

# 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,<sup>1</sup> central nervous system,<sup>2</sup> kidney,<sup>3</sup> and liver.<sup>4</sup> 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.<sup>5–9</sup>

In normal spontaneous ventilation, humans are able to vary the breathing pattern within specific amplitude and time domains,<sup>10</sup> 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.<sup>1,11</sup> 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.<sup>1</sup> Right ventricle afterload also increases, mainly due to alveolar vessel compression, as lung volume rises.<sup>12</sup>

### Impact of Lung and Chest Wall Volume

Pulmonary vascular resistance is lowest at functional residual capacity, increasing at either higher or lower lung volumes.<sup>13</sup> 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

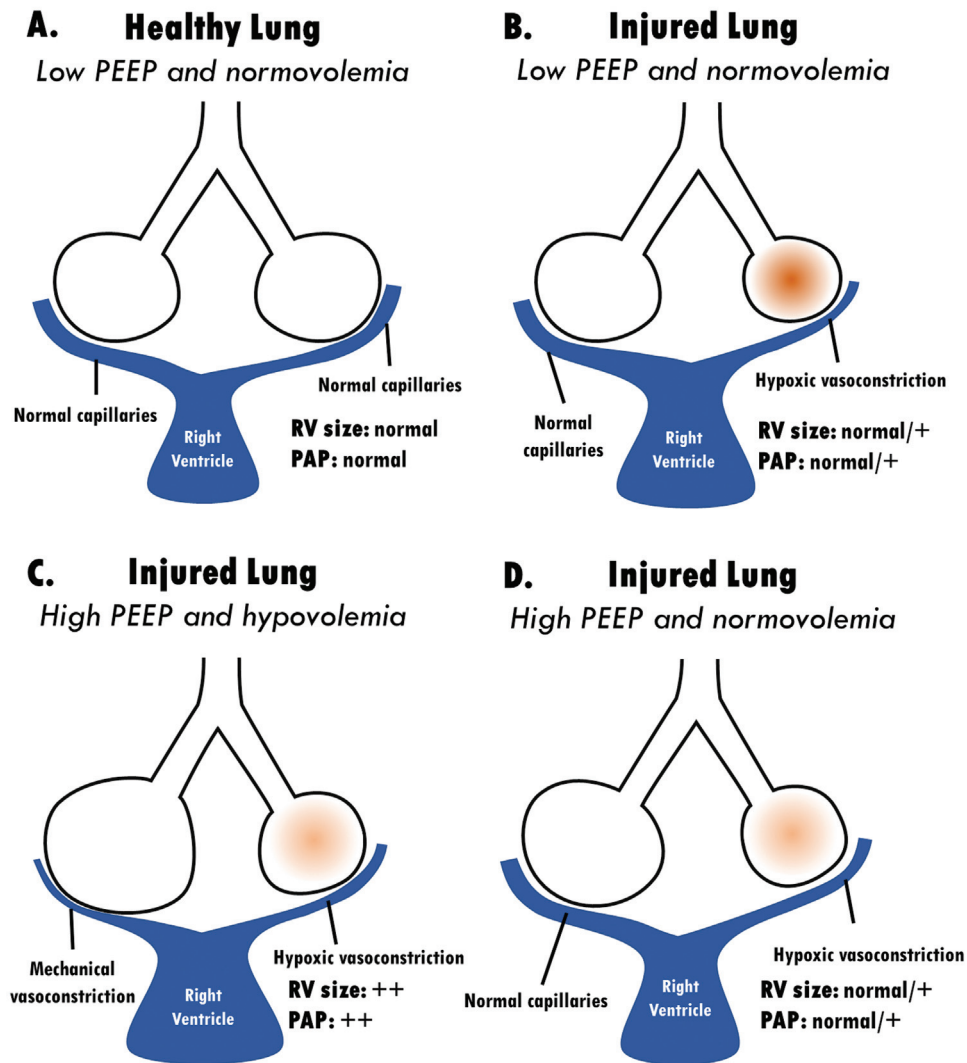
Understanding the fundamentals of these cardiopulmonary interactions is critical to assessing fluid responsiveness in critically ill patients. Not all patients who respond to fluid challenge need additional fluids; this information should be obtained from laboratory and clinical data. For pulse pressure 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  $\geq 30$  mL/cmH<sub>2</sub>O.<sup>14</sup> Both PPV and SVV are defined as the ratio of their maximal minus the minimal values to the mean values.<sup>15</sup> 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.<sup>16,17</sup>

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,<sup>18</sup> (A-v) CO<sub>2</sub>,<sup>19</sup> and peripheral mottling.<sup>20</sup> 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.<sup>21</sup> As CBF is closely related to regional cerebral metabolism, it is highly dependent on CO<sub>2</sub> levels and changes in PaCO<sub>2</sub>. It has been observed that increasing CO<sub>2</sub> tension relaxes cerebral arteries in vitro.<sup>22</sup> In vivo, localized perivascular changes in PaCO<sub>2</sub> 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 PaCO<sub>2</sub>, the CBF changes by 3% over the range of 20 to 60 mm Hg.<sup>23</sup> Therefore, hypoventilation resulting in hypercapnia causes vasodilatation and higher CBF, while hyperventilation leads to vasoconstriction and lower CBF. In a recent study, Robba et al<sup>24</sup> 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,<sup>25</sup> 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 study<sup>26</sup> evaluated the effects of two levels of PEEP (5 and 15 cmH<sub>2</sub>O) 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<sub>2</sub>O 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 Crs, 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.<sup>27</sup> 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  $9 \pm 5$  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.<sup>2</sup>

### 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,<sup>28</sup> 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 patients<sup>29</sup>; in one study, a need for mechanical ventilation was the main factor associated with 89% mortality in patients with AKI.<sup>30</sup>

### Hemodynamics

As previously described, positive-pressure ventilation increases ITP, which reduces renal blood flow, glomerular filtration rate, sodium excretion, and urinary output.<sup>31</sup> 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.<sup>3</sup> 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,<sup>32</sup> 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.<sup>33</sup> 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.<sup>34</sup> Other authors have observed increases not only in inflammation, but also in lung and kidney

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

### Ventilatory Parameters and Renal Failure

One systematic review and meta-analysis showed that invasive mechanical ventilation increases the odds of AKI.<sup>39</sup> Neither  $V_T$  nor PEEP had any effect on risk of developing AKI. However, this meta-analysis failed to include two important clinical trials.<sup>40,41</sup> The ARDS Network trial<sup>40</sup> 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;  $20 \pm 11$  vs.  $18 \pm 11$  days,  $p = 0.005$ ). The EXPRESS study<sup>41</sup> 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.<sup>42</sup>

One large study<sup>43</sup> 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.<sup>44</sup>

Experimental studies have sought to understand the impact of specific ventilatory strategies on liver function. Kredel et al<sup>4</sup> examined the hepatic consequences of pressure-controlled ventilation with a  $V_T$  of 6 mL/kg and PEEP adjusted to 3 cmH<sub>2</sub>O above the lower inflection point of the pressure-volume curve or as high-frequency oscillatory ventilation ( $\geq 12$  Hz) with a mean airway pressure 3 cmH<sub>2</sub>O 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

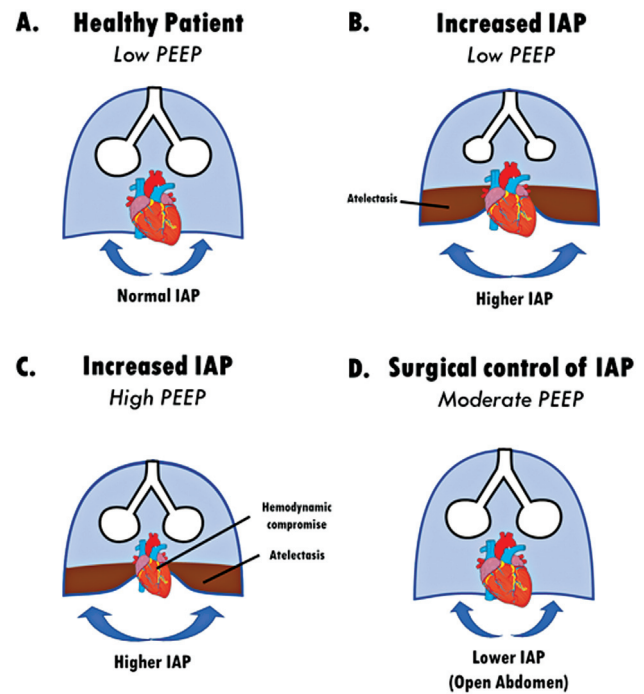
The normal IAP is approximately 5 to 7 mm Hg.<sup>5</sup> IAH is defined by a sustained or repeated pathological elevation in IAP  $\geq 12$  mm Hg, while abdominal compartment syndrome is defined as a sustained IAP  $>20$  mm Hg (with or

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,<sup>6,7,45</sup> with a reduction in lung volumes and increase in pleural pressure,<sup>46,47</sup> causing atelectasis and impaired lung function.<sup>48</sup>

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 cmH<sub>2</sub>O (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.<sup>6</sup> In a subsequent study, the PEEP level was adjusted to match the IAP in a porcine model of IAH with healthy lungs.<sup>8</sup> 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.<sup>7</sup> 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 cmH<sub>2</sub>O) in direct lung injury increased lung elastance, while intermediate PEEP levels (7 cmH<sub>2</sub>O) in indirect lung injury increased expression of inflammatory markers.<sup>49</sup> 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 cmH<sub>2</sub>O.<sup>50</sup> 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 Pplat<sup>51</sup> 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 cmH<sub>2</sub>O, the adjusted target Pplat is equivalent to target Pplat + 4 cmH<sub>2</sub>O; meaning that if target (safe upper limit) Pplat is 30 cmH<sub>2</sub>O, the adjusted target Pplat is 34 cmH<sub>2</sub>O. 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<sub>T</sub> 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,<sup>9</sup> 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<sub>T</sub> 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 patients<sup>52</sup> and surgical patients<sup>53</sup>; 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<sub>tp</sub>) are expected across different lung regions.<sup>54</sup> Taking into account that 10 cmH<sub>2</sub>O 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 cmH<sub>2</sub>O in the two-thirds above the transducer and 5 cmH<sub>2</sub>O in the one-third below it are expected, because density is higher in the dependent zones.<sup>55</sup> To estimate P<sub>pl</sub> from esophageal pressure (P<sub>es</sub>) obtained from single and absolute values, some assumptions can be done, as follows:

Estimated P<sub>pl</sub> near sternum (non-dependent) = P<sub>es</sub> – 5 cmH<sub>2</sub>O

Estimated P<sub>pl</sub> near vertebra (dependent) = P<sub>es</sub> + 5 cmH<sub>2</sub>O

The P<sub>pl</sub> estimation should be corrected according to airway pressure (P<sub>aw</sub>), such that P<sub>pl</sub> = P<sub>aw</sub> – P<sub>es</sub>:

P<sub>pl</sub> = P<sub>aw</sub> – (P<sub>es</sub> – 5 cmH<sub>2</sub>O) in non-dependent areas = P<sub>aw</sub> – P<sub>es</sub> + 5 cmH<sub>2</sub>O

P<sub>pl</sub> = P<sub>aw</sub> – (P<sub>es</sub> + 5 cmH<sub>2</sub>O) in dependent areas = P<sub>aw</sub> – P<sub>es</sub> – 5 cmH<sub>2</sub>O

The following assumptions should be made:

1. The absolute difference (not corrected) P<sub>aw</sub> – P<sub>es</sub> at end expiration or inspiration is the P<sub>tp</sub> in the middle part of the lung.
2. The variation in P<sub>pl</sub> (ΔP<sub>pl</sub>) equals the ΔP<sub>es</sub> such that the measurements of lung and chest wall elastances might be accurate.
3. At end expiration (dependent regions), the absolute P<sub>tp</sub> is computed as PEEP – P<sub>es</sub> – 5 cmH<sub>2</sub>O.
4. At end inspiration (non-dependent regions), the absolute P<sub>tp</sub> is computed as P<sub>plat</sub> – P<sub>es</sub> + 5 cmH<sub>2</sub>O.
5. At end inspiration (non-dependent regions), the absolute P<sub>tp</sub> might be computed as P<sub>plat</sub> × EL/E<sub>tot</sub>; EL = ΔP<sub>L</sub>/ΔV; E<sub>tot</sub> = ΔP<sub>rs</sub>/ΔV;

where EL is the lung elastance and E<sub>tot</sub> 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<sub>T</sub>, 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<sub>plat,RS</sub>), driving pressure (ΔP<sub>RS</sub>), 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<sub>T</sub> 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<sub>T</sub>) Size

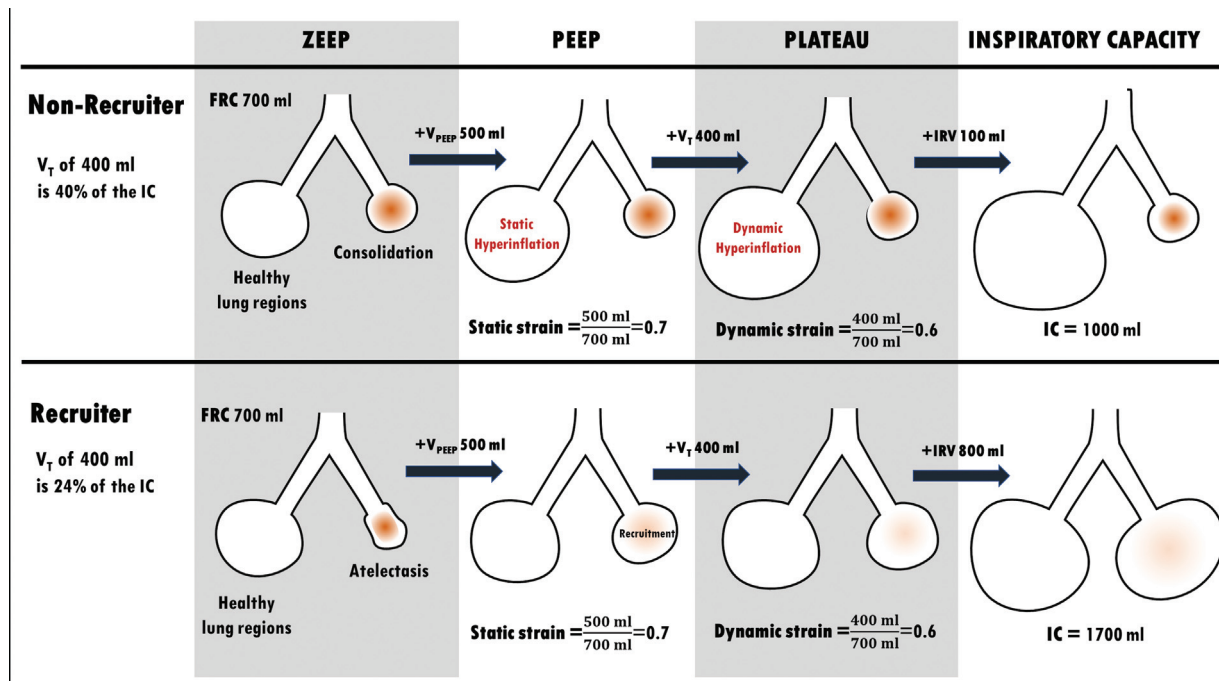
Recently, a meta-analysis of pooled data from large randomized studies comparing different V<sub>T</sub> showed that low V<sub>T</sub> (defined as <10 mL/kg) should be preferentially used during surgery before the development of lung injury.<sup>56</sup> Preemptive application of low V<sub>T</sub> decreased the need for postoperative ventilatory support (invasive and non-invasive). One study in this meta-analysis<sup>57</sup> showed that a V<sub>T</sub> of 6 to 8 mL/kg of ideal body weight versus V<sub>T</sub> of 10 to 12 mL/kg resulted in fewer pulmonary and extrapulmonary complications. However, patients ventilated with low V<sub>T</sub> also had PEEP levels ranging from 6 to 8 cmH<sub>2</sub>O with periodic RMs, while the group of patients ventilated with high V<sub>T</sub> had no PEEP.

### Strain and Standardization of V<sub>T</sub> on IC

Strain is defined as V<sub>T</sub> according to end-expiratory lung volume (EELV). An additional standardization of V<sub>T</sub> 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 cmH<sub>2</sub>O or in case a minimal PEEP 5 cmH<sub>2</sub>O and inspiratory pressure at 30 cmH<sub>2</sub>O. 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<sub>T</sub> on inspiratory capacity, takes automatically in count the distortion of lung parenchyma due to PEEP. Anyway, the standardization of V<sub>T</sub> 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<sub>T</sub> 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,<sup>1</sup> 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 trial<sup>58</sup> was designed to test the hypothesis that a ventilation strategy with a high PEEP level (12 cmH<sub>2</sub>O) plus RMs compared with low PEEP level (2 cmH<sub>2</sub>O) 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 cmH<sub>2</sub>O, which suggests effective lung recruitment without relevant overdistension; (2) low  $V_T$  combined with PEEP = 2 cmH<sub>2</sub>O 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.<sup>41,59,60</sup> 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,<sup>41,60</sup> presented more ventilator-free and organ failure-free days, and improved respiratory system compliance.<sup>41</sup> 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.<sup>61</sup> 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,<sup>62</sup> 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  $\text{cmH}_2\text{O}$  at day 1 to 8.6  $\text{cmH}_2\text{O}$  at day 7. As a consequence of moderate PEEP application, a certain degree of manageable atelectasis is expected.<sup>63</sup> 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,<sup>40</sup> the authors did not discuss the RR, which was approximately 30 breaths/min, to facilitate  $\text{CO}_2$  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  $\text{CO}_2$  clearance without cardiovascular impairment, Vieillard-Baron et al<sup>64</sup> 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

$\text{CO}_2$  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,<sup>65</sup> 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.<sup>66</sup> 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.<sup>67</sup> 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.<sup>68</sup> On the other hand, a decelerating flow waveform has been associated with better lung mechanics and gas exchange in positive-pressure ventilation.<sup>69</sup>

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 cmH<sub>2</sub>O.<sup>40</sup> However, depending on the patients' respiratory system mechanics, keeping  $P_{plat,RS}$  below 30 cmH<sub>2</sub>O 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  $P_{plat,RS} < 30$  cmH<sub>2</sub>O. Therefore, the authors suggested that the  $P_{plat,RS}$  upper limit should be reduced to 28 cmH<sub>2</sub>O.<sup>70</sup> Moreover,  $P_{plat,RS} > 25$  cmH<sub>2</sub>O 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  $P_{plat,RS}$ .<sup>71</sup> They divided the  $P_{plat,RS}$  into three ranges (<27 cmH<sub>2</sub>O; 27–30 cmH<sub>2</sub>O; > 30 cmH<sub>2</sub>O). Mortality increased as  $P_{plat,RS}$  increased,<sup>71</sup> corroborating the previous study.

### Respiratory System Driving Pressure ( $\Delta P_{RS}$ )

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,  $\Delta P_{RS}$  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  $\Delta P_{RS}$  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  $\Delta P_{RS} > 15$  cmH<sub>2</sub>O was associated with a higher mortality rate in ARDS patients.<sup>52</sup> In contrast,  $V_T$ ,  $P_{plat,RS}$ , and PEEP were not independently correlated with increased mortality.<sup>52</sup> Increasing PEEP will have different effects on  $\Delta P_{RS}$  depending on the degree of lung pathology. If increasing PEEP results in lung tissue recruitment, a decrease in  $\Delta P_{RS}$  is expected. On the other hand, if increasing PEEP does not recruit lung tissue, the lung may become overstretched, and the  $\Delta P_{RS}$  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  $\Delta P_{RS}$  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,<sup>72</sup> which has been generated based on the classic equation of motion,<sup>73</sup> 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 hold<sup>74</sup>:

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

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.<sup>75</sup> The average RR was  $25.7 \pm 7.4$  breaths/min, which is a common value observed in daily intensive-care practice. The authors showed that the impact of  $\Delta P$  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.<sup>75</sup> 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.<sup>76</sup> In short, RR should be considered to estimate lung damage.

In a seminal preclinical study,<sup>77</sup> 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.<sup>78</sup>

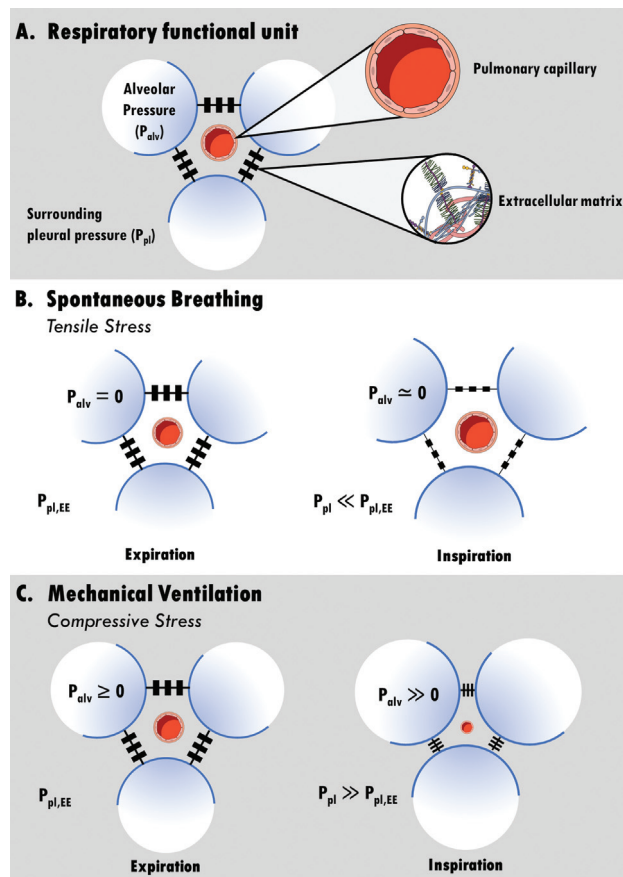
### Is Assisted Mechanical Ventilation Associated with VILI?

As previously described, spontaneous breathing differs from controlled mechanical ventilation. However, during pressure-support ventilation, VILI may occur due to several factors<sup>1</sup>: increased spontaneous breathing effort and, thus, transpulmonary driving pressure<sup>79</sup> and tensile stress<sup>80</sup> (→ Fig. 4)<sup>2</sup>; patient-ventilator asynchrony<sup>3,81</sup> *pendelluft* and inhomogeneous stretch across the lungs<sup>82</sup>; and<sup>4</sup> alveolar edema, as negative pleural pressures can be transmitted to the alveoli, increasing capillary perfusion.<sup>83</sup> In a model of mild ARDS,<sup>84</sup> 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,<sup>85</sup> (2) inhomogeneous distribution of ventilation,<sup>82</sup> (3) changes in lung perfusion,<sup>86</sup> and (4) patient-ventilator asynchronies during noninvasive positive-pressure ventilation.<sup>87</sup>

### 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  $\beta$ -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,<sup>88</sup> 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.<sup>89</sup>

### 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 $\alpha$ , IL-8, and monocyte chemoattractant protein 1. In experimental settings, HMGB-1 expression was positively regulated by cyclic excessive mechanical stretch (18%),<sup>90</sup> 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.

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