

Physiological and Pathophysiological Consequences of Mechanical Ventilation

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Abstract

Mechanical ventilation is a life-support system used to ensure blood gas exchange and to assist the respiratory muscles in ventilating the lung during the acute phase of lung disease or following surgery. Positive-pressure mechanical ventilation differs considerably from normal physiologic breathing. This may lead to several negative physiological consequences, both on the lungs and on peripheral organs. First, hemodynamic changes can affect cardiovascular performance, cerebral perfusion pressure (CPP), and drainage of renal veins. Second, the negative effect of mechanical ventilation (compression stress) on the alveolar-capillary membrane and extracellular matrix may cause local and systemic inflammation, promoting lung and peripheral-organ injury. Third, intra-abdominal hypertension may further impair lung and peripheral-organ function during controlled and assisted ventilation. Mechanical ventilation should be optimized and personalized in each patient according to individual clinical needs. Multiple parameters must be adjusted appropriately to minimize ventilator-induced lung injury (VILI), including: inspiratory stress (the respiratory system inspiratory plateau pressure); dynamic strain (the ratio between tidal volume and the end-expiratory lung volume, or inspiratory capacity); static strain (the end-expiratory lung volume determined by positive end-expiratory pressure [PEEP]); driving pressure (the difference between the respiratory system inspiratory plateau pressure and PEEP); and mechanical power (the amount of mechanical energy imparted as a function of respiratory rate). More recently, patient self-inflicted lung injury (P-SILI) has been proposed as a potential mechanism promoting VILI. In the present chapter, we will discuss the physiological and pathophysiological consequences of mechanical ventilation and how to personalize mechanical ventilation parameters.

Keywords

- ▶ mechanical ventilation
- ▶ cardiopulmonary interaction
- ▶ lung mechanics
- ▶ ventilator-induced lung injury
- ▶ alveolar-capillary membrane
- ▶ ventilatory variables

The physiological consequences of mechanical ventilation are related to increased intrathoracic pressure, which inherently affects the heart,¹ central nervous system,² kidney,³ and liver.⁴ Furthermore, clinical conditions that lead to high intra-abdominal pressure deserve special attention during

respiratory system monitoring, as the abdominal compartment is an integral part of the chest wall.^{5–9}

In normal spontaneous ventilation, humans are able to vary the breathing pattern within specific amplitude and time domains,¹⁰ and increase or decrease the ventilation rate

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as a consequence of metabolic fluctuations. On the other hand, mechanical ventilators pressurize the respiratory system using a tidal volume (V_T), positive end-expiratory pressure (PEEP), respiratory rate (RR), and inspiratory airway flow (V') which are selected by the operator. Application of these mechanical breath variables can cause injury to pulmonary tissue, which is not clinically apparent and is associated with a negative prognosis.

We will discuss the physiological and pathophysiological repercussions of mechanical ventilation on the cardiovascular system, central nervous system, kidney, and liver, and analyze how intra-abdominal hypertension (IAH) alters the impact of mechanical ventilation on these organ systems. We will also examine the ventilatory variables to be set and parameters to be monitored, highlighting the mechanisms implicated in ventilation-induced lung injury (VILI) during controlled and assisted mechanical ventilation, as well as translating these mechanisms to clinical practice.

Consequences of Mechanical Ventilation

Positive-Pressure Ventilation and the Cardiovascular System

The heart and lungs are in proximity within the thorax, and the lungs serve as a conduit between the right and left heart chambers, which dictates the interdependence of these organs. Spontaneous and mechanical ventilation induce changes in intrapleural or intrathoracic pressure and lung volume, which can independently affect cardiovascular function through changes in atrial filling or preload; impedance to ventricular emptying or afterload; heart rate; and myocardial contractility. Spontaneous inspiration yields a negative pleural pressure and reduction in intrathoracic pressure. Conversely, positive-pressure ventilation increases intrathoracic pressure and right atrial pressure, regardless of the addition of PEEP. Intrathoracic pressure increases with every passive mechanical breath, which, in turn, changes the end-diastolic volume and compliance of the right and left ventricles.^{1,11} During positive-pressure inspiration, vena cava flow and right ventricular dimension reduce, with an increased transseptal pressure gradient. As a consequence, the septum shifts rightward, increasing left ventricular volume and tending to increase stroke volume as well.¹ Right ventricle afterload also increases, mainly due to alveolar vessel compression, as lung volume rises.¹²

Impact of Lung and Chest Wall Volume

Pulmonary vascular resistance is lowest at functional residual capacity, increasing at either higher or lower lung volumes.¹³ To minimize the increase in pulmonary vascular resistance during controlled mechanical ventilation, pulmonary capillaries must be recruited by fluid volume infusion, which might further impair lung function. During assisted ventilation, depending on the level of support and activation of respiratory muscles, pulmonary capillaries recruit during inspiration and derecruit during expiration, minimizing the need for fluid administration. The recruitment and derecruitment of pulmonary capillaries are a poorly considered

mechanisms for alveolar capillary and extracellular matrix lung damage during different types of mechanical ventilation (► Fig. 1).

Assessment of Fluid Responsiveness

Understanding the fundamentals of these cardiopulmonary interactions is critical to assessing fluid responsiveness in critically ill patients. Not all patients who respond to fluid challenge need additional fluids; this information should be obtained from laboratory and clinical data. For pulse pressure variation (PPV) and systolic volume variation (SVV) to be accurate predictors of fluid responsiveness, patients must be sedated and paralyzed, under controlled mechanical ventilation with $V_T \geq 8$ mL/kg, regular cardiac rhythm, and respiratory system compliance ≥ 30 mL/cmH₂O.¹⁴ Both PPV and SVV are defined as the ratio of their maximal minus the minimal values to the mean values.¹⁵ Several studies have showed that an SVV greater than 10% or a PPV greater than 13 to 15% is predictive of fluid responsiveness, and, in fact, either is superior to static indices such as central venous pressure.^{16,17}

Nevertheless, it is not always necessary to reach the upper part of the stroke volume curve, as this may induce fluid overload. To keep hemodynamic stability at rest, several metabolic parameters could be monitored, such as lactic acid,¹⁸ (A-v) CO₂,¹⁹ and peripheral mottling.²⁰ However, these parameters should not be used alone, and could be incorporated to dynamic hemodynamic indexes.

Positive-Pressure Ventilation and the Central Nervous System

Cerebral Blood Flow

Cerebral blood flow (CBF) depends on a pressure differential between the arterial and venous sides of the cerebral circulation and is inversely proportional to cerebral vascular resistance. Since pressure on the venous side is difficult to measure, intracranial pressure (ICP) is used to estimate cerebral perfusion pressure (CPP). CPP is equal to the difference of mean arterial pressure and ICP. Normal ICP values in adults are <10 mm Hg, and a CPP of 60 mm Hg is commonly accepted as the minimum threshold for adequate cerebral perfusion.²¹ As CBF is closely related to regional cerebral metabolism, it is highly dependent on CO₂ levels and changes in PaCO₂. It has been observed that increasing CO₂ tension relaxes cerebral arteries in vitro.²² In vivo, localized perivascular changes in PaCO₂ or pH can change vascular diameter, indicating that elements of the vessel wall are responsible for effecting changes in vessel diameter. Both endothelial/smooth-muscle cells and extravascular cells (perivascular nerve cells, neurons, and glia) may be involved. For each mm Hg change in PaCO₂, the CBF changes by 3% over the range of 20 to 60 mm Hg.²³ Therefore, hypoventilation resulting in hypercapnia causes vasodilatation and higher CBF, while hyperventilation leads to vasoconstriction and lower CBF. In a recent study, Robba et al²⁴ showed, in COVID-19 patients, that inhaled nitric oxide and prone positioning improved systemic and cerebral oxygenation; recruitment maneuvers (RMs) did not improve

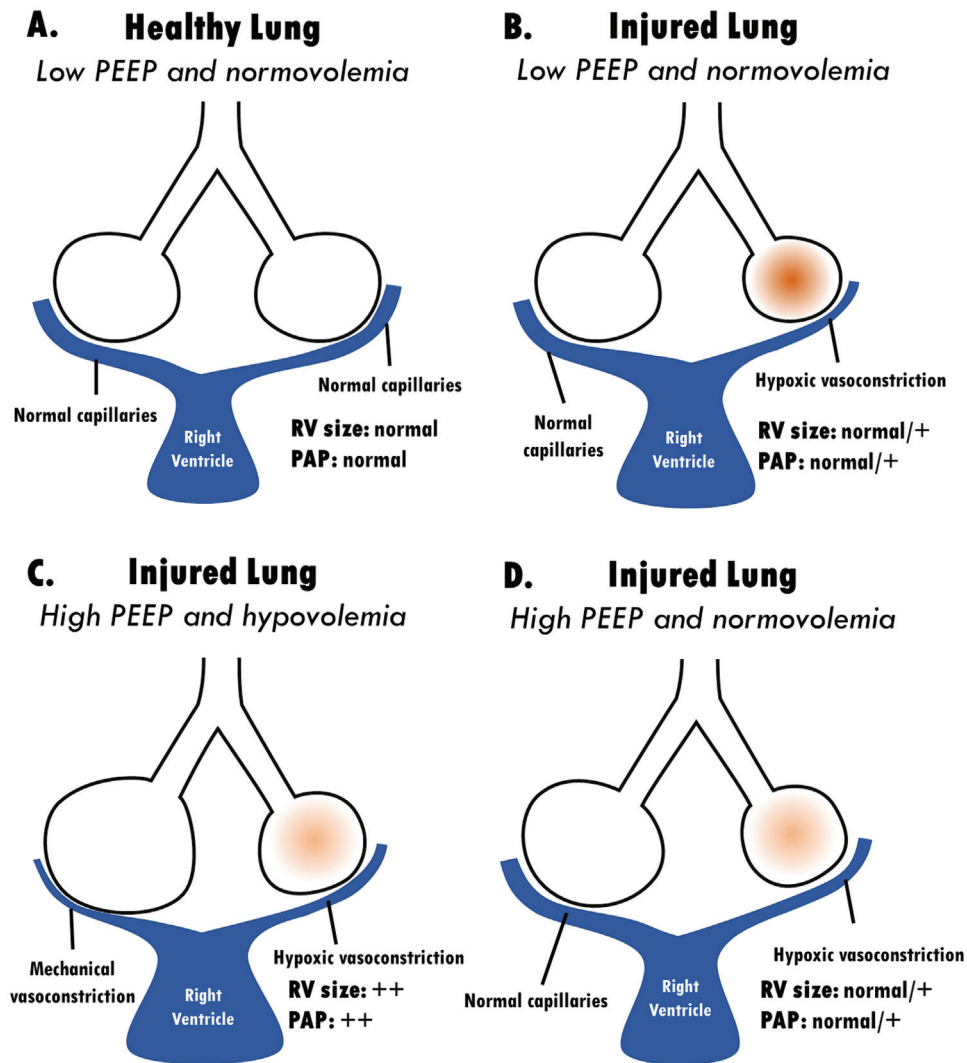


Fig. 1 Panel A illustrates the pulmonary circulation in a non-injured lung ventilated with low PEEP in normovolemia, resulting in well-aerated alveoli perfused by pulmonary capillaries of normal size. When an injured lung composed by heterogeneous distribution of lung damage receives lower PEEP under normovolemic conditions (Panel B), capillaries perfusing non-aerated or poorly-aerated regions are subjected to hypoxic vasoconstriction, which may translate into slightly increased PAP and RV size. The application of high PEEP in a hypovolemic patient with lung injury (Panel C) results in mechanical vasoconstriction due to the hyperinflation of residual healthy lung regions and capillary de-recruitment further compressing the vessels already vasoconstricted due to hypoxia, thus increasing PAP and enlarging the RV. The same high PEEP applied in conditions of normovolemia (Panel D) does not induce capillary de-recruitment and allows aeration to be restored, maintaining adequate perfusion and modest increases in PAP and RV size. PAP, pulmonary artery pressure; PEEP, positive end-expiratory pressure; RV, right ventricle.

systemic oxygenation, but worsened cerebral oxygenation (rSO_2); respiratory dialysis/extracorporeal carbon dioxide removal reduced both systemic and cerebral oxygenation, and, in the whole population, significant correlations were found between SpO_2 and rSO_2 and between rSO_2 and PaO_2 .

Positive End-Expiratory Pressure

According to a recent guideline,²⁵ in mechanically ventilated patients with acute brain injury without acute respiratory distress syndrome (ARDS) who do not have clinically significant ICP elevation, the same level of PEEP should be used as in patients without brain injury. Furthermore, in those with significant ICP elevation but no increase in ICP due to PEEP increase, the same level of PEEP should be used

as in patients without acute brain injury. A recent observational study²⁶ evaluated the effects of two levels of PEEP (5 and 15 cmH_2O) on respiratory mechanics, quantitative lung computed tomography (qCT) findings, and relationship with ICP changes in brain-injured patients. They found that a PEEP increment from 5 to 15 cmH_2O led to higher oxygenation, $PaCO_2$, and ICP values, with alveolar recruitment of 2.5% of total lung weight. Interestingly, ICP increase with PEEP was correlated to higher $PaCO_2$, poor alveolar recruitment, reduction of Cr_s , and decreased MAP. This study suggests that the potential benefits of PEEP augmentation in acutely brain-injured patients should consider hemodynamic status, including the ICP values, respiratory mechanics, and lung morphology.

Inflammatory Response

Systemic inflammatory response seems to be important in the development of pulmonary failure after acute brain injury. An intracranial inflammatory response occurs after brain injury, and pro-inflammatory cytokines—interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF)—are produced locally in injured cerebral tissue.²⁷ This scenario, compounded by a massive sympathetic response, creates an inflammatory environment that increases lung susceptibility to further injurious events. All components of protective ventilation (low tidal volume, moderate to high PEEP, and RMs with permissive hypercapnia) may interact with the underlying course of acute brain injury. One multicenter, prospective, observational study showed that neurological, compared with non-neurological, patients are ventilated with similar V_T (approximately 9 ± 5 mL/kg) but lower respiratory rates (RRs) and PEEP levels. In addition, a higher mortality rate has been observed in patients with stroke, especially hemorrhagic stroke, which is probably related to neurological dysfunction.²

Positive-Pressure Ventilation and the Kidney

Patients with acute kidney injury (AKI) have twofold higher odds of developing respiratory failure requiring mechanical ventilation compared with those without AKI,²⁸ as well as the need for mechanical ventilation in those without previous AKI is associated with significant increases in the risk to develop AKI. Indeed, needing mechanical ventilation is an independent predictor of mortality in these patients²⁹; in one study, a need for mechanical ventilation was the main factor associated with 89% mortality in patients with AKI.³⁰

Hemodynamics

As previously described, positive-pressure ventilation increases ITP, which reduces renal blood flow, glomerular filtration rate, sodium excretion, and urinary output.³¹ Increases in ITP are expected to have a congestive effect on the RV and right atrium, which may lead to renal congestion. This, in turn, can lead to increasing intracapsular pressure via formation of renal interstitial edema.³ Renal hemodynamics can be further impaired by intra-abdominal pressure (IAP). High levels of IAP can be caused by the magnitude of positive pressure ventilation, respiratory system elastance, and pre-existing abdominal pressure due to high-volume fluid infusion. Elevated IAP can compromise microvascular blood flow,³² leading to kidney edema as a consequence of reduced venous drainage. Besides positive ITP, high levels of IAP can be an additional etiologic factor in kidney edema.

Inflammatory Response

Inflammatory alterations can be a consequence of systemic effects of inflammatory mediators released in response to different ventilatory strategies acting on the lungs.³³ In a mouse model of experimental intratracheal hydrochloric acid instillation, high V_T (17 mL/kg), compared with a protective V_T (6 mL/kg), increased IL-6, and VEGFR2 levels in the lungs and kidney.³⁴ Other authors have observed increases not only in inflammation, but also in lung and kidney

apoptosis after injurious ventilation.³⁵ Several mediators can exert potential effects that contribute to kidney injury.³⁶ Among these, two deserve a particularly closer look: soluble Fas ligand (sFasL), a mediator of apoptosis, and IL1- β , a proinflammatory cytokine. The FasL-Fas system can induce glomerular apoptosis associated with proteinuria and loss of mesangial cells.³⁷ In addition, IL1- β may facilitate the apoptosis process by acting toward platelet-activating factor and triggering an inflammatory reaction.³⁸

Ventilatory Parameters and Renal Failure

One systematic review and meta-analysis showed that invasive mechanical ventilation increases the odds of AKI.³⁹ Neither V_T nor PEEP had any effect on risk of developing AKI. However, this meta-analysis failed to include two important clinical trials.^{40,41} The ARDS Network trial⁴⁰ demonstrated that patients ventilated with low V_T (6 mL/kg) had more renal failure-free days as opposed to those in the high- V_T group (12 mL/kg; 20 ± 11 vs. 18 ± 11 days, $p = 0.005$). The EXPRESS study⁴¹ showed no difference between patients ventilated with low or high PEEP in relation to renal failure-free days. In short, the relationship between lung injury and AKI remains poorly understood and deserves attention.

Positive-Pressure Ventilation and the Liver

Deterioration in gas exchange in acute liver failure can be caused by hydrothorax, atelectasis, ARDS, and reduced respiratory system compliance due to raised IAP. In addition, intrapulmonary shunting and the hepatopulmonary syndrome have also been implicated.⁴²

One large study⁴³ evaluated patients admitted to a specialized liver ICU over a 6-year period and found an association between mechanical ventilation in ICU for patients with cirrhosis and high ICU mortality within 1 year (89%). Furthermore, the authors observed that a duration of mechanical ventilation >9 days during ICU stay represented a risk factor for death in the year after ICU discharge. A similar scenario can be observed in cirrhotic patients.⁴⁴

Experimental studies have sought to understand the impact of specific ventilatory strategies on liver function. Kredel et al⁴ examined the hepatic consequences of pressure-controlled ventilation with a V_T of 6 mL/kg and PEEP adjusted to 3 cmH₂O above the lower inflection point of the pressure-volume curve or as high-frequency oscillatory ventilation (≥ 12 Hz) with a mean airway pressure 3 cmH₂O above the lower inflection point combined with arteriovenous extracorporeal lung assist. Aspartate aminotransferase increased approximately threefold in the pressure-controlled ventilation group and fivefold in patients who received high-frequency oscillatory ventilation with arteriovenous extracorporeal lung assist.

Positive-Pressure Ventilation and Intra-Abdominal Hypertension

The normal IAP is approximately 5 to 7 mm Hg.⁵ IAH is defined by a sustained or repeated pathological elevation in IAP ≥ 12 mm Hg, while abdominal compartment syndrome is defined as a sustained IAP >20 mm Hg (with or

without a difference between mean arterial pressure and IAP, i.e., abdominal perfusion pressure, of 60 mm Hg or greater) that is associated with new organ dysfunction or failure. IAH can be further graded as follows: grade I, IAP 12 to 15 mm Hg; grade II, IAP 16 to 20 mm Hg; grade III, IAP 21 to 25 mm Hg; and grade IV, IAP >25 mm Hg. There are well-recognized risk factors for IAH and abdominal compartment syndrome, such as abdominal surgery, major trauma, gastroparesis, gastric distention, ileus, acute pancreatitis, damage control laparotomy, massive fluid resuscitation or positive fluid balance, and mechanical ventilation. Once developed, IAH can promote a cephalic shift of the diaphragm,^{6,7,45} with a reduction in lung volumes and increase in pleural pressure,^{46,47} causing atelectasis and impaired lung function.⁴⁸

One way to counteract the effect of elevated IAP on the lung is to apply PEEP. However, it has been shown that PEEP levels up to 15 cmH₂O (11 mm Hg) cannot prevent the functional residual capacity decline caused by IAH (18 mm Hg), and are actually associated with reduced oxygen delivery as a consequence of reduced cardiac output.⁶ In a subsequent study, the PEEP level was adjusted to match the IAP in a porcine model of IAH with healthy lungs.⁸ End-expiratory lung volume was maintained, but no improvements in arterial oxygen tension were observed, and, in fact, cardiac output decreased. However, in acute lung injury, IAP-matching PEEP was found to reduce shunt and dead-space fraction as well as respiratory system elastance, due to a reduction in chest wall elastance.⁷ Furthermore, high IAP-matching PEEP caused a reduction in CO. By comparing different lung-injury etiologies in IAH models, Santos et al showed that higher PEEP levels (10 cmH₂O) in direct lung injury increased lung elastance, while intermediate PEEP levels (7 cmH₂O) in indirect lung injury increased expression of inflammatory markers.⁴⁹ This evidence suggests that, in healthy-lung conditions, IAP-matching PEEP may not be tolerated. In a condition of lung injury, the IAP-matching PEEP approach can be effective, but close cardiac output monitoring is needed. On the other hand, PEEP should not exceed IAH levels because it is associated with decreased hemodynamics due to reduced compliance of the chest wall, mainly due to the abdominal compartment (→ Fig. 2). The suggested upper limit for PEEP during IAH is 15 cmH₂O.⁵⁰ During PEEP increments, there is a concomitant increase in plateau pressure, which also needs attention because there is interplay between PEEP, IAP, and individual mechanics contributing to the plateau pressure level. Thus, the target Pplat⁵¹ can be calculated as follows:

$$\text{Target Pplat}_{\text{adjusted}} = \text{target Pplat} + (\text{IAP} - 13 \text{ cmH}_2\text{O})/2$$

In other words, if a patient shows a IAP of 21 cmH₂O, the adjusted target Pplat is equivalent to target Pplat + 4 cmH₂O; meaning that if target (safe upper limit) Pplat is 30 cmH₂O, the adjusted target Pplat is 34 cmH₂O. During mechanical ventilation, it is important to dichotomize the information that comes from the respiratory system from that originating in the lungs. Changes in the respiratory system can be monitored by measurement of airway driving pressure, which represents V_T divided by respiratory system compli-

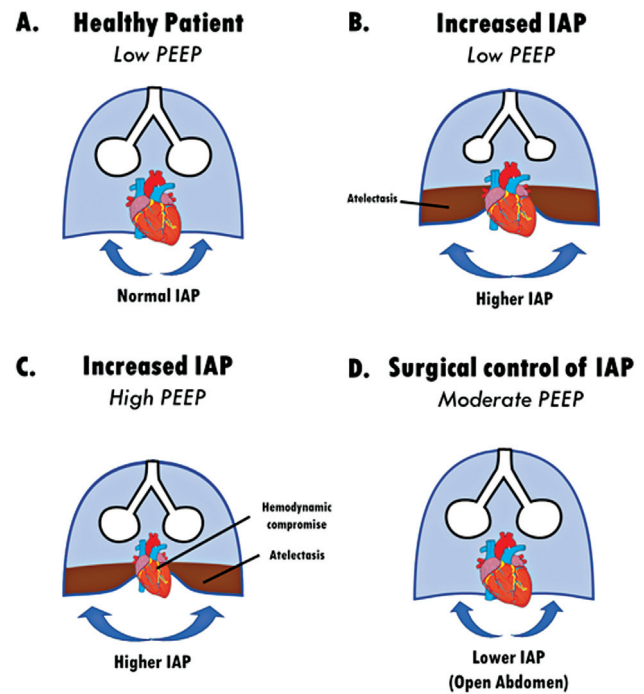


Fig. 2 Panel A illustrates a healthy patient with normal IAP ventilated with low PEEP. When low PEEP is applied to a patient with increased IAP (Panel B), relevant loss of aeration occurs with limited impact on hemodynamics. The application of higher PEEP (Panel C) could only partially restore aeration at the price of compromising the hemodynamics. Surgical control of IAP, e.g., obtained with decompressive laparotomy in conjunction with moderate PEEP levels, allowed aeration to be restored without negatively impacting hemodynamics.

ance. However, this index can be affected in conditions of altered chest wall compliance and should not simply be generalized to the lungs. Transpulmonary driving pressure would represent a better option, as it eliminates the chest wall compartment. This was the subject of a study by Cortes-Puentes et al,⁹ who monitored airway driving pressure and transpulmonary driving pressure in an experimental setting that allowed reversible modification of chest wall compliance, by increasing the IAP up to 15 mm Hg (grade I IAH). Stiffening the chest wall by elevating IAP increased the calculated airway driving pressure of a fixed V_T and PEEP combination more than the transpulmonary driving pressure did. This is important, as there are recommended safety values for airway driving pressure in critically ill patients⁵² and surgical patients⁵³; however, increases in airway driving pressure can be driven not only by lung abnormalities, but also by the presence of IAH, for instance. Therefore, IAH should be monitored to discriminate the changes in airway driving pressure overtime.

Insights from Esophageal Pressure Monitoring

With the increase in IAP, there is an expected pressure transfer from the abdominal compartment to pleural compartment. A given increase in IAP, often half of this pressure, is transferred to the chest wall, at least in dependent lung regions. One cannot directly measure the pleural pressure (Ppl) at the bedside but can measure the esophageal pressure

at the lower end of the esophagus. Different transpulmonary pressures (P_{tp}) are expected across different lung regions.⁵⁴ Taking into account that 10 cmH₂O represents the total pressure vertical gradient and an esophageal catheter placed at two-thirds of the way down from the sternum in supine position, pressures of 5 cmH₂O in the two-thirds above the transducer and 5 cmH₂O in the one-third below it are expected, because density is higher in the dependent zones.⁵⁵ To estimate P_{pl} from esophageal pressure (P_{es}) obtained from single and absolute values, some assumptions can be done, as follows:

Estimated P_{pl} near sternum (non-dependent) = P_{es} – 5 cmH₂O

Estimated P_{pl} near vertebra (dependent) = P_{es} + 5 cmH₂O

The P_{pl} estimation should be corrected according to airway pressure (P_{aw}), such that P_{pl} = P_{aw} – P_{es}:

P_{pl} = P_{aw} – (P_{es} – 5 cmH₂O) in non-dependent areas = P_{aw} – P_{es} + 5 cmH₂O

P_{pl} = P_{aw} – (P_{es} + 5 cmH₂O) in dependent areas = P_{aw} – P_{es} – 5 cmH₂O

The following assumptions should be made:

1. The absolute difference (not corrected) P_{aw} – P_{es} at end expiration or inspiration is the P_{tp} in the middle part of the lung.
2. The variation in P_{pl} (ΔP_{pl}) equals the ΔP_{es} such that the measurements of lung and chest wall elastances might be accurate.
3. At end expiration (dependent regions), the absolute P_{tp} is computed as PEEP – P_{es} – 5 cmH₂O.
4. At end inspiration (non-dependent regions), the absolute P_{tp} is computed as P_{plat} – P_{es} + 5 cmH₂O.
5. At end inspiration (non-dependent regions), the absolute P_{tp} might be computed as P_{plat} × EL/E_{tot}; EL = ΔP_L/ΔV; E_{tot} = ΔP_{rs}/ΔV;

where EL is the lung elastance and E_{tot} is the total elastance.

Ventilatory Variables to Be Set and Parameters to Be Monitored during Mechanical Ventilation

Mechanical ventilators pressurize the respiratory system using V_T, PEEP, RR, and inspiratory airway flow, which are adjusted by the operator. Application of these mechanical breath variables can cause injury to pulmonary tissue that is not clinically apparent and is associated with a negative prognosis. Importantly, respiratory system plateau pressure (P_{plat,RS}), driving pressure (ΔP_{RS}), and more recently, mechanical power has been shown to correlate with VILI. These mechanical breath parameters, if improperly adjusted, have been shown to exacerbate the main mechanisms associated with VILI: volutrauma (inappropriate V_T leading to alveolar overdistension) or atelectrauma (cyclic closing and opening

of small airways and alveoli due to low PEEP levels). These two forms of mechanical injury to lung tissue can trigger biotrauma, which is characterized by the decompartmentalization of inflammatory mediators formerly located in the alveolar space and their translocation to the adjacent bloodstream, which can result in distal organ injury.

Variables to Be Set during Mechanical Ventilation

Tidal Volume (V_T) Size

Recently, a meta-analysis of pooled data from large randomized studies comparing different V_T showed that low V_T (defined as <10 mL/kg) should be preferentially used during surgery before the development of lung injury.⁵⁶ Preemptive application of low V_T decreased the need for postoperative ventilatory support (invasive and non-invasive). One study in this meta-analysis⁵⁷ showed that a V_T of 6 to 8 mL/kg of ideal body weight versus V_T of 10 to 12 mL/kg resulted in fewer pulmonary and extrapulmonary complications. However, patients ventilated with low V_T also had PEEP levels ranging from 6 to 8 cmH₂O with periodic RMs, while the group of patients ventilated with high V_T had no PEEP.

Strain and Standardization of V_T on IC

Strain is defined as V_T according to end-expiratory lung volume (EELV). An additional standardization of V_T is according to inspiratory capacity (the sum of functional residual capacity, tidal volume, and inspiratory reserve volume). The correction for inspiratory capacity is easier to be performed at bedside and more accurate compared with standardization to EELV. Inspiratory capacity may be measured as the volume difference between PEEP at 0 cmH₂O or in case a minimal PEEP 5 cmH₂O and inspiratory pressure at 30 cmH₂O. In case of a patient non-recruiter, the application of PEEP increases EELV mainly by overdistending alveoli; otherwise in case of a patient recruiter, the application of PEEP increases EELV both increasing the volume of previously aerated lung regions and reopening collapsed alveoli. Thus, the strain may be similar but the effect on the lung structure is completely different being more injurious in non-recruiters. On the contrary, the standardization of V_T on inspiratory capacity, takes automatically in count the distortion of lung parenchyma due to PEEP. Anyway, the standardization of V_T on inspiration may be roughly equivalent to that on EELV (in recruiters or in non-recruiters), since the inspiratory capacity is correlated to EELV in ARDS (► Fig. 3).

Strain Rate and Lung Damage

Lungs behave as a viscoelastic system. For example, when they are deformed and held constant, the lungs relieve tension, so-called “stress relaxation.” Due to their mechanical nature, it is conceivable that different parenchymal distortions may occur depending on how fast V_T or strain is modified over a period of time. By comparing low (1.8/s) and high (4.6/s) strain rates at similar overall strain (2.1), Protti et al showed that high strain rates may increase the risk of pulmonary edema, possibly because they augment lung viscoelastic behavior. In heterogeneous alveolar units

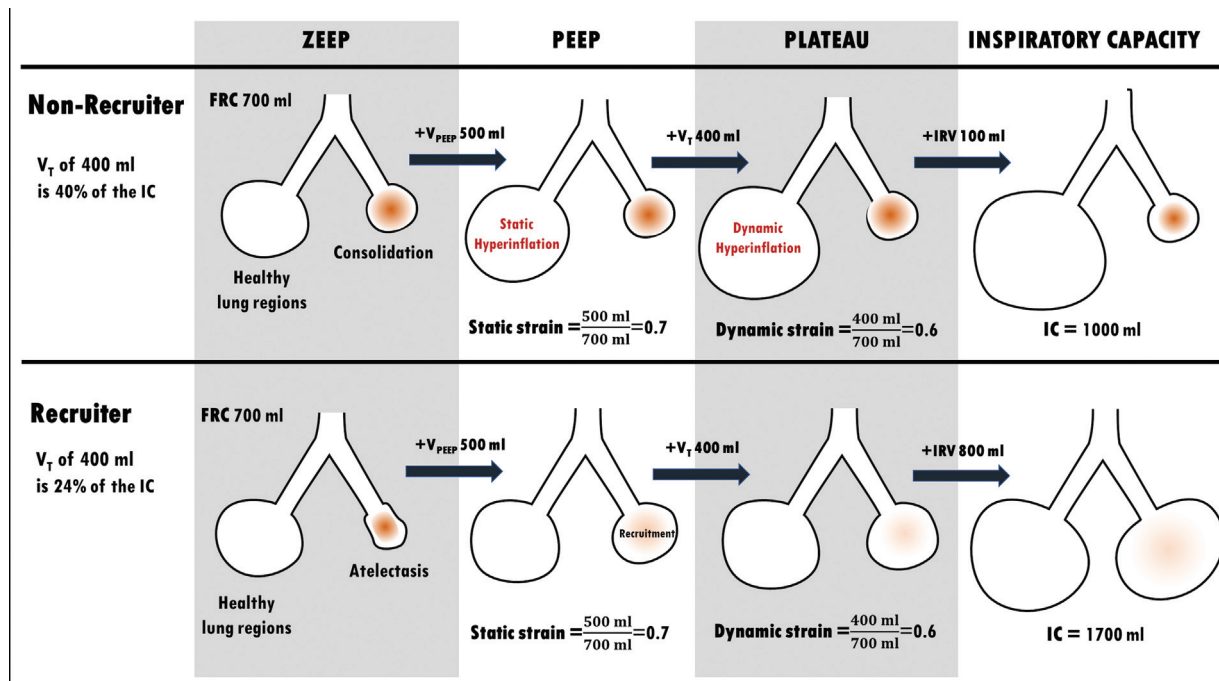


Fig. 3 This figure illustrates the response to increasing pressures in one patient with consolidation and no potential for recruitment (upper panels) and another with recruitable atelectasis (lower panels). Both patients shared a baseline FRC of 700 mL, a VPEEP of 500 mL at the same PEEP level and were ventilated with a V_T of 400 mL. PEEP and tidal ventilation induced static and dynamic hyperinflation only in the patient with no potential for recruitment, despite having identical static and dynamic strain (VPEEP/FRC and V_T /FRC, respectively). Measuring IC reveals the different space available to ventilation in both patients. As a result, the same V_T is 40 and 24% of the IC in the non-recruiter and recruiter patients, respectively. FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; PEEP, positive end-expiratory pressure; VPEEP, PEEP-induced increase in end-expiratory lung volume; V_T , tidal volume; ZEEP, zero end-expiratory pressure.

with varying regional aeration, tidal energy can concentrate on a small mass of pulmonary tissue, spreading lung damage with successive cycles. In the clinical setting, changes in V_T are usually applied abruptly. The extracellular matrix requires an adaptive “stress relaxation” time to mitigate the damaging strain associated with large V_T . These internal adjustments occur over both short (over a respiratory cycle) and extended time scales,¹ depending on the degree of lung injury. Felix et al showed that increasing strain gradually (shorter adaptation time) rather than abruptly (no adaptation time) attenuated lung injury, likely by preemptive adaptation of the epithelial cells and extracellular matrix. However, a more gradual increase in tidal strain (longer adaptation time) compared with the shorter adaptation time led to more cumulative transfer of mechanical power and did not prevent lung damage, suggesting that the longer adaptation time strategy initiated injurious strain at an earlier time.

PEEP during Surgery

To evaluate whether the absence of PEEP worsens prognosis when combined with high V_T , a study was performed separating these two mechanical ventilation parameters. The PROVHILO trial⁵⁸ was designed to test the hypothesis that a ventilation strategy with a high PEEP level (12 cmH₂O) plus RMs compared with low PEEP level (2 cmH₂O) combined with the same V_T (7.1 mL/kg of predicted body weight) during general anesthesia for open abdominal surgery would protect against postoperative pulmonary complications. Since V_T was comparable in the two arms of the study, the

positive effect, if any, could only be attributed to the PEEP applied during surgery. The authors showed that the incidence of postoperative pulmonary complications in the first 5 days after surgery was comparable between the two groups. Although the hypothesis in the PROVHILO trial was not supported, the authors did answer several relevant questions: (1) dynamic respiratory system compliance improved with PEEP = 12 cmH₂O, which suggests effective lung recruitment without relevant overdistension; (2) low V_T combined with PEEP = 2 cmH₂O was not associated with poorer clinical outcome; (3) less hemodynamic impairment was observed in the low-PEEP compared with high-PEEP arm plus RMs. Thus, ventilator strategy may lead to different outcomes depending on the patient’s underlying condition.

PEEP in ARDS

Unlike during surgery, optimal PEEP settings in critically ill patients—especially in ARDS patients—remain unclear. Three large, randomized, controlled trials studied higher versus lower PEEP in ARDS patients.^{41,59,60} Although the methods used to adjust PEEP level differed between studies and some imbalances were observed between the compared arms, no beneficial improvement was observed in survival. Nevertheless, patients allocated to higher PEEP strategies required less rescue therapies,^{41,60} presented more ventilator-free and organ failure-free days, and improved respiratory system compliance.⁴¹ Pooling all these data and analyzing the most severe ARDS patients ($\text{PaO}_2/\text{FiO}_2 \leq 200$), randomization to higher PEEP strategies was associated with lower mortality

(34.1 vs. 39.1%), with an adjusted relative risk of 0.90 (95% CI, 0.81–1.00; $p = 0.049$). On the other hand, in those with mild ARDS when assigned to higher PEEP strategies ($\text{PaO}_2/\text{FiO}_2$ between 201 and 300), there was a trend toward higher mortality with an adjusted relative risk of 1.37 (95% CI, 0.98–1.92; $p = 0.07$). Although there has been no consensus, these analyses suggest that the use of a higher PEEP strategy in severe ARDS patients is beneficial.

The impact of PEEP on lung recruitment in ARDS patients can vary. In a study of 19 patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 150$), nine exhibited significant alveolar recruitment while in the remaining 10 the alveolar volume recruited was reduced without improvement in oxygenation. Similar behavior has been observed in computed tomography studies where the degree of alveolar recruitment varied among ARDS patients.⁶¹ This variable effect on lung recruitment may explain the negative results found in these three large trials comparing lower and higher PEEP strategies in ARDS patients.

In a recent systematic review and meta-analysis of RCTs,⁶² the authors compared ventilation strategies comprising higher PEEP and/or RMs to conventional strategies with lower PEEP levels and no RMs, used either alone or in combination. After applying inclusion and exclusion criteria, 10 studies were included in the meta-analysis. In unselected patients with ARDS who were mechanically ventilated with protective low V_T , the use of higher PEEP and/or RMs did not result in reduced mortality nor incidence of barotrauma compared with a strategy using a PEEP level aimed at achieving minimal acceptable oxygenation goals. This PEEP level to achieve minimal acceptable oxygenation ranged from 10.1 cmH_2O at day 1 to 8.6 cmH_2O at day 7. As a consequence of moderate PEEP application, a certain degree of manageable atelectasis is expected.⁶³ In this line, Goligher et al showed that early increase in oxygenation associated with increased PEEP was associated with decreased hospital mortality, particularly in patients with more severe baseline hypoxemia.

Respiratory Rate

RR is set, in addition to tidal volume and PEEP, to maintain an appropriate minute ventilation and meet the patients' metabolic demand. In a landmark study demonstrating that low V_T reduced mortality in acute respiratory failure,⁴⁰ the authors did not discuss the RR, which was approximately 30 breaths/min, to facilitate CO_2 clearance. At an RR set to 30 breaths/min, the respiratory cycle lasts 2 seconds. If the inspiratory:expiratory ratio (I:E) is adjusted to 1:1, this gives 1 second in both inspiration and expiration. If I:E is adjusted to 1:2, this gives 0.66 and 1.33 seconds in inspiration and expiration, respectively. Therefore, either the expiration time is shortened, which may induce intrinsic PEEP, or the inspiration time is reduced (or high strain rate), which may compromise ventilation. To test if high RR can improve CO_2 clearance without cardiovascular impairment, Vieillard-Baron et al⁶⁴ compared a conventional (low rate, 15 breaths/min) versus a high-rate strategy (30 breaths/min). Interestingly, the authors made efforts to control the inspiratory flow (at 50 L/min) in both groups. They showed that the increase in RR up to a range commonly used in an ICU was not only inefficient in improving

CO_2 clearance, but also produced intrinsic PEEP. Furthermore, the increased RR was associated with significant hemodynamic consequences, including impaired venous return and abdominal vena cava enlargement.

In the ARDS Network trial,⁶⁵ the low- V_T group (6 mL/kg predicted body weight) showed a mean RR equal to 29 bpm on day 1 and 30 bpm on day 7, compared with 16 bpm on day 1 and 20 bpm on day 7 in the high- V_T group (12 mL/kg predicted body weight). On day 1, the mechanical power was 30.6 J/min in the low- V_T group and 33.1 J/min in the high- V_T group. Due to the reduction in V_T toward the protective range, an increase in RR is expected to maintain minute ventilation at safe levels to avoid acidosis. In terms of mechanical power, no major differences were observed between the low and high V_T groups. Both were in the injurious range.⁶⁶ Nevertheless, the ARDS Network trial showed a substantial mortality decrease which may be related to safe level of PBW V_T and plateau pressure.

Inspiratory and Expiratory Airway Flows

The flow scalar takes on either a predictable, repeatable shape, or a variable shape depending on the ventilation mode employed. In volume-control modes of ventilation, the flow waveform would typically be square or have a descending ramp conformation.⁶⁷ Independent of the flow pattern, flow itself is an important determinant of stress in the lung, since it enhances the transmission of kinetic energy. This energy is closely associated with the shear stress applied to the cells within respiratory bronchi. Some reports have associated inspiratory flow profiles with gas exchange, work of breathing, and cardiovascular functions. Among these studies, from a macroenvironment point of view, an accelerating flow waveform has been associated with hemodynamic compromise and higher chance of barotrauma.⁶⁸ On the other hand, a decelerating flow waveform has been associated with better lung mechanics and gas exchange in positive-pressure ventilation.⁶⁹

Not only is inspiratory airway flow associated with major pathophysiologic consequences, but expiratory flow is also an important indicator of changes in lung mechanics as acute lung injury progresses. Expiration is a passive process that uses elastic energy stored during inflation to drive expiratory airflow. If the potential energy stored after inspiration is low, and not sufficient to return the system to a relaxed equilibrium before the next inspiration begins, flow continues throughout expiration and alveolar pressure remains positive at end expiration, exceeding the clinician-selected PEEP value. This is the so-called auto-PEEP or intrinsic PEEP (PEEPi), which can lead to hyperinflation, after several respiratory cycles.

Ventilatory Parameters to Be Monitored during Mechanical Ventilation

Respiratory System Plateau Pressure ($P_{\text{plat,RS}}$)

$P_{\text{plat,RS}}$ is measured by extending the time at inspiration in order for lung pressure to equilibrate at that volume. The magnitude of $P_{\text{plat,RS}}$ depends on respiratory system, lung, and chest wall compliance, as well as V_T , and represents the

elastic recoil pressure of the lung. Although a high $P_{plat,RS}$ can suggest a risk of alveolar overdistension, the threshold used to guide mechanical ventilation adjustments is still a matter of discussion. In the ARDSNet study, in addition to low- V_T ventilation, P_{plat} was controlled. In the low V_T arm, the authors used a $P_{plat,RS}$ lower than or equal to 30 cmH₂O.⁴⁰ However, depending on the patients' respiratory system mechanics, keeping $P_{plat,RS}$ below 30 cmH₂O may not be protective in all patients with ARDS. It has been shown that some patients can develop tidal hyperinflation even with low V_T (6 mL/kg) and $P_{plat,RS} < 30$ cmH₂O. Therefore, the authors suggested that the $P_{plat,RS}$ upper limit should be reduced to 28 cmH₂O.⁷⁰ Moreover, $P_{plat,RS} > 25$ cmH₂O at 24 hours after admission was an independent risk factor for mortality. Villar et al used a screening tool to identify individual patients at greater risk of death by using age, oxygenation index, and $P_{plat,RS}$.⁷¹ They divided the $P_{plat,RS}$ into three ranges (<27 cmH₂O; 27–30 cmH₂O; > 30 cmH₂O). Mortality increased as $P_{plat,RS}$ increased,⁷¹ corroborating the previous study.

Respiratory System Driving Pressure (ΔP_{RS})

After a major surgery with prominent atelectasis or in patients with ARDS, the area available for ventilation is reduced. This is reflected, at the bedside, by low respiratory system compliance. Usually, V_T is normalized to predicted body weight to scale the lung size. However, not all lung tissue is available for ventilation. Thus, ΔP_{RS} represents the V_T normalized by the respiratory system compliance. This index may indicate the functional size of the lung and may be a better predictor of outcome in patients with and without lung injury. Recent studies reported that ΔP_{RS} is an excellent marker of ventilator settings that may cause VILI and can unify the forces that cause tissue damage in the ARDS-affected lung. A retrospective study analyzing data from the low- V_T ARDSnet study found that $\Delta P_{RS} > 15$ cmH₂O was associated with a higher mortality rate in ARDS patients.⁵² In contrast, V_T , $P_{plat,RS}$, and PEEP were not independently correlated with increased mortality.⁵² Increasing PEEP will have different effects on ΔP_{RS} depending on the degree of lung pathology. If increasing PEEP results in lung tissue recruitment, a decrease in ΔP_{RS} is expected. On the other hand, if increasing PEEP does not recruit lung tissue, the lung may become overstretched, and the ΔP_{RS} will remain unchanged or increase. In a meta-analysis of individual patient data including 2,250 patients in 17 randomized controlled trials, Neto et al showed that changes in PEEP level resulting in increased ΔP_{RS} were associated with postoperative pulmonary complications.

The Concept of Energy

The previously discussed ventilator variables generate the energy applied to the respiratory system during one breath cycle. The energy applied to the respiratory system is computed based on the airway pressure–volume curve, considering that it is linear up to the total lung capacity region. To compute the actual energy being imparted to the lungs, the following energies must be subtracted: (1) the energy nec-

essary to move the chest wall; (2) the energy necessary to overcome the tracheal tube and tracheobronchial tree during inspiration; and (3) the energy recovered at the mouth.

Mechanical Power

The energy applied into the lungs at a given RR is called mechanical power, which is effectively energy expressed per minute.

The most simplified version of the mechanical power equation,⁷² which has been generated based on the classic equation of motion,⁷³ is as follows:

Volume-controlled ventilation (VCV) with inspiratory hold:

$$MP = 0.098 \times V_T \times RR \times (P_{peak,RS} - \Delta P_{RS}/2) \quad (1)$$

VCV without inspiratory hold⁷⁴:

$$MP = [V_T \times RR \times (P_{peak,RS} + PEEP + Flow/6)]/20 \quad (2)$$

Pressure-controlled ventilation:

$$MP = 0.098 \times V_T \times RR \times (\Delta P_{RS} + PEEP) \quad (3)$$

Different parameters may contribute differently to mechanical power, such as $V_T/\Delta P_{RS}$, inspiratory flow, PEEP, and RR. During the ARDS Network trial, when patients were recruited (1996–1999), there was no discussion about mechanical power, and the contribution of such an increased RR to potential harm to the respiratory system of critically ill patients was unknown. A recent study of 4,549 patients with ARDS showed that RR is an independent predictor of mortality.⁷⁵ The average RR was 25.7 ± 7.4 breaths/min, which is a common value observed in daily intensive-care practice. The authors showed that the impact of ΔP on mortality was four times greater than that of the RR, but the RR was still independently associated with mortality. They suggest, according to theoretical and practical issues at the bedside, the concept of using $4 \times \Delta P + 1 \times RR$ ($4^* \Delta P^* RR$) to quantify the impact of changes in ventilatory strategy on VILI.⁷⁵ On the other hand, it has been argued that the simplicity of $4^* \Delta P^* RR$ is not superior to bedside calculation of mechanical power through simplified equation.⁷⁶ In short, RR should be considered to estimate lung damage.

In a seminal preclinical study,⁷⁷ the authors varied the mechanical power applied to the respiratory system by changing the RR while keeping the V_T and transpulmonary pressure constant, to identify a power threshold for VILI. They showed that, in healthy piglets, widespread edema developed only when the delivered transpulmonary mechanical power exceeded 12.1 J/min. As injured lungs need a high mechanical power to be ventilated at the same V_T , lung collapse results in a reduction of lung area that can be ventilated, which requires more pressure and flow. This, in turn, increases the delivered mechanical power without a change in V_T . This vicious cycle might explain the increase

in lung damage as the impact of mechanical power is amplified.

Ventilator-Induced Lung Injury

Ventilator-induced lung injury (VILI) is commonly attributed to the application of excessive V_T (volutrauma) or airway pressure (barotrauma). Volutrauma and barotrauma are primarily caused by unphysiological lung distortion or strain (the ratio between V_T and functional residual capacity) and stress (transpulmonary pressure), acting either globally or locally. In a large animal model, formation of edema in healthy lungs was shown to occur only when a global strain ratio of between 1.5 and 2 was reached or exceeded.⁷⁸

Is Assisted Mechanical Ventilation Associated with VILI?

As previously described, spontaneous breathing differs from controlled mechanical ventilation. However, during pressure-support ventilation, VILI may occur due to several factors¹: increased spontaneous breathing effort and, thus, transpulmonary driving pressure⁷⁹ and tensile stress⁸⁰ (→ Fig. 4)²; patient-ventilator asynchrony^{3,81} *pendelluft* and inhomogeneous stretch across the lungs⁸²; and⁴ alveolar edema, as negative pleural pressures can be transmitted to the alveoli, increasing capillary perfusion.⁸³ In a model of mild ARDS,⁸⁴ Pinto et al showed that, at similar dynamic transpulmonary driving pressure, with and without adjusted inspiratory time, pressure-controlled compared with pressure-support ventilation resulted in increased diffuse alveolar damage score and airspace heterogeneity, reduced E-cadherin expression in lung tissue, and increased gene expression of IL-6, among others. In addition, no major differences were observed between pressure-support ventilation and pressure-controlled ventilation when a protective V_T and static transpulmonary driving pressure were used. Lung injury was proportional to static transpulmonary driving pressure levels.

In extending this discussion to COVID-19 patients, the concept of patient self-inflicted lung injury (P-SILI) has become particularly important. These patients present with dyspnea and hypoxemia, which may require noninvasive or invasive respiratory support. Due to limited availability of ICU beds, a relatively high number of patients were treated with noninvasive respiratory support for many days, which may lead to P-SILI. Four potential mechanisms of P-SILI in COVID-19 have been suggested: (1) increased lung stress/strain,⁸⁵ (2) inhomogeneous distribution of ventilation,⁸² (3) changes in lung perfusion,⁸⁶ and (4) patient-ventilator asynchronies during noninvasive positive-pressure ventilation.⁸⁷

Mechanical Stimulus into Molecular Signals: The Cellular Version of the Facts

The development of VILI can be triggered by a complex interplay of potentially injurious factors: (1) regional overdistension of the alveoli caused by application of high volumes and/or alveolar pressures; (2) modifications of local

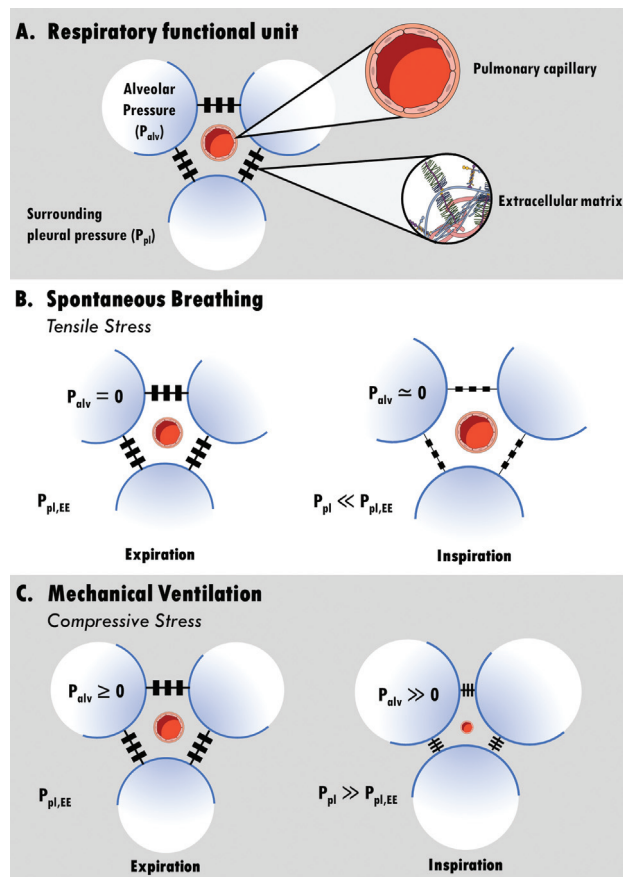


Fig. 4 Panel A illustrates the components of a lung functional unit. Capillaries and components of extracellular matrix (ECM) are located in the lung interstitial spaces. Scaffolding is the most fundamental role of the ECM, connecting adjacent alveoli. **Panel B** shows that during spontaneous breathing, the expiratory pleural pressure is negative, and the alveolar pressure is 0; whereas during inspiration, pleural pressure further decreases resulting in tensile stress applied to the extracellular matrix, resulting in a modest increase in capillary size. **Panel C** shows that during positive pressure mechanical ventilation, the expiratory pleural pressure depends on the application of extrinsic positive end-expiratory pressure (PEEP); during inspiration, the extracellular matrix is subjected to compressive stress and the capillary size is consequently reduced. P_{alv} , alveolar pressure; P_{pl} , pleural pressure; $P_{pl,EE}$, end-expiratory pleural pressure.

stress, which deforms cells and their supporting matrix into abnormal shapes and dimensions compared with normal spontaneous breathing; (3) abrasion of the epithelial airspace, observed in particular with ventilation at low V_T and due to the repeated recruitment and derecruitment of unstable lung units; (4) conversion of surfactant molecules into inactive surfactant aggregates as a consequence of large alveolar surface area oscillations; and (5) increased stresses between neighboring cells and between cells and the surrounding tissue caused by the interdependence phenomenon. Two main mechanisms cause VILI-induced tissue injury: (1) direct damage to the alveolar capillary membrane and ECM; and (2) mechanotransduction, which is the conversion of a mechanical stimulus into intracellular biochemical and molecular signals. In the microenvironment, several mechanical forces act on Type I and II epithelial cells, as well as on endothelial cells, during positive-pressure ventilation.

Type I Epithelial Cells

Alveolar epithelial cells form a relatively impermeable barrier that is dependent on the formation and maintenance of tight junctions. More than 95% of the surface area of the alveolus is covered by Type I epithelial cells. These cells can adapt to cyclic stretch through gene expression, depending not only on the amount of stress (amplitude), but also the duration of the applied stress (period). One pathway closely associated with epithelial tight junctions is Wnt signaling. A previous study showed that high- V_T ventilation for 4 hours caused upregulation of Wnt5a protein levels and was associated with increased levels of total β -catenin, which can modulate adherens junctions and tight junctions between epithelial cells. In addition, claudin-18 and -4 have been shown to play important roles in regulating the composition and permeability of alveolar epithelial tight junctions.

Type II Epithelial Cells

Although Type I epithelial cells cover 93% of the alveolar surface,⁸⁸ due to their spread-out distribution and elongation at the alveolar capillary membrane, they are less numerous than Type II epithelial cells at the alveolar scale. Typically, Type II cells tend to reside near the corner-like areas of the alveolus. It is reasonable to think that, if repetitive cyclic deformation is allowed to continue, more injury will be imposed to the epithelial cells, and that both the amplitude and the period of perturbations are relevant. Although it is difficult to extrapolate what is the proportion of alveoli expansion in terms of monolayer cell stretch, previous studies have demonstrated that mild stretch (4%) can correspond to a low V_T (5–6 mL/kg of ideal body weight). Interestingly, epithelial cell distortion within physiological range is desired, since Type II alveolar cells can release dipalmitoylphosphatidylcholine, a surfactant lipid, thus improving lung function. Furthermore, limiting the deformation amplitude has been shown to result in significant reductions in cell death at identical peak deformations. Adding one more piece to the puzzle, Roan et al not only studied stretch in Type II cells but also combined it with high oxygen concentration (80–90%). This is relevant, since most ARDS patients on mechanical ventilation can receive supplemental oxygen for prolonged periods. The authors demonstrated that cyclic stretch of hyperoxia-treated cells caused increased detachment of the cells, which correlated with significant alterations in F-actin and microtubules in the cytoskeleton.⁸⁹

Endothelial Cells

Each alveolus is surrounded by a dense capillary network. Therefore, if excessive mechanical stretch is taking place, there will be greater odds of endothelial dysfunction and increased vascular leak. In this context, a study found that excessive mechanical stretch (18% elongation from baseline condition) stimulated the formation of microparticles shed from the cell surface of injured tissue, which is a sign of endothelial dysfunction. Interestingly, when these microparticles were injected intratracheally in a healthy animal, they induced lung inflammation. In addition to microparticle release, specific inflammatory mediators are produced as a result of cyclic stretch. One of these mediators is the high-

mobility group box protein 1 (HMGB-1), which is closely associated with triggering of several proinflammatory cytokines, including TNF α , IL-8, and monocyte chemoattractant protein 1. In experimental settings, HMGB-1 expression was positively regulated by cyclic excessive mechanical stretch (18%),⁹⁰ but not by physiological cyclic mechanical stretch (5%).

Translation to Clinical Practice

Tidal volume, PEEP, RR, airflow, driving pressure, plateau pressure, transpulmonary pressure, energy, and mechanical power are well-recognized determinants of VILI, thus impairing clinical outcome. They may affect not only the lungs (extracellular matrix, epithelial, and endothelial cell damage), but also hemodynamics and distal organs. In addition to controlling these parameters, lung physiology and biological markers should be measured to mitigate VILI. Personalized mechanical ventilation is recommended and requires investment of both personnel and resources, including experimental and clinical trials.

Conclusion

Mechanical ventilation is an essential supportive therapy during the perioperative period and may help reduce mortality in patients with ARDS. Evidence suggests that positive-pressure ventilation can exert negative physiological consequences not only on the lungs, but also on distal organs. These effects may be intermediated by hemodynamic fluctuations and/or by the release of inflammatory mediators through different mechanisms. Some ventilator variables available from the clinician can be controlled (tidal volume, PEEP level, RR, inspiratory and expiratory airway flow), while others represent ventilation consequences with prognostic value (plateau and driving pressures). The association of mechanical power with patient outcome requires elucidation. It is important to better elucidate the precise mechanisms of VILI on alveolar-capillary membrane, including the extracellular matrix, and to clarify how VILI affects distal organs for developing new therapeutic strategies.

Conflict of Interest

None declared.

References

- Mitchell JR, Whitelaw WA, Sas R, Smith ER, Tyberg JV, Belenkie I. RV filling modulates LV function by direct ventricular interaction during mechanical ventilation. *Am J Physiol Heart Circ Physiol* 2005;289(02):H549–H557
- Pelosi P, Ferguson ND, Frutos-Vivar F, et al. Ventila Study Group. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med* 2011;39(06):1482–1492
- Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. *Am J Respir Crit Care Med* 2016;194(04):402–414
- Kredel M, Muellenbach RM, Johannes A, Brederlau J, Roewer N, Wunder C. Hepatic effects of lung-protective pressure-controlled ventilation and a combination of high-frequency oscillatory

- ventilation and extracorporeal lung assist in experimental lung injury. *Med Sci Monit* 2011;17(10):BR275–BR281
- 5 Kirkpatrick AW, Roberts DJ, De Waele J, et al. Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013;39(07):1190–1206
 - 6 Regli A, Hockings LE, Musk GC, et al. Commonly applied positive end-expiratory pressures do not prevent functional residual capacity decline in the setting of intra-abdominal hypertension: a pig model. *Crit Care* 2010;14(04):R128
 - 7 Regli A, Mahendran R, Fysh ET, et al. Matching positive end-expiratory pressure to intra-abdominal pressure improves oxygenation in a porcine sick lung model of intra-abdominal hypertension. *Crit Care* 2012;16(05):R208
 - 8 Regli A, Chakera J, De Keulenaer BL, et al. Matching positive end-expiratory pressure to intra-abdominal pressure prevents end-expiratory lung volume decline in a pig model of intra-abdominal hypertension. *Crit Care Med* 2012;40(06):1879–1886
 - 9 Cortes-Puentes GA, Keenan JC, Adams AB, Parker ED, Dries DJ, Marini JJ. Impact of chest wall modifications and lung injury on the correspondence between airway and transpulmonary driving pressures. *Crit Care Med* 2015;43(08):e287–e295
 - 10 Tobin MJ, Mador MJ, Guenther SM, Lodato RF, Sackner MA. Variability of resting respiratory drive and timing in healthy subjects. *J Appl Physiol* (1985) 1988;65(01):309–317
 - 11 Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B, Permutt S. Effect of lung inflation on lung blood volume and pulmonary venous flow. *J Appl Physiol* (1985) 1985;58(03):954–963
 - 12 Hakim TS, Michel RP, Chang HK. Effect of lung inflation on pulmonary vascular resistance by arterial and venous occlusion. *J Appl Physiol* 1982;53(05):1110–1115
 - 13 Simmons D, Linde L, Miller J, O'Reilly R. Relation between lung volume and pulmonary vascular resistance. *Circ Res* 1961;9:465–471
 - 14 Mahjoub Y, Lejeune V, Muller L, et al. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth* 2014;112(04):681–685
 - 15 Pinsky MR. Functional haemodynamic monitoring. *Curr Opin Crit Care* 2014;20(03):288–293
 - 16 Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002;121(06):2000–2008
 - 17 Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000;162(01):134–138
 - 18 Kimmoun A, Baux E, Das V, et al. Outcomes of patients admitted to intensive care units for acute manifestation of small-vessel vasculitis: a multicenter, retrospective study. *Crit Care* 2016;20:27
 - 19 He H, Long Y, Liu D, Wang X, Tang B. The prognostic value of central venous-to-arterial CO₂ difference/arterial-central venous O₂ difference ratio in septic shock patients with central venous O₂ saturation ≥ 80 . *Shock* 2017;48(05):551–557
 - 20 Dumas G, Lavillegrand JR, Joffre J, et al. Mottling score is a strong predictor of 14-day mortality in septic patients whatever vasopressor doses and other tissue perfusion parameters. *Crit Care* 2019;23(01):211
 - 21 The Brain Trauma Foundation. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Guidelines for cerebral perfusion pressure. *J Neurotrauma* 2000;17(6-7):507–511
 - 22 Brian JE Jr. Carbon dioxide and the cerebral circulation. *Anesthesiology* 1998;88(05):1365–1386
 - 23 Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. *Acta Neurochir Suppl (Wien)* 1990;49:1–64
 - 24 Robba C, Ball L, Battaglini D, et al. Early effects of ventilatory rescue therapies on systemic and cerebral oxygenation in mechanically ventilated COVID-19 patients with acute respiratory distress syndrome: a prospective observational study. *Crit Care* 2021;25(01):111
 - 25 Robba C, Poole D, McNett M, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. *Intensive Care Med* 2020;46(12):2397–2410
 - 26 Robba C, Ball L, Nogas S, et al. Effects of positive end-expiratory pressure on lung recruitment, respiratory mechanics, and intracranial pressure in mechanically ventilated brain-injured patients. *Front Physiol* 2021;12:711273
 - 27 Ott L, McClain CJ, Gillespie M, Young B. Cytokines and metabolic dysfunction after severe head injury. *J Neurotrauma* 1994;11(05):447–472
 - 28 Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. *Curr Opin Nephrol Hypertens* 2007;16(03):227–236
 - 29 Uchino S, Kellum JA, Bellomo R, et al. Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005;294(07):813–818
 - 30 Walcher A, Faubel S, Keniston A, Dennen P. In critically ill patients requiring CRRT, AKI is associated with increased respiratory failure and death versus ESRD. *Ren Fail* 2011;33(10):935–942
 - 31 Annat G, Viale JP, Bui Xuan B, et al. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. *Anesthesiology* 1983;58(02):136–141
 - 32 Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. *J Am Coll Cardiol* 2013;62(06):485–495
 - 33 Uhlig S, Ranieri M, Slutsky AS. Biotrauma hypothesis of ventilator-induced lung injury. *Am J Respir Crit Care Med* 2004;169(02):314–315
 - 34 Gurkan OU, O'Donnell C, Brower R, Ruckdeschel E, Becker PM. Differential effects of mechanical ventilatory strategy on lung injury and systemic organ inflammation in mice. *Am J Physiol Lung Cell Mol Physiol* 2003;285(03):L710–L718
 - 35 Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003;289(16):2104–2112
 - 36 Kuiper JW, Groeneveld AB, Slutsky AS, Plötz FB. Mechanical ventilation and acute renal failure. *Crit Care Med* 2005;33(06):1408–1415
 - 37 Ortiz A, Lorz C, Egado J. The Fas ligand/Fas system in renal injury. *Nephrol Dial Transplant* 1999;14(08):1831–1834
 - 38 Wu B, Iwakiri R, Ootani A, Fujise T, Tsunada S, Fujimoto K. Platelet-activating factor promotes mucosal apoptosis via FasL-mediated caspase-9 active pathway in rat small intestine after ischemia-reperfusion. *FASEB J* 2003;17(09):1156–1158
 - 39 van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care* 2013;17(03):R98
 - 40 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301–1308
 - 41 Mercat A, Richard JC, Vielle B, et al. Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults

- with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(06):646–655
- 42 Audimoolam VK, McPhail MJ, Wendon JA, et al. Lung injury and its prognostic significance in acute liver failure. *Crit Care Med* 2014; 42(03):592–600
 - 43 Levesque E, Saliba F, Ichai P, Samuel D. Outcome of patients with cirrhosis requiring mechanical ventilation in ICU. *J Hepatol* 2014; 60(03):570–578
 - 44 Gacouin A, Locufier M, Uhel F, et al. Liver cirrhosis is independently associated with 90-day mortality in ARDS patients. *Shock* 2016;45(01):16–21
 - 45 Quintel M, Pelosi P, Caironi P, et al. An increase of abdominal pressure increases pulmonary edema in oleic acid-induced lung injury. *Am J Respir Crit Care Med* 2004;169(04):534–541
 - 46 Santos CL, Moraes L, Santos RS, et al. Effects of different tidal volumes in pulmonary and extrapulmonary lung injury with or without intraabdominal hypertension. *Intensive Care Med* 2012; 38(03):499–508
 - 47 Pelosi P, Luecke T, Rocco PR. Chest wall mechanics and abdominal pressure during general anaesthesia in normal and obese individuals and in acute lung injury. *Curr Opin Crit Care* 2011;17(01): 72–79
 - 48 Ranieri VM, Brienza N, Santostasi S, 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(4 Pt 1):1082–1091
 - 49 Santos CL, Moraes L, Santos RS, et al. The biological effects of higher and lower positive end-expiratory pressure in pulmonary and extrapulmonary acute lung injury with intra-abdominal hypertension. *Crit Care* 2014;18(03):R121
 - 50 Regli A, Pelosi P, Malbrain MLNG. Ventilation in patients with intra-abdominal hypertension: what every critical care physician needs to know. *Ann Intensive Care* 2019;9(01):52
 - 51 Ball L, Pelosi P. How I ventilate an obese patient. *Crit Care* 2019;23(01):176
 - 52 Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372(08):747–755
 - 53 Neto AS, Hemmes SN, Barbas CS, 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(04): 272–280
 - 54 Silva PL, Gama de Abreu M. Regional distribution of transpulmonary pressure. *Ann Transl Med* 2018;6(19):385
 - 55 Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149(01):8–13
 - 56 Guay J, Ochroch EA. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. *Cochrane Database Syst Rev* 2015;(12):CD011151
 - 57 Futier E, Pereira B, Jaber S. Intraoperative low-tidal-volume ventilation. *N Engl J Med* 2013;369(19):1862–1863
 - 58 Felix NS, Samary CS, Cruz FF, Rocha NN, Fernandes MVS, Machado JA, Bose-Madureira RL, Capelozzi VL, Pelosi P, Silva PL, Marini JJ, Rocco PRM. Gradually Increasing Tidal Volume May Mitigate Experimental Lung Injury in Rats. *Anesthesiology* 2019 May;130(05):767–777
 - 59 Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJPROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014;384(9942):495–503
 - 60 Brower RG, Lanken PN, MacIntyre N, et al. 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(04):327–336
 - 61 Meade MO, Cook DJ, Guyatt GH, et al. Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(06):637–645
 - 62 Pelosi P, Ball L, Barbas CSV, et al. Personalized mechanical ventilation in acute respiratory distress syndrome. *Crit Care* 2021;25(01):250
 - 63 Ball L, Serpa Neto A, Trifiletti V, et al. PROVE Network: PROtective Ventilation Network. Effects of higher PEEP and recruitment manoeuvres on mortality in patients with ARDS: a systematic review, meta-analysis, meta-regression and trial sequential analysis of randomized controlled trials. *Intensive Care Med Exp* 2020;8(Suppl 1):39
 - 64 Pelosi P, Rocco PRM, Gama de Abreu M. Close down the lungs and keep them resting to minimize ventilator-induced lung injury. *Crit Care* 2018;22(01):72
 - 65 Vieillard-Baron A, Prin S, Augarde R, et al. Increasing respiratory rate to improve CO₂ clearance during mechanical ventilation is not a panacea in acute respiratory failure. *Crit Care Med* 2002;30(07):1407–1412
 - 66 Goligher EC, Hodgson CL, Adhikari NKJ, Meade MO, Wunsch H, Uleryk E, Gajic O, Amato MPB, Ferguson ND, Rubenfeld GD, Fan E. Lung Recruitment Maneuvers for Adult Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* 2017 Oct;14(Supplement_4):S304–S311. Doi: 10.1513/AnnalsATS.201704-3400T
 - 67 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BTWheeler AAcute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301–1308
 - 68 Parhar KKS, Zjadewicz K, Soo A, et al. Epidemiology, mechanical power, and 3-year outcomes in acute respiratory distress syndrome patients using standardized screening. an observational cohort study. *Ann Am Thorac Soc* 2019;16(10): 1263–1272
 - 69 Koh SO. Mode of mechanical ventilation: volume controlled mode. *Crit Care Clin* 2007;23(02):161–167, viii
 - 70 Smith RA, Venus B. Cardiopulmonary effect of various inspiratory flow profiles during controlled mechanical ventilation in a porcine lung model. *Crit Care Med* 1988;16(08):769–772
 - 71 Al-Saady N, Bennett ED. Decelerating inspiratory flow waveform improves lung mechanics and gas exchange in patients on intermittent positive-pressure ventilation. *Intensive Care Med* 1985; 11(02):68–75
 - 72 Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007;175(02):160–166
 - 73 Villar J, Ambrós A, Soler JA, et al. Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network. Age, PaO₂/FIO₂, and plateau pressure score: a proposal for a simple outcome score in patients with the acute respiratory distress syndrome. *Crit Care Med* 2016;44(07):1361–1369
 - 74 Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42(10):1567–1575
 - 75 Otis AB, Fenn WO, Rahn H. Mechanics of breathing in man. *J Appl Physiol* 1950;2(11):592–607
 - 76 Giosa L, Busana M, Pasticci I, et al. Mechanical power at a glance: a simple surrogate for volume-controlled ventilation. *Intensive Care Med Exp* 2019;7(01):61
 - 77 Costa ELV, Slutsky AS, Brochard LJ, et al. Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021;204(03):303–311

- 78 Camporota L, Busana M, Marini JJ, Gattinoni L. The 4DPRR index and mechanical power: a step ahead or four steps backward? *Am J Respir Crit Care Med* 2021;204(04):491–492
- 79 Cressoni M, Gotti M, Chiurazzi C, et al. Mechanical power and development of ventilator-induced lung injury. *Anesthesiology* 2016;124(05):1100–1108
- 80 Protti A, Cressoni M, Santini A, et al. Lung stress and strain during mechanical ventilation: any safe threshold? *Am J Respir Crit Care Med* 2011;183(10):1354–1362
- 81 Yoshida T, Fujino Y, Amato MB, 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(08):985–992
- 82 Pelosi P, Rocco PR. Effects of mechanical ventilation on the extracellular matrix. *Intensive Care Med* 2008;34(04):631–639
- 83 Brochard L, Slutsky AS, Pesenti A. Reply: “A Word of Caution Regarding Patient Self-inflicted Lung Injury and Prophylactic Intubation” and “Hyperventilation (Not Ventilator)-Induced Lung Injury”. *Am J Respir Crit Care Med* 2017;196(07):937–938
- 84 Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188(12):1420–1427
- 85 Kallet RH, Alonso JA, Luce JM, Matthay MA. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. *Chest* 1999;116(06):1826–1832
- 86 Pinto EF, Santos RS, Antunes MA, et al. Static and dynamic transpulmonary driving pressures affect lung and diaphragm injury during pressure-controlled versus pressure-support ventilation in experimental mild lung injury in rats. *Anesthesiology* 2020;132(02):307–320
- 87 Bellani G, Grasselli G, Teggie-Droghi M, et al. Do spontaneous and mechanical breathing have similar effects on average transpulmonary and alveolar pressure? A clinical crossover study. *Crit Care* 2016;20(01):142
- 88 Busana M, Giosa L, Cressoni M, et al. The impact of ventilation-perfusion inequality in COVID-19: a computational model. *J Appl Physiol* (1985) 2021;130(03):865–876
- 89 Blanch L, Villagra A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;41(04):633–641
- 90 Crapo JD, Crapo RO, Jensen RL, Mercer RR, Weibel ER. Evaluation of lung diffusing capacity by physiological and morphometric techniques. *J Appl Physiol* (1985) 1988;64(05):2083–2091
- 91 Roan E, Wilhelm K, Bada A, et al. Hyperoxia alters the mechanical properties of alveolar epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2012;302(12):L1235–L1241
- 92 Ding N, Wang F, Xiao H, Xu L, She S. Mechanical ventilation enhances HMGB1 expression in an LPS-induced lung injury model. *PLoS One* 2013;8(09):e74633