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 CO_2; 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 H_2O 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 (Paw) *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 (Pplat) 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 (Pel), flow-resistive pressure (Pres), and inertial pressure (Pin) as follows:

$$\begin{aligned} \text{Pvent} + \text{Pmus} &= \text{Pel} + \text{Pres} + \text{Pin} \\ &= f_1(\text{V}) + f_2(\dot{\text{V}}) + f_3(\ddot{\text{V}}), \end{aligned} \quad (1)$$

where Pvent is ventilator pressure; Pmus is muscle pressure; f_1, f_2, and f_3 are functions describing the relationships between Pel and volume (V), Pres and the rate of change in volume (flow, $\dot{V}$), and Pin 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 Paw. By assuming linear relationships in these functions, the motion of the system can be described:

$$\text{Paw} + \text{Pmus} = \text{Ers}\cdot\Delta\text{V} + \text{Rrs}\cdot\dot{\text{V}} + \text{Irs}\cdot\ddot{\text{V}}, \quad (2)$$

where Ers represents respiratory system elastance (the inverse of compliance), ΔV is the volume difference from the resting volume, Rrs represents respiratory system resistance, and Irs 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 Pmus is nil. ΔV is the sum of inspired volume (Vinsp) above end-expiratory lung volume (EELV) and EELV above FRC. The product of Ers and EELV above FRC is equivalent to the total Pel at the end of expiration (total positive end-expiratory pressure [PEEPtot], namely, the sum of PEEP and intrinsic PEEP). Equation 2 can then be presented as:

$$\text{Paw} = \text{Ers}\cdot\text{Vinsp} + \text{Rrs}\cdot\dot{\text{V}} + \text{PEEPtot}. \quad (3)$$

Paw, Vinsp, and $\dot{V}$ are directly monitored or set by the ventilator, whereas Ers, Rrs, and PEEPtot need to be calculated. The use of a constant flow on the ventilator greatly facilitates this calculation. An end-expiratory occlusion (EEO), when Vinsp and $\dot{V}$ are nil, allows measuring PEEPtot. An end-inspiratory occlusion (EIO) after delivering V_T allows calculating Paw_{EIO}, defined as Pplat, and calculating Equations 4 and 5:

$$\text{Paw}_{\text{EIO}} = \text{Ers}\cdot\text{V}_T + \text{PEEPtot} \quad (4)$$

$$\text{Ers} = (\text{Pplat} - \text{PEEPtot})/\text{V}_T. \quad (5)$$

When $\dot{V}$ is constant, Pres will remain approximately constant throughout inspiration. The peak Paw (Ppeak) occurs at the end of inspiration:

$$\text{Ppeak} = \text{Ers}\cdot\text{V}_T + \text{Rrs}\cdot\dot{\text{V}} + \text{PEEPtot}. \quad (6)$$

Subtracting Equation 4 from Equation 6 allows the calculation of Rrs:

$$\text{Ppeak} - \text{Paw}_{\text{EIO}} = \text{Rrs}\cdot\dot{\text{V}} \quad (7)$$

$$\text{Rrs} = (\text{Ppeak} - \text{Pplat})/\dot{\text{V}}. \quad (8)$$

Of note, the calculated Rrs 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. Paw under static conditions is equal to alveolar pressure (Palv), but may not reflect Palv 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

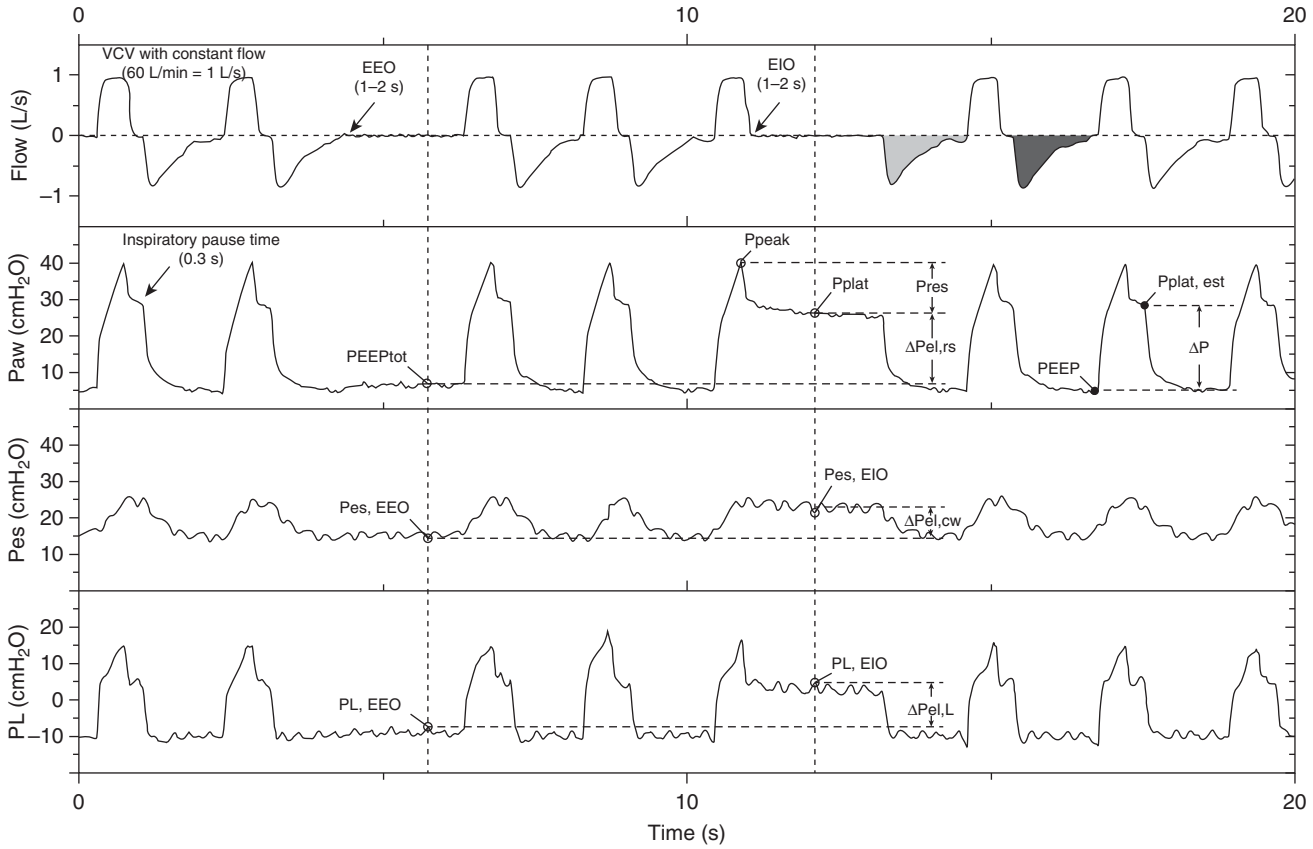

Figure 1. Static measurements of respiratory mechanics. Essential variables of respiratory mechanics can be measured by performing an end-expiratory occlusion (EEO) and an end-inspiratory occlusion (EIO) for 1–2 seconds or by using volume-controlled ventilation with a constant inspiratory flow and an inspiratory pause time of 0.3 seconds. When EEO and EIO are used, potential leakage needs to be excluded by comparing the difference in V_T between the breath with occlusion (*light gray area of flow*) and the one without occlusion (*dark gray area*). ΔP = driving pressure as the difference between plateau pressure and positive end-expiratory pressure; $\Delta P_{el,cw}$ = the change in chest wall elastic pressure; $\Delta P_{el,L}$ = the change in lung elastic pressure; $\Delta P_{el,rs}$ = the change in elastic pressure of respiratory system; Paw = airway pressure; PEEP = positive end-expiratory pressure; PEEPtot = total positive end-expiratory pressure; Pes = esophageal pressure; $P_{es,EEO}$ = esophageal pressure at end-expiratory occlusion; $P_{es,EIO}$ = esophageal pressure at end-inspiratory occlusion; P_L = transpulmonary pressure; $P_{L,EEO}$ = transpulmonary pressure at end-expiratory occlusion; $P_{L,EIO}$ = transpulmonary pressure at end-inspiratory occlusion; Ppeak = peak airway pressure; Pplat = plateau pressure; Pplat,est = estimated plateau pressure; Pres = resistive pressure; VCV = volume-controlled ventilation;

using static Paw (Pplat and PEEPtot) reflects the summed influence of both alveolar units (in parallel) and chest wall (in series). Small airways may also have some compliance, but they contribute with less than 3% of static lung compliance (40, 41).

Static Measurements for Partitioning Lungs and Chest Wall

The measurement of Paw allows the description of the total respiratory system. To differentiate the mechanical properties of the lungs from those of the chest wall requires measuring the pleural pressure (Ppl). The pressure applied on the lungs is the difference between Paw and Ppl, and is called the P_L (42). When the respiratory muscles are relaxed, the pressure applied on the chest wall (Pcw) is the difference between Ppl and body surface pressure (Pbs); the pressure applied on the total respiratory system (Prs) is the difference between Paw and Pbs. Hence,

$$\begin{aligned} Prs &= Paw - Pbs \\ &= (Paw - Ppl) + (Ppl - Pbs) \\ &= P_L + Pcw. \end{aligned} \quad (9)$$

Pbs is usually atmospheric pressure, which, by convention, is referred to as zero. All of the mechanical properties of the respiratory system can be partitioned into lungs and chest wall by separating pressures. For example, Paw at EIO would be the sum of P_L and Pcw:

$$Pplat = P_{L,EIO} + Pcw_{,EIO}. \quad (10)$$

The change in the elastic pressure of the respiratory system is the sum of the change in lung elastic pressure and the change in chest wall elastic pressure (Figure 1), and:

$$Ers = E_L + Ecw, \quad (11)$$

where E_L and Ecw denote lung and chest wall elastance (the inverse of lung and chest wall compliance). Estimating Ppl with an esophageal balloon catheter has made all these calculations possible (Figure 2) (43, 44). As the esophageal pressure (Pes) obtained through a catheter approximates Ppl, Equations 9 and 10 can be restated by replacing Ppl with Pes. P_L is calculated as the difference between Paw and Pes, and reflects the distending pressure of the lung. These measurements are illustrated in Figure 1. Two detailed reviews of the application of Pes, technical instructions, and interpretations have recently been published (43, 44). One important limitation is that the Ppl is not uniform, and a pressure gradient between

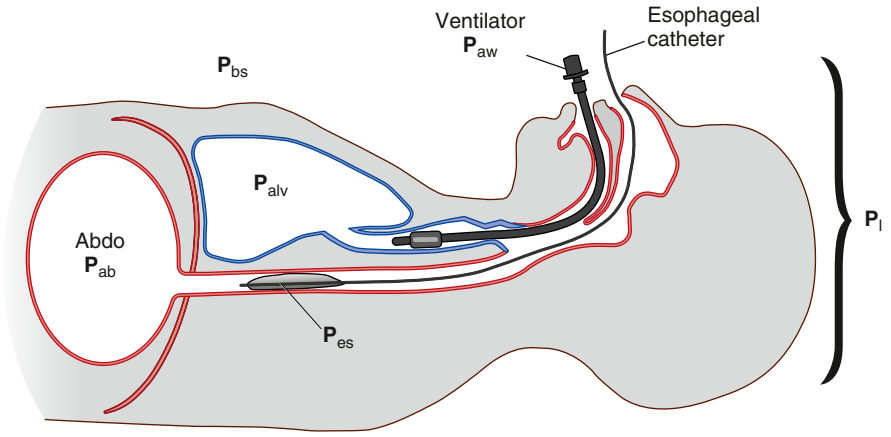

Figure 2. The clinician can directly measure the pressure from the ventilator at the airway opening (airway pressure [Paw]) and reference it to body surface pressure (Pbs). Esophageal pressure (Pes) may also be directly measured with a balloon manometer. Transpulmonary pressure (P_L) = Paw − Pes. The 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 V_T 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 V_T (51). The longer the inspiratory pause, the higher the pressure decay (typically amounting to 2–3 cm H_2O). 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 V_T 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 CO_2 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

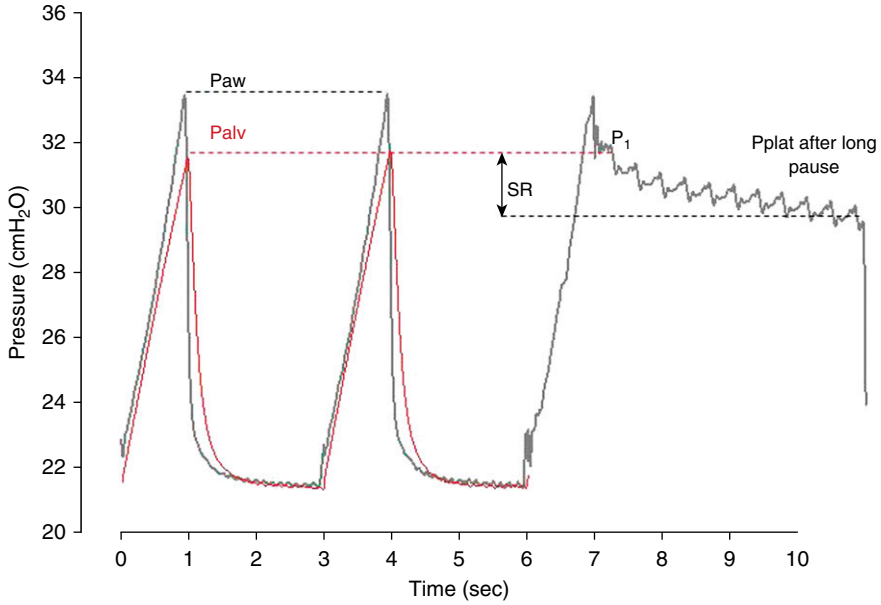

Figure 3. Tracings of airway pressure (Paw) in a pig model of acute respiratory distress syndrome (*gray lines*), superimposed with estimated values for alveolar pressure (Palv; *red lines*; Palv was obtained by multiple linear regression technique [MLR] according to the motion equation described in Equation 3). Note that the traditional plateau pressure (Pplat) 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 Palv achieved in previous cycles (under dynamic conditions). Recent studies have suggested that such dynamic swings in Palv (peak minus valley of Palv), representing the effective driving pressure (ΔP), better predict the risk of ventilator-induced lung injury (VILI) than traditional measures. Thus, the traditional Pplat 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 Pplat or ΔP. By using this short procedure, the estimates of Pplat would be closer to Paw immediately after occlusion (P_1) described in classic physiology, and closer to peak Palv 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 P_L. To mitigate alveolar distension and volutrauma, rigorous limitation of V_T and pressures are recommended (18–22).

V_T, Pplat

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 Pplat 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
Crs, ml/cm H_2O	38	1.6% of VC ml/cm H_2O	An average VC in normal subjects is around 4,000 ml; the predicted Crs would be 1.6% × 4,000 = 64 ml/cm H_2O
C_L, ml/cm H_2O	55	2.9% of VC ml/cm H_2O	Roughly predicted range: 90–140 ml/cm H_2O
Ccw, ml/cm H_2O	125	3.6% of VC ml/cm H_2O	Roughly predicted range: 100–200 ml/cm H_2O
Ers, cm H_2O/L	26	0.62 cm H_2O/1% VC (L)	An average VC in normal subjects is 4 L; this gives a predicted Ers as 0.62 ÷ 4% = 16 cm H_2O
E_L, cm H_2O/L	18	0.34 cm H_2O/1% VC (L)	An average predicted value would be around 9 cm H_2O/L
Ecw, cm H_2O/L	8	0.28 cm H_2O/1% VC (L)	An average predicted value would be around 7 cm H_2O/L
E_L/Ers	0.70	0.55	Estimated from predicted values of E_L and Ers
Rrs, cm H_2O/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; C_L = lung compliance; Crs = respiratory system compliance; Ecw = chest wall elastance; E_L = lung elastance; E_L/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 H_2O 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 Pplat between 28 and 30 cm H_2O 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 Pplat has improved mortality in ARDS, there is no clear limit to these variables below which further decreases will not improve outcomes (75).

Pplat is the sum of PEEP or PEEPtot and ΔP. A high Pplat, close to 30 cm H_2O, is an important alarm for the clinician. The incidence of complications, such as pneumothoraces, have markedly decreased since the use of lower Pplat (76). Excessive ΔP, and therefore excessive Pplat, 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 Pplat resulting from increased PEEP may be associated with different effects on ΔP, making clinical interpretation difficult; when ΔP was stratified, Pplat between around 22–34 cm H_2O 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, ΔPel,rs = ΔV × Ers. ΔP equals V_T/Crs, and Crs 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 H_2O, a level that has been associated with VILI (80–83).

Limiting ΔP—possibly keeping it below 14 cm H_2O (1, 29)—can be achieved either by decreasing V_T or increasing Crs. V_T reduction may require volumes that do not support adequate oxygenation or sufficient CO_2 elimination. Increasing Crs by altering PEEP may not always be achievable. Clinical trials to prospectively test the use of ΔP for optimizing ventilatory management are needed.

P_L

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 Ppl 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 Pes. Absolute values of Pes 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 ΔPel,rs a reasonable surrogate of ΔPel,L in many circumstances. Sometimes, it makes sense to better estimate the cyclic alveolar wall stress through a direct measurement of ΔPel,L (95) (instead of ΔPel,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

abdomen). Whether ΔP_L better predicts clinical outcomes than the more easily measured ΔP requires further study (96).

Stress Index

Conventional detection of recruitment and overdistension during MV involves analysis of the change in compliance (represented by changes in the slope of the static pressure–volume curve). Ranieri and colleagues (97) found that, by using constant-flow inflation, the dynamic pressure–volume curve during MV could provide the same information as the static curve. As Pres remains constant during inflation at constant flow, the change in Paw reflects the change in Pel. Because volume is the integral of flow rate over time, the pressure–time curve at a constant flow can be used as a surrogate for the quasistatic pressure–volume curve. Through fitting pressure (either Paw or P_L) as a power function of time:

$$\text{pressure} = a \cdot \text{time}^b + c, \qquad (12)$$

where coefficients a, b, and c are constants, the shape of pressure–time curve can be described by coefficient b and termed the "stress index." A convex pattern ($b < 0.9$) of the pressure–time curve indicates intratidal recruitment, a straight line ($0.9 < b < 1.1$) indicates linear compliance, and a concave pattern ($b > 1.1$) indicates hyperinflation (98). An alternative approach has been used by fitting the volume as a quadratic function of pressure, and analyzing the signal of the quadratic coefficient E2 (elastance dependent on volume) to indicate either intratidal recruitment or overdistension (99).

Experimental studies have confirmed these shape thresholds and their association with VILI, but a number of caveats exist regarding interpretation in situations of pleural effusions, high intra-abdominal pressure (100), or heterogeneous lung disease (99). A concave pattern of pressure–time curve may relate to progressive decrease in recruitment rather than specifically overdistension (101). Moreover, the stress index was developed with larger V_T values than are currently used, increasing the technical difficulties in obtaining reliable values, especially at high inspiratory flow. Finally, it requires dedicated software. Simply observing the shape of the pressure–time curve during constant flow is sometimes insightful when titrating PEEP or V_T at the bedside (Figure 4).

Stress and Strain

Lungs of patients with the same body weight ventilated with the same V_T may be subjected to different forces dependent on the size of the functional lung. This is expressed by the mechanical concepts of stress and strain.

Stress is the net force acting on a material structure, for instance, a lung strip connecting the hilum to visceral pleura, causing deformation (i.e., strain), divided by the cross-sectional area of this strip. In respiratory mechanics, lung stress reflects the net distending pressures applied on the lung parenchyma, opposed by the elastic pressures generated by the tensioned alveolar walls and lung scaffold. Stress is equal to P_L (Paw − Ppl) under zero flow conditions. Strain represents the deformation experienced by a structure, and is defined as the change in length (Δl) or volume compared with the structure's initial length (l_0) or volume, assumed to be the natural, unstressed condition:

$$\text{strain} = \Delta l / l_0, \qquad (13)$$

and, with respect to lung mechanics:

$$\text{strain} = V_T / FRC. \qquad (14)$$

FRC is here assumed as the nonstressed, resting lung condition. The concept of strain demonstrates how it is possible, with the same ideal body weight and V_T, but different FRC (e.g., by disease), to have different risks of injury. The generation of strain above specific levels is associated with clinical and biochemical markers of lung injury. In healthy pigs, MV with strain greater than 1.5–2 was systematically associated with the development of VILI (102). Similarly, in an observational human study, patients with ARDS and high strain showed a fourfold increase of IL-6 and IL-8 concentrations in bronchoalveolar lavage fluid compared with those with normal strain (103). Recently, it was demonstrated that fludeoxyglucose F 18 uptake in the normally aerated tissue (the baby lung) was strongly associated with high strain in those regions (104, 105).

Although measuring FRC and resting lung volume is still challenging (106), altered compliance is a marker of the lung volume reduction caused by disease. As such, ΔP, reflecting the ratio between V_T and the functional lung size, provides an indirect approach to estimate V_T-induced strain at the bedside.

P_L and Strain

It may be possible to estimate strain from measurements of stress, as the two values are

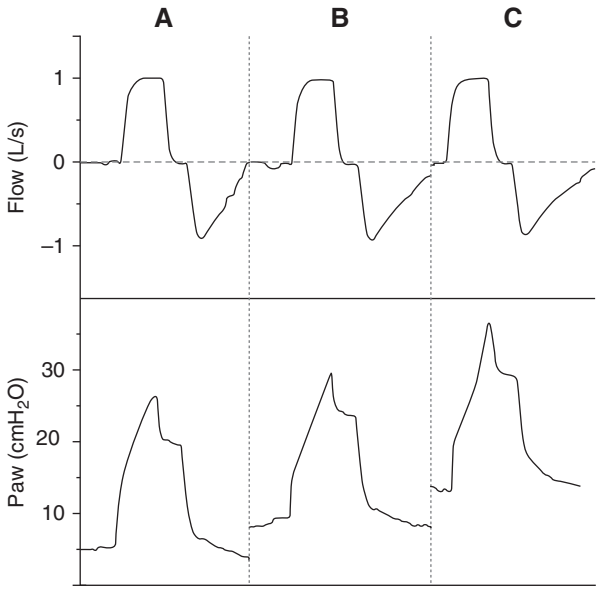

Figure 4. Stress index. Examination of the late portion of the inspiratory pressure–time curve may provide information on the effect of positive end-expiratory pressure (PEEP) on tidal recruitment. (*A*) Demonstration of a convex shape, consistent with a stress index less than 1, on a PEEP of 5 cm H_2O. (*B*) Demonstration of a flat shape, consistent with a stress index of 1, on a PEEP of 10 cm H_2O. (*C*) Demonstration of a concave shape, consistent with a stress index greater than 1, on a PEEP of 15 cm H_2O. These patterns are correlated with intratidal alveolar recruitment, stable alveolar mechanics, and tidal hyperinflation, respectively. Paw = airway pressure.

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., ~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

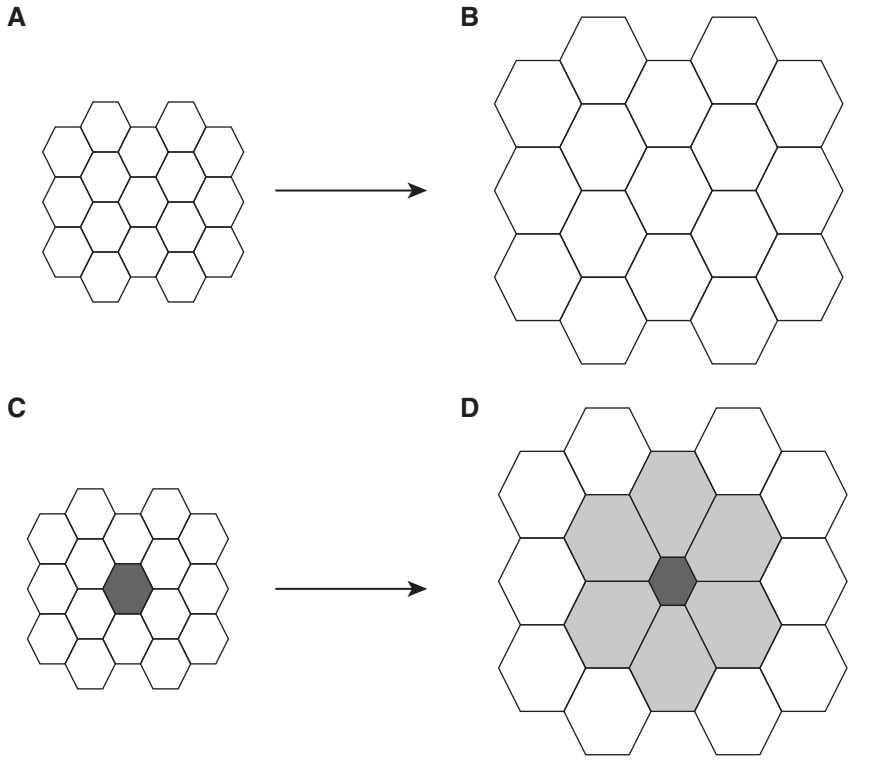

Figure 5. A stress raiser is a local area of inhomogeneous tissue that multiplies local stress and strain in the tissues around it when a given stress is directed through it. An equivalent volume of gas is ventilated into normal lung (*A*) and into a region of lung with a stress raiser—a collapsed or 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.

distribution of stress, as well as areas of localized increases in stress (Figure 5). Accordingly, when one of two neighboring lung units decreases in elasticity (due to collapse or consolidation), the stress of the adjacent open unit may increase severalfold (122). The borders between normal and abnormal lung units have been termed "stress raisers"—regions where values of stress greatly exceed global values (123, 124). The concept of stress raisers is well established in structural engineering of inanimate systems (125), and may provide a partial explanation of why ventilating pressures or strains that are benign in healthy subjects may be injurious in patients with ARDS (126). A recent study demonstrated that inhomogeneities responsible for the stress raiser phenomenon represent 14–23% of the lung parenchyma in ARDS, and that PEEP decreased their prevalence (123).

Conclusions

The use of small V_T, low ΔP, and low Pplat in ARDS is supported by physiological data and controlled trials. The use of PEEP to minimize cyclic derecruitment, atelectrauma, inhomogeneity, and stress raisers has a strong biologic rationale. Despite the improvements in mortality with the use of these concepts, controversy remains with respect to titration of V_T and PEEP. Measurement of ΔP, P_L, or strain allows individualized V_T prescriptions to minimize the risks of VILI. Similarly, bedside assessment of recruitment may allow clinicians to determine patients most likely to benefit from the application of a high PEEP. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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