602–2610.
66. Estenne M, Yernault JC, De Troyer A. Rib cage and diaphragm–abdomen compliance in humans: effects of age and posture. *J Appl Physiol (1985)* 1985;59:1842–1848.
67. Rylander C, Högman M, Perchiizzi G, Magnusson A, Hedenstierna G. Functional residual capacity and respiratory mechanics as indicators of aeration and collapse in experimental lung injury. *Anesth Analg* 2004;98:782–789.
68. Heinze H, Eichler W. Measurements of functional residual capacity during intensive care treatment: the technical aspects and its possible clinical applications. *Acta Anaesthesiol Scand* 2009;53: 1121–1130.

69. 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.
70. Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L. The “baby lung” became an adult. *Intensive Care Med* 2016;42: 663–673.
71. Kaplan JD, Calandrino FS, Schuster DP. A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. *Am Rev Respir Dis* 1991;143:150–154.
72. Sandiford P, Province MA, Schuster DP. Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:737–742.
73. Bellani G, Messa C, Guerra L, Spagnoli E, Foti G, Patroniti N, Fumagalli R, Musch G, Fazio F, Pesenti A. Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: a [18F]-fluoro-2-deoxy-D-glucose PET/CT study. *Crit Care Med* 2009;37:2216–2222.
74. Borges JB, Costa ELV, Bergquist M, Lucchetta L, Widström C, Maripuu E, Suarez-Sipmann F, Larsson A, Amato MBP, Hedenstierna G. Lung inflammation persists after 27 hours of protective Acute Respiratory Distress Syndrome Network Strategy and is concentrated in the nondependent lung. *Crit Care Med* 2015;43:e123–e132.
75. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172:1241–1245.
76. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med* 2002;28:406–413.
77. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006;354:1775–1786.
78. Lumb A, Nunn J, editors. Nunn’s applied respiratory physiology. Edinburgh, London: Churchill Livingstone/Elsevier; 2010.
79. Chiumello D, Carlesso E, Brioni M, Cressoni M. Airway driving pressure and lung stress in ARDS patients. *Crit Care* 2016;20:276.
80. Chiumello D, Carlesso E, Cadringer P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008;178:346–355.
81. Ranieri VM, Brienza N, Santostasi S, Puntillo F, Mascia L, Vitale N, Giuliani R, Memeo V, Bruno F, Fiore T, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *Am J Respir Crit Care Med* 1997;156:1082–1091.
82. Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, Mascia L, Pesenti A, Zangrillo A, Gattinoni L, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. *Intensive Care Med* 2012;38:395–403.
83. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology* 2002;96: 795–802.
84. Talmor D, Sarge T, Malhotra A, O’Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359:2095–2104.
85. Talmor D, Sarge T, O’Donnell CR, Ritz R, Malhotra A, Lisbon A, Loring SH. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med* 2006;34:1389–1394.
86. Fish E, Novack V, Banner-Goodspeed VM, Sarge T, Loring S, Talmor D. The Esophageal Pressure–Guided Ventilation 2 (EPVent2) trial protocol: a multicentre, randomised clinical trial of mechanical ventilation guided by transpulmonary pressure. *BMJ Open* 2014;4: e006356.
87. Gattinoni L, Chiumello D, Carlesso E, Valenza F. Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care* 2004;8:350–355.
88. Mojoli F, Iotti GA, Torriglia F, Pozzi M, Volta CA, Bianzina S, Braschi A, Brochard L. *In vivo* calibration of esophageal pressure in the mechanically ventilated patient makes measurements reliable. *Crit Care* 2016;20:98.
89. Tejerina E, Pelosi P, Muriel A, Peñuelas O, Sutherasan Y, Frutos-Vivar F, Nin N, Davies AR, Rios F, Violi DA, et al.; for VENTILA group. Association between ventilatory settings and development of acute respiratory distress syndrome in mechanically ventilated patients due to brain injury. *J Crit Care* 2017;38:341–345.
90. Serpa Neto A, Schmidt M, Azevedo LCP, Bein T, Brochard L, Beutler G, Combes A, Costa ELV, Hodgson C, Lindskov C, et al.; ReVA Research Network and the PROVE Network Investigators. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis : mechanical ventilation during ECMO. *Intensive Care Med* 2016;42:1672–1684.
91. Neto AS, Hemmes SNT, Barbas CSV, Beiderlinden M, Fernandez-Bustamante A, Futier E, Gajic O, El-Tahan MR, Ghamdi AA, Günay E, et al.; PROVE Network Investigators. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med* 2016;4:272–280.
92. Pirrone M, Fisher D, Chipman D, Imber DAE, Corona J, Mietto C, Kacmarek RM, Berra L. Recruitment maneuvers and positive end-expiratory pressure titration in morbidly obese ICU patients. *Crit Care Med* 2016;44:300–307.
93. Hedenstierna G, Santesson J. Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. *Acta Anaesthesiol Scand* 1976;20:248–254.
94. Chiumello D, Colombo A, Algieri I, Mietto C, Carlesso E, Crimella F, Cressoni M, Quintel M, Gattinoni L. Effect of body mass index in acute respiratory distress syndrome. *Br J Anaesth* 2016;116: 113–121.
95. Baedorf Kassis E, Loring SH, Talmor D. Mortality and pulmonary mechanics in relation to respiratory system and transpulmonary driving pressures in ARDS. *Intensive Care Med* 2016;42:1206–1213.
96. Chen L, Xu M, Chen G-Q, Soliman I, Rittayamai N, Sklar M, Shklar O, Martins C, Greco P, Every H, et al. Respiratory mechanics in acute respiratory distress syndrome: variables and indexes associated with clinical outcome [abstract]. *Am J Respir Crit Care Med* 2016;193: A1839.
97. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J. Volume–pressure curve of the respiratory system predicts effects of PEEP in ARDS: “occlusion” versus “constant flow” technique. *Am J Respir Crit Care Med* 1994;149:19–27.
98. Ranieri VM, Zhang H, Mascia L, Aubin M, Lin CY, Mullen JB, Grasso S, Binnie M, Volgyesi GA, Eng P, et al. Pressure–time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology* 2000;93:1320–1328.
99. Carvalho AR, Spieth PM, Pelosi P, Vidal Melo MF, Koch T, Jandre FC, Giannella-Neto A, de Abreu MG. Ability of dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration. *Intensive Care Med* 2008;34:2291–2299.
100. Formenti P, Graf J, Santos A, Gard KE, Faltesek K, Adams AB, Dries DJ, Marini JJ. Non-pulmonary factors strongly influence the stress index. *Intensive Care Med* 2011;37:594–600. [Published erratum appears in *Intensive Care Med* 37:727.]
101. Hickling KG. The pressure–volume curve is greatly modified by recruitment: a mathematical model of ARDS lungs. *Am J Respir Crit Care Med* 1998;158:194–202.
102. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, et al. Lung stress and strain during mechanical ventilation: any safe threshold? *Am J Respir Crit Care Med* 2011;183:1354–1362.
103. González-López A, García-Prieto E, Batalla-Solís E, Amado-Rodríguez L, Avello N, Blanch L, Albaiceta GM. Lung strain and biological response in mechanically ventilated patients. *Intensive Care Med* 2012;38:240–247.

104. Bellani G, Guerra L, Musch G, Zanella A, Patroniti N, Mauri T, Messa C, Pesenti A. Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med* 2011;183:1193–1199.
105. Wellman TJ, Winkler T, Costa ELV, Musch G, Harris RS, Zheng H, Venegas JG, Vidal Melo MF. Effect of local tidal lung strain on inflammation in normal and lipopolysaccharide-exposed sheep*. *Crit Care Med* 2014;42:e491–e500.
106. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard JCM, Diehl JL, Mancebo J, Rouby JJ, *et al.* PEEP-induced changes in lung volume in acute respiratory distress syndrome: two methods to estimate alveolar recruitment. *Intensive Care Med* 2011;37:1595–1604.
107. De Robertis E, Liu JM, Blomquist S, Dahm PL, Thörne J, Jonson B. Elastic properties of the lung and the chest wall in young and adult healthy pigs. *Eur Respir J* 2001;17:703–711.
108. Suki B, Bates JHT. Lung tissue mechanics as an emergent phenomenon. *J Appl Physiol (1985)* 2011;110:1111–1118.
109. Bruhn A, Bugeo D, Riquelme F, Varas J, Retamal J, Besa C, Cabrera C, Bugeo G. Tidal volume is a major determinant of cyclic recruitment–derecruitment in acute respiratory distress syndrome. *Minerva Anestesiol* 2011;77:418–426.
110. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Hermann P, Mascia L, Quintel M, *et al.* Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007;175:160–166.
111. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009;111:826–835.
112. Protti A, Chiumello D, Cressoni M, Carlesso E, Mietto C, Berto V, Lazzerini M, Quintel M, Gattinoni L. Relationship between gas exchange response to prone position and lung recruitability during acute respiratory failure. *Intensive Care Med* 2009;35:1011–1017.
113. Brunner JX, Wysocki M. Is there an optimal breath pattern to minimize stress and strain during mechanical ventilation? *Intensive Care Med* 2009;35:1479–1483.
114. Mentzelopoulos SD, Roussos C, Zakyntinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. *Eur Respir J* 2005;25:534–544.
115. Paula LF, Wellman TJ, Winkler T, Spieth PM, Güldner A, Venegas JG, Gama de Abreu M, Carvalho AR, Vidal Melo MF. Regional tidal lung strain in mechanically ventilated normal lungs. *J Appl Physiol* 2016;121:1335–1347.
116. Protti A, Votta E, Gattinoni L. Which is the most important strain in the pathogenesis of ventilator-induced lung injury: dynamic or static? *Curr Opin Crit Care* 2014;20:33–38.
117. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, *et al.* Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Crit Care Med* 2013;41:1046–1055.
118. Rouby J-J, Puybasset L, Nieszowska A, Lu Q. Acute respiratory distress syndrome: lessons from computed tomography of the whole lung. *Crit Care Med* 2003;31(4 suppl):S285–S295.
119. Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L. Pressure–volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med* 1999;159:1172–1178.
120. Lu Q, Vieira SR, Richecoeur J, Puybasset L, Kalfon P, Coriat P, Rouby JJ. A simple automated method for measuring pressure–volume curves during mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:275–282.
121. Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ARDS: setting positive end-expiratory pressure in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1429–1438.
122. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970;28:596–608.
123. Cressoni M, Cadringer P, Chiurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, *et al.* Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189:149–158.
124. Rausch SMK, Haberthür D, Stampanoni M, Schittny JC, Wall WA. Local strain distribution in real three-dimensional alveolar geometries. *Ann Biomed Eng* 2011;39:2835–2843.
125. Gross D, Hauger W, Schröder J, Wall W, Bonet J. Engineering mechanics 2. Berlin, Heidelberg: Springer; 2011.
126. Retamal J, Bergamini BC, Carvalho AR, Bozza FA, Borzone G, Borges JB, Larsson A, Hedenstierna G, Bugeo G, Bruhn A. Non-lobar atelectasis generates inflammation and structural alveolar injury in the surrounding healthy tissue during mechanical ventilation. *Crit Care* 2014;18:505.