Review Article

The basics of respiratory mechanics: ventilator-derived parameters

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Abstract: Mechanical ventilation is a life-support system used to maintain adequate lung function in patients who are critically ill or undergoing general anesthesia. The benefits and harms of mechanical ventilation depend not only on the operator's setting of the machine (input), but also on their interpretation of ventilator-derived parameters (outputs), which should guide ventilator strategies. Once the inputs—tidal volume (V_T), positive end-expiratory pressure (PEEP), respiratory rate (RR), and inspiratory airflow (V')—have been adjusted, the following outputs should be measured: intrinsic PEEP, peak (Ppeak) and plateau (Pplat) pressures, driving pressure (ΔP), transpulmonary pressure (P_L), mechanical energy, mechanical power, and intensity. During assisted mechanical ventilation, in addition to these parameters, the pressure generated 100 ms after onset of inspiratory effort ($P_{0.1}$) and the pressure-time product per minute (PTP/min) should also be evaluated. The aforementioned parameters should be seen as a set of outputs, all of which need to be strictly monitored at bedside in order to develop a personalized, case-by-case approach to mechanical ventilation. Additionally, more clinical research to evaluate the safe thresholds of each parameter in injured and uninjured lungs is required.

Keywords: Mechanical ventilation; tidal volume; positive end-expiratory pressure (PEEP); respiratory rate; inspiratory flow; plateau pressure; driving pressure; transpulmonary pressure; mechanical energy; mechanical power

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Introduction

Mechanical ventilation is a life-support system used to maintain adequate lung function in patients who are critically ill or undergoing general anesthesia (1,2); however, it may cause lung damage. The benefits and harms of mechanical ventilation depend not only on the adjustment of ventilator parameters, but also on the interpretation of ventilator-derived parameters, which should be used to guide ventilatory strategies. The basis of this process relies on the interaction between physical forces acting on lung structures during mechanical ventilation adjusted by the operator and the lung and chest wall mechanics of the patient (3). Once the inputs—tidal volume (V_T), positive end-expiratory pressure (PEEP), respiratory rate (RR), and inspiratory airflow (V')—have been adjusted, the information obtained from the mechanical ventilator (the outputs or ventilator-derived parameters) can be examined. Regardless of ventilator mode, the following ventilator-derived parameters should be measured in order to mitigate harmful effects (2,4): intrinsic PEEP (PEEPi), peak (Ppeak) and plateau (Pplat) pressures, driving pressure (ΔP), and

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transpulmonary pressure (P_L). During assisted mechanical ventilation, in addition to these parameters, the pressure generated 100 ms after onset of inspiratory effort ($P_{0.1}$) and pressure-time product per minute (PTP/min) should also be evaluated. In this review, we will discuss the ventilator parameters adjusted by the operator (inputs) and ventilator parameters obtained after interaction with respiratory system structures during mechanical ventilation (outputs). Moreover, new ventilator-derived parameters, such as mechanical energy, mechanical power, and intensity, will be discussed in light of recent evidence (5-7).

Inputs: ventilator parameters set by the operator

Tidal volume (V_T)

In both uninjured and injured lungs, the use of low V_T has been preferred over high V_T.

In patients under general anesthesia, no association has been observed between V_T and postoperative pulmonary complications (PPCs) (8). Additionally, pressure-controlled ventilation (PCV) has been compared to volume-controlled ventilation (VCV), focusing on PPCs; this comparison is important to distinguish the potential role of strict control of V_T during VCV. The frequency of PPCs was higher in PCV than in VCV. This could be attributed to the difficulty in controlling V_T during PCV, thus highlighting the importance of V_T.

In the emergency department, mechanically ventilated patients with injured and uninjured lungs could also benefit from the use of low V_Ts (9).

In the intensive care unit (ICU), even though two meta-analyses suggest that patients with uninjured lungs could benefit from ventilation with low V_T (10,11), a prospective study reported no association between V_T and outcomes (12), which may be attributed to the fact that V_T in this study was much lower than in the aforementioned meta-analyses (10,11). In out-of-hospital cardiac arrest, V_T reduction has been associated with favorable neurocognitive outcome and more ventilator-free days (13). In short, the benefit of reduced V_T in ICU patients with uninjured lungs remains unclear. Two ongoing randomized clinical trials, Protective Ventilation in patients without ARDS at start of ventilation (PReVENT) (14) and Preventive Strategies in Acute Respiratory Distress Syndrome (EPALI) (Clinicaltrials.org registration number: NCT02070666), may elucidate this issue.

In patients with the acute respiratory distress syndrome (ARDS), predicted body weight (PBW), taking into account both sex and height, has been used to set V_T (15-17). The following PBW equations have been used: men, 50.0+0.905× (height in cm) −152.4; women: 45.5+0.905× (height in cm) −152.4. To mitigate the risk of ventilator induced lung injury (VILI) in ARDS patients, the National Institute of Health ARDS Network protocol suggests the use of V_T =6 mL/kg PBW and Pplat limited to 30 cmH_2O. If Pplat exceeds 30 cmH_2O with a V_T of 6 mL/kg PBW, the protocol recommends a reduction in VT (to 4–5 mL/kg PBW) if pHa >7.15. Since ARDS lungs present great variability due to edema, atelectasis, and consolidation, V_T should probably be set according to aerated lung volume, e.g., functional residual capacity (FRC) or total lung capacity (TLC) (18-20).

Nevertheless, further studies are required to evaluate the safe limit of FRC and TLC when used to set V_T. In this line, in patients with severe ARDS and very low lung compliance, even setting V_T below 6 mL/kg PBW can result in high strain (V_T/FRC) (19). This scenario may be considered unsafe; thus, rescue therapies are needed, such as extracorporeal support (21).

Additionally, V_T should be set according to ΔP [Pplat-PEEP or V_T/Crs (respiratory system compliance)]. Since Crs is directly related to lung size, ΔP reflects the level of V_T in relation to the aerated lung volume. However, in the presence of reduced chest wall mechanics, ΔP does not reflect V_T. In this line, considering the same ΔP, a patient with a stiff chest wall has less lung overinflation than one with a normal chest wall (22). Therefore, transpulmonary driving pressure (ΔP_L, the difference in transpulmonary pressure between end-expiration and end-inspiration) (23) should be evaluated, and V_T could be limited to keep ΔP_L in a safe range (19,24).

Positive end-expiratory pressure (PEEP)

PEEP is the alveolar pressure above the atmospheric pressure at end-expiration. PEEP applied through mechanical ventilation (i.e., extrinsic PEEP) allows delivery of positive pressure at the end of expiration to prevent unstable lung units from collapsing. Low levels of PEEP (3 to 5 cmH_2O) are routinely used in patients on mechanical ventilation. This practice is important to: (I) keep lungs open at the end of expiration, thus promoting alveolar stabilization (25); (II) prevent opening and closing of distal small airways and alveolar units (26); and (III) increase lymphatic flow through the thoracic duct, which may facilitate drainage of lung edema (27). However, higher levels of PEEP may cause regional overdistension and

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impairment of cardiac performance (28). The pros and cons of PEEP depend on the degree of lung injury (29).

In patients under general anesthesia, intraoperative mechanical ventilation with V_T =8 mL/kg and high PEEP (12 cmH_2O), when compared with low PEEP (2 cmH_2O), does not prevent PPCs, as shown in the Protective Ventilation using High versus Low positive end-expiratory pressure (PROVHILO) trial (30). Further research is required to evaluate moderate levels of PEEP (5–8 cmH_2O).

In the emergency department, the use of higher PEEP levels was associated with improvement in ventilator- and hospital-free days in patients with ARDS (9) and uninjured lungs (31).

In ICU patients with uninjured lungs, a meta-analysis reported that benefit from PEEP is lacking in terms of duration of mechanical ventilation and mortality rate (32). In ICU patients at risk of ARDS, higher PEEP levels are required than in those without ARDS risk (12). More recently, ICU patients after cardiac surgery were found to exhibit fewer lung complications with high PEEP (33). Certainly, further studies are required to compare low *vs.* high PEEP levels in ICU patients without ARDS.

Three major studies have assessed high *vs.* low PEEP levels combined with low V_T for ARDS patients (16,17,34). In the ALVEOLI trial (34), mortality did not differ between low and high PEEP levels. High PEEP resulted in improved oxygenation (17) as well as more ventilator-free days and organ failure-free days (16); however, mortality rate did not differ between PEEP arms. A meta-analysis that used the data from the aforementioned three trials found that higher PEEP levels were associated with improved survival in severe ARDS (35). In moderate ARDS, lower PEEP (<12 cmH_2O), compared to higher PEEP, was associated with greater risk of hospital mortality (26%) (36). In a recent randomized clinical trial comparing individualized PEEP titration after recruitment maneuvers (RMs) *vs.* low PEEP without RMs in patients with moderate-to-severe ARDS, an increase in 28-day mortality was observed in the recruited group (37).

Several strategies have been used to determine optimal PEEP, such as: (I) evaluation of the lower inflection point of the pressure-volume curve, which reflects the transition from low to high compliance, and application of PEEP 2 cmH_2O greater than this point; (II) the use of algorithms combining PEEP and fraction of inspired oxygen (FiO_2); and (III) measurement of transpulmonary pressure with an esophageal catheter (38). Certainly, the best approach is to individualize PEEP for each patient.

Respiratory rate

Respiratory rate must be adjusted during mechanical ventilation to maintain a minute volume appropriate to the patient's metabolic demands. Although higher RR is often needed to maintain CO_2 levels within safe range (39), it can alter the inspiratory-to-expiratory ratio, thus leading to intrinsic PEEP due to short expiratory time. In this context, Vieillard-Baron *et al.* compared two levels of RR—15 breaths per minute (bpm) *vs.* 30 bpm—while maintaining lower Pplat (<25 cmH_2O). No difference in $PaCO_2$ due to increased intrinsic PEEP or dead space ventilation was observed between groups (40). Increased RR may also cause lung damage due to cyclic recruitment/derecruitment.

Inspiratory airflow

Inspiratory airflow must be adjusted during mechanical ventilation, since it may also cause lung damage (41-43). The mechanism whereby inspiratory airflow contributes to lung injury seems to be influenced by the viscoelastic properties of lung tissue. High inspiratory airflow enhances damage to the lung parenchyma because the viscoelastic accommodation has no time to dissipate damaging forces when inflation occurs rapidly. This type of mechanism of injury usually occurs in asymmetrical lungs.

High inspiratory airflow is an important determinant of pulmonary stress, since it enhances the transmission of kinetic energy to lung structures, increases shear stress parallel to the surface of the airways and alveolar walls, leads to deformation of the pulmonary parenchyma and bronchial epithelial cells, and releases pro-fibrogenic (43) and pro-inflammatory (44) mediators. Therefore, controlling inspiratory airflow might provide additional lung protection (43,44).

Outputs: ventilator parameters obtained as a result of the interaction between mechanical ventilator and respiratory system

During mechanical ventilation, several ventilator-derived parameters should be monitored: PEEPi, P_{peak}, P_{plat}, ΔP, P_L, $P_{0.1}$, PTP/min, mechanical energy, mechanical power, and intensity.

Intrinsic PEEP

Intrinsic PEEP (PEEPi) reflects the residual pressure when the expiratory phase may not be completed to full

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exhalation. This residual pressure is higher than the point of equilibrium of the respiratory system's elastic properties (45). One easy form to detect its presence is to perform an expiratory pause and check the end-expiratory pressure. PEEPi is usually associated with obstructive diseases (46), but may be present during other conditions; therefore, it is considered an important ventilator-derived parameter for monitoring. For example, obese patients under mechanical ventilation are prone to developing PEEPi, mainly in the supine position. Both external PEEP application and changing position (beach-chair) may alter PEEPi (47).

Peak pressure

Peak pressure is the maximum pressure measured at end inspiration. Ppeak includes the elastic and resistive components (airway, lung tissue, and equipment, e.g., endotracheal tube). At bedside, the difference between Ppeak and Pplat can be easily visualized during an inspiratory pause in controlled mechanical ventilation with constant airflow. Immediately after the inspiratory pause, a rapid airway pressure decay, which represents the pressure dissipated to overcome airway resistance, is observed. The difference between Ppeak and Pplat divided by the airflow is the airway resistance. In normal subjects, airway resistance values do not exceed 15–20 cmH_2O/L/s under controlled mechanical ventilation (48). Several factors can modify Ppeak, such as endotracheal tube diameter (49,50), airflow intensity, plugging, or bronchospasm.

During controlled mechanical ventilation, Ppeak depends on V_T, RR, and airflow, whereas during assisted mechanical ventilation, the patient's effort also contributes to Ppeak.

In a multicenter, prospective cohort study of 2,377 patients with severe respiratory failure, conducted in 459 ICUs from 50 countries across five continents (36), the authors reported the importance of monitoring Ppeak besides other ventilator-derived parameters. Higher Ppeak, especially above 40 cmH_2O, is associated with increased mortality rates (51).

Plateau pressure

Plateau pressure can be measured during an inspiratory pause when the respiratory muscles are relaxed and is equal to alveolar pressure when airflow is zero. Pplat can be affected by changes in V_T and Crs, but not by changes in airflow and airway resistance (52).

In ICU patients without ARDS, lower Pplat values associated with V_T ≤7 mL/kg PBW lead to reduced PPCs and a trend toward increased survival (P=0.052) (11). In ARDS patients, Pplat <30 cmH_2O was associated with lower mortality (15). An observational study with ARDS patients suggested that Pplat <28 cmH_2O is more beneficial in those with a large percentage of non-aerated lung tissue (53). More recently, in patients with severe ARDS, the LUNG SAFE study (36) reported that Pplat <25 cmH_2O was not associated with decreased risk of hospital mortality. However, patients with a median Pplat ≥23 cmH_2O on day 1 of ARDS diagnosis had higher mortality.

Driving pressure

Driving pressure is defined as Pplat-PEEP or V_T normalized to Crs (23,54,55). During intraoperative ventilation, ΔP seems to be an important parameter for the optimization of mechanical ventilation (8,12).

In mechanically ventilated ICU patients without ARDS (55), ΔP was not associated with hospital mortality. The authors attributed this result to the fact that Crs was not a major risk factor for mortality in those patients without ARDS. Conversely, Tejerina *et al.* (56) showed that, in patients with brain injury but uninjured lungs, low ΔP resulted in a better outcome.

In a study of ARDS patients, ΔP was considered the variable most strongly associated with survival, as opposed to V_T and PEEP (54). The authors observed that increasing PEEP level for a short period could lead to different changes in ΔP. If the increase in PEEP level leads to increased aeration of lung tissue through recruitment, a decrease in ΔP is expected. On the other hand, if PEEP increases and does not recruit lung tissue, the lungs may become overstretched, and ΔP may remain unchanged or even increase over time (*Figure 1*).

The LUNG SAFE study (36) showed that ΔP <14 cmH_2O was associated with decreased risk of hospital mortality in patients with moderate-to-severe ARDS.

Transpulmonary pressure

Transpulmonary pressure, by definition, is the difference between airway pressure (Paw) and pleural pressure (Ppl). In the clinical setting, esophageal manometry is the only clinically available method to separate airway pressure applied to the respiratory system into its chest wall (i.e., Ppl) and lung component (P_L) (57-59). P_L measurement has been proposed because it can determine the pressure

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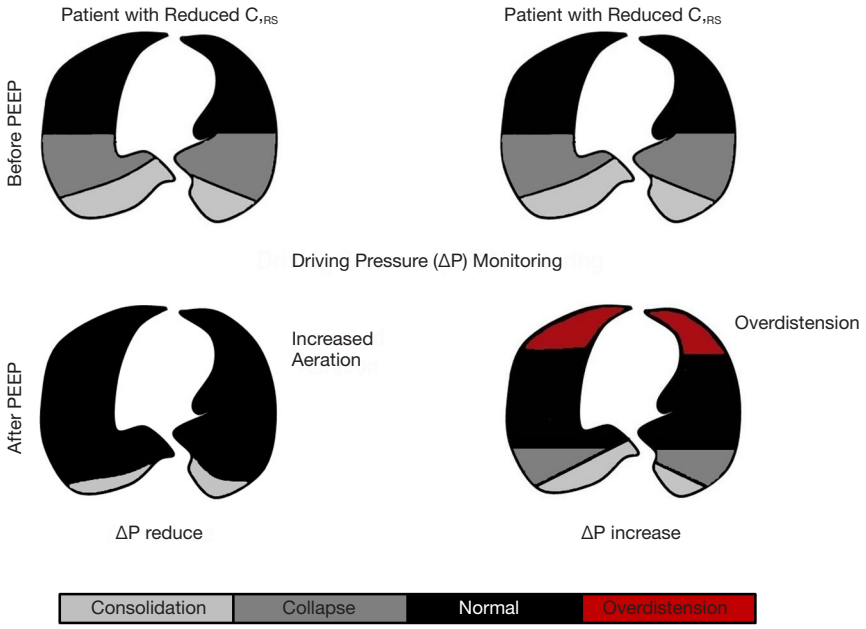

Figure 1 Schematic drawing showing two theoretical patients with comparable and reduced respiratory system compliance ($C_{,RS}$) before and after PEEP increment. As explained in the main text, the increase in PEEP level can lead to different responses that can be easily evaluated at bedside through the interpretation of ΔP values.

required to keep the lungs open (38,60,61) and it can assess inspiratory effort (62,63). In influenza A(H1N1)-associated ARDS, Grasso *et al.* (61) observed that the pressure applied to the airways was not transmitted to the lung parenchyma but dissipated against a stiff chest wall, providing further evidence of the importance of measuring P_L.

During assisted mechanical ventilation, the esophageal catheter may not cover the entire vertical gradient while respiratory muscle activity is present. In this context, Yoshida *et al.* (64) showed that esophageal pressure variation significantly underestimated pleural pressure variation in dependent regions. In addition, directly measured swings in pleural pressure (–14.9) were significantly greater in dependent lung than swings in Pes (–7.1). Esophageal pressure may underestimate the local pleural pressure, especially in those areas near the diaphragm which present higher degrees of P_L.

Transpulmonary driving pressure (ΔP_L)

The transpulmonary driving pressure (ΔP_L) is defined as the difference between P_L at end-inspiration ($P_{Lend-insp}$) and P_L at end-expiration ($P_{Lend-exp}$). It reflects the distending pressure taken by the lungs when V_T is delivered. The use of ΔP_L offers some advantages. First, ΔP_L removes the stress caused by PEEP, which does not necessarily contribute to lung injury and sometimes can mitigate it (65). Second, ΔP_L removes the distending pressure taken by the chest wall (66). Hence, it seems that ΔP_L might be a better surrogate of lung stress and may even be a better predictor of clinical outcomes than ΔP (67). ΔP_L is calculated as:

$$\Delta P_L = (P_{PLAT} - P_{ESO,\,end\text{-}insp}) - (PEEP_{TOT} - P_{ESO,\,end\text{-}exp}) \quad [1]$$

In experimental ARDS, low P_L did not increase lung inflammation, despite leading to alveolar collapse. Intermediate levels of ΔP_L reduced alveolar collapse, increased overdistension, and resulted in alveolar instability. At high P_L levels, alveolar hyperinflation was detected, but no further lung inflammation was observed (23). This study highlighted the importance of permissive atelectasis to protect lung damage, as recently published (68) and discussed in two editorials (69,70).

P_L is also an important ventilator parameter to be monitored during assisted mechanical ventilation. Bellani *et al.* tested the hypothesis that, for a given inspired volume and flow, and for the same mechanical properties (i.e.,

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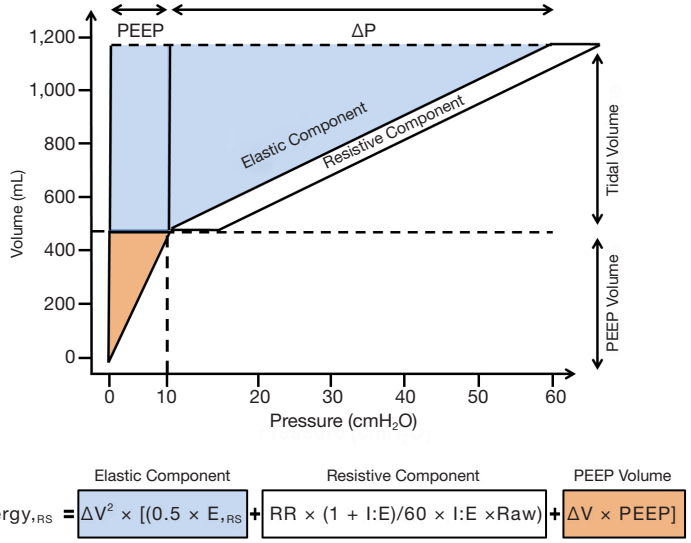

Figure 2 Pressure-volume curve of the respiratory system, depicting all components needed to calculate the mechanical energy transferred from the mechanical ventilator to the respiratory system. The blue area depicts the elastic property of the respiratory system with the respective fraction in the energy formula [$\Delta V^2 \times (0.5 \times E_{RS})$]. The white area represents the resistive property of the respiratory system, which is associated with the respective fraction in the energy formula [RR × (1+ I:E)/60× I:E × Raw]. The orange area represents the PEEP volume, depicted in the energy formula by ΔV × PEEP. Modified from Tonetti *et al.* (79).

compliance and resistance) of the lung, ΔP_L during assisted and controlled mechanical ventilation should not differ within the same patient (71). They found no difference in ΔP_L at comparable volumes and flows. However, the authors pointed out that, if assisted breaths contributed to lung damage, this would not be due solely to ΔP_L; the vertical gradient leading to different local pleural pressures and, ultimately, local ΔP_L ranges should also be acknowledged (64,72).

Esophageal pressure generated 100 ms after onset of inspiratory effort ($P_{0.1}$)

The esophageal pressure generated 100 ms after the onset of an occluded inspiratory effort ($P_{0.1}$) has been used as a measurement of respiratory drive (73), and it could be used to optimize the level of pressure support in individual patients (74). In a recent prospective, randomized, crossover physiologic study, $P_{0.1}$ was evaluated in the presence of different degrees of inspiratory efforts in patients recovering from acute respiratory failure (75). Inspiratory effort was found to correlate strongly with $P_{0.1}$. Therefore, this parameter may have yet-unrecognized importance as a marker of respiratory drive during mechanical ventilation, and efforts should be made to increase awareness of its potential utility (76).

Pressure-time product per minute

Pressure-time product is a measure of the mechanical work of breathing. By integrating the pressure developed by the respiratory muscles over the duration of the contraction (i.e., chest wall elastic recoil pressure), it is possible to obtain the respiratory PTP. Field *et al.* (77) found that the oxygen consumption of the respiratory muscles is only weakly correlated with the mechanical work of breathing (the product $\Delta P \cdot \Delta V$), whereas it is well reflected by the PTP. PTP takes into account the isometric phase of muscle contraction, thus representing a good indicator of energy expenditure (78). A common way of expressing PTP is through standardization by the sample period of a respiratory cycle (T_{TOT}).

New ventilator-derived parameters: markers of patient–machine interaction

Mechanical energy

The energy delivered per breath to the airways and lungs is defined as the area between the inspiratory limb of pressure (x) *vs.* the volume axis (y), measured in joules (J) (79) (*Figure 2*).

Two equations have been proposed to calculate mechanical energy: one simple (80) and another more

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complex (7). If properly adjusted, both should yield similar results. Nevertheless, some technical differences between the two should be addressed.

Simple equation:

$$Energy_L = \Delta P_L^2/E_L \quad [2]$$

where ΔP_L is the transpulmonary driving pressure and EL is the lung elastance.

Complex equation:

$$Energy_L = \Delta V^2 \times [(0.5\times E_{RS} + RR \times (1+ I:E)/60\times I:E \times R_{aw}) + \Delta V \times PEEP] \quad [3]$$

where ΔV is the variation of tidal volume, E_{RS} is the respiratory system elastance, I:E is the inspiratory to expiratory ratio, and Raw is the airway resistance.

The simplified equation can be easily used in the clinical setting (5,80,81). This equation computes the most important component (driving mechanical power), without taking into account resistive properties or the contribution PEEP, unlike the equation proposed by Gattinoni *et al.* (7). However, it is difficult to directly link the mechanical energy dissipated in the proximal airways to alveolar injury. The addition of PEEP to the complex equation takes into account the contribution of static strain, which is associated with potential energy storage within the elastic tissues of the respiratory system (81).

Mechanical power and intensity

Mechanical power represents the mechanical energy multiplied by the RR. In a previous study (6), different mechanical power values were applied to the respiratory system in healthy pigs by changing the RR while keeping the V_T and P_L constant, aiming to identify a mechanical power threshold for lung damage. The authors reported development of edema only when the delivered transpulmonary mechanical power exceeded 12.1 J/min. In the presence of lung damage, the ventilated lung area is reduced, thus requiring greater driving pressure and airflow. This, in turn, increases the mechanical power delivered without changes in V_T.

The so-called intensity (i.e., mechanical power normalized to the lung tissue) should also be considered. Depending on the mechanical power, intensity may be comparable in volutrauma and atelectrauma (5). If power increases without changes in lung surface area, the intensity will be higher; on the other hand, if both power and lung surface area increase (e.g., due to lung recruitment), the intensity may reduce or remain constant.

Conclusions

The benefits and harms of mechanical ventilation in critically ill patients with uninjured or injured lungs, as well as in patients undergoing general anesthesia, depend not only on ventilator settings, but also on the interpretation of ventilator-derived parameters. Both parameters adjusted by the operator (V_T, PEEP, RR, and V') and ventilator-derived parameters (PEEPi, Ppeak, Pplat, ΔP, P_L, mechanical energy, mechanical power, intensity, $P_{0.1}$, and PTP) need to be strictly monitored at bedside, in order to develop a case-by-case approach to mechanical ventilation. Furthermore, additional clinical studies are required to ascertain the safe thresholds of each of these parameter in injured and uninjured lungs.

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Footnote

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