



## Review Article

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# Protective ventilation from ICU to operating room: state of art and new horizons

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The prevention of ventilator-associated lung injury (VALI) and postoperative pulmonary complications (PPC) is of paramount importance for improving outcomes both in the operating room and in the intensive care unit (ICU). Protective respiratory support includes a wide spectrum of interventions to decrease pulmonary stress-strain injuries. The motto 'low tidal volume for all' should become routine, both during major surgery and in the ICU, while application of a high positive end-expiratory pressure (PEEP) strategy and of alveolar recruitment maneuvers requires a personalized approach and warrants further investigation. Patient self-inflicted lung injury is an important type of VALI, which should be diagnosed and mitigated at the early stage, during restoration of spontaneous breathing.

This narrative review highlights the strategies used for protective positive pressure ventilation. The emerging concepts of damaging energy and power, as well as pathways to personalization of the respiratory settings, are discussed in detail. In the future, individualized approaches to protective ventilation may involve multiple respiratory settings extending beyond low tidal volume and PEEP, implemented in parallel with quantifying the risk of VALI and PPC.

**Keywords:** Low tidal volume; Patient self-inflicted lung injury; Positive pressure ventilation; Protective ventilation; Ventilation-associated lung injury.

## Introduction

Positive pressure ventilation (PPV) is one of the key methods in critical care medicine for maintaining gas exchange and providing an opportunity for recovery from direct or indirect pulmonary injury. Additionally, controlled PPV is required in many surgical interventions conducted under general anesthesia. In both perioperative settings and severe acute respiratory distress syndrome (ARDS), ventilation is associated with neuromuscular blockade and allows precise control of respiratory parameters and gas exchange. However, similar to many other invasive techniques, ventilation can be accompanied by both pulmonary and extrapulmonary complications and is associated with life-threatening respiratory events and remote organ dysfunction.

The problem of ventilator-associated lung injury (VALI) emerged in the previous century and remains a challenge in the new millennium. At this time, we are convinced that the PPV settings should be personalized to protect against VALI arising from the potentially injuring power of the patient-respirator interaction. Furthermore, all patients requiring protective ventilation can be formally divided into subsets depending on the type of prophylaxis: primary and secondary (for perioperative period or intensive care unit

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[ICU] patients with intact lungs) and tertiary and quaternary (for ICU patients with hypoxemia, mostly due to ARDS) (Fig. 1).

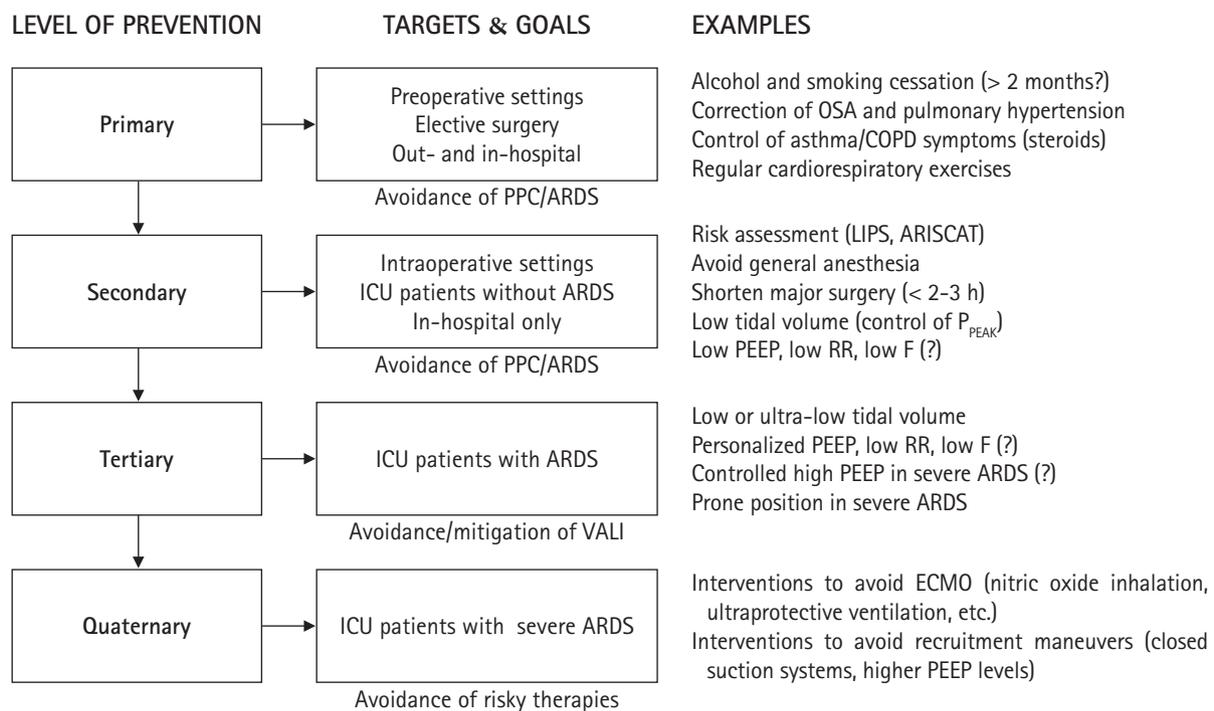
Only a few major evidence-based interventions can be strongly recommended to prevent VALI in ARDS cases and improve survival. These are low tidal volume ( $V_T$ ) ventilation, neuromuscular blockade, and prone positioning [1,2]. In fact, in 2020 we can only guide evidence-based critical care based on 27 multicenter randomized controlled trials that have demonstrated improved ICU survival, of which at least five (almost 20%) involve protective ventilation approaches [2]. In perioperative settings and in ICU patients with intact lungs, only low  $V_T$  ventilation is suggested as a means to produce any substantial benefits [3–5]. Until now, the search for the ‘holy grail’ of the truly personalized PPV settings continues, and the existing body of evidence is somewhat contradictory. The novel concept of ventilation energy and power opens new avenues of exploration, which involves the improvement of multiple respiratory determinants [6,7]. Therefore, many cate-

gories of both ICU and surgical patients may benefit from precise and personalized respiratory support, supported by new principles (Fig. 2) [8,9].

### Biophysics of ventilator-associated lung injury

Four well-recognized mechanisms of VALI involve voluotrauma, barotrauma, atelectotrauma, and bio-trauma; however, new insights are proposed reconsidering complications related to mechanical ventilation, including adverse cardiopulmonary interactions, shear injury at the borderline of aerated and atelectatic tissue, lung deflation injury, and effort-induced or patient self-inflicted lung injury (P-SILI) (Table 1) [10–12].

Stress and strain are the key characteristics of every physical material, including lung tissue. Thus, the concept of parenchymal stress and strain is an important part of the modern theory of VALI biophysics [13,14].



**Fig. 1.** Levels, targets, and intervention strategies for prevention of PPC and ventilator-associated lung injury.

The prophylaxis of negative effects of mechanical ventilation includes four definitive levels: primary, secondary, tertiary, and quaternary. The primary prophylaxis should prevent PPC and VALI before they ever occur by preoperative correction of comorbidities and modification of factors predisposing patients to complications, including ventilation itself (i.e., regional anesthesia). The goal of secondary prevention is to limit the negative impact of intraoperative mechanical ventilation when it has already been started. The tertiary prophylaxis should attenuate the natural course of PPC or ARDS when they have already developed. Finally, the quaternary prevention aims to provide the most rational therapy by all available means leading to avoidance of highly invasive and/or risky respiratory interventions. OSA: obstructive sleep apnea, COPD: chronic obstructive pulmonary disease, PPC: postoperative pulmonary complications, ARDS: acute respiratory distress syndrome, ICU: intensive care unit, LIPS: lung injury prediction score, ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia score,  $P_{PEAK}$ : peak pressure, PEEP: positive end-expiratory pressure, RR: respiratory rate, F: inspiratory flow, VALI: ventilator-associated lung injury, ECMO: extracorporeal membrane oxygenation.

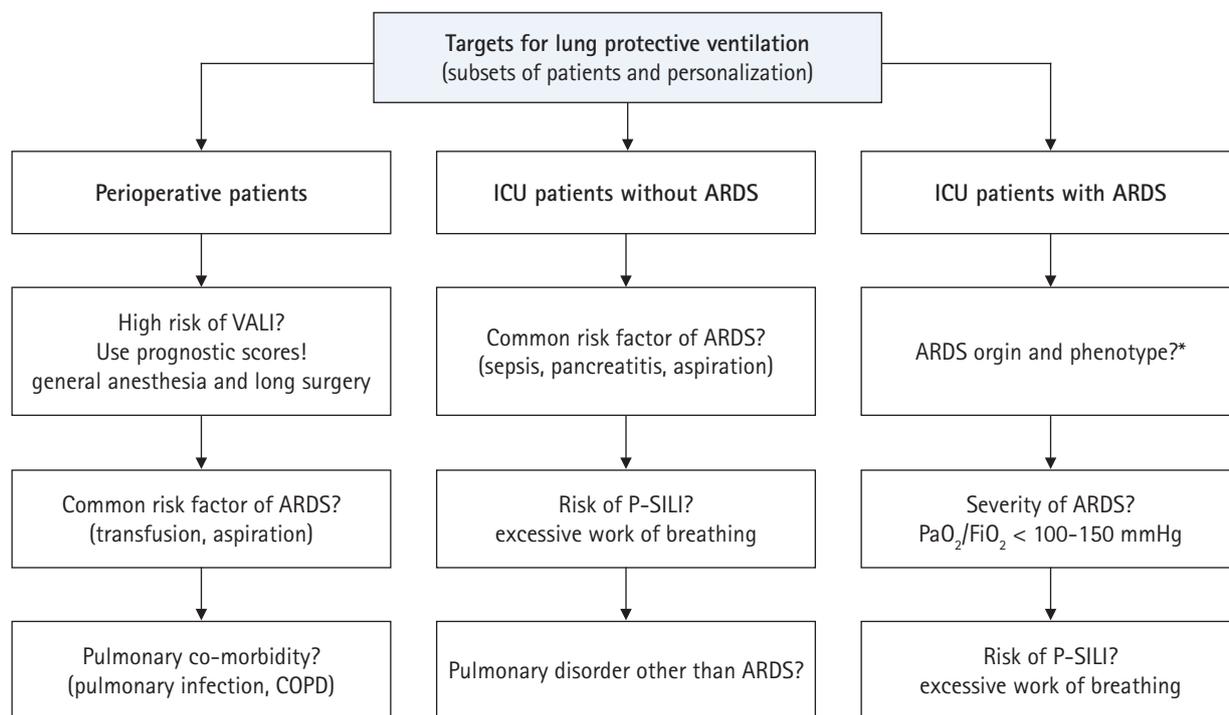
*Stress* is defined as an outward mechanical force applied to the alveolar area and can be clinically interpreted and quantified as a ‘pressure’, applying the same physical units. At the bedside, the driving ( $P_{DRIVE}$ ) pressure is calculated as the difference between the plateau pressure ( $P_{PLAT}$ ) and positive end-expiratory pressure (PEEP), and it can adequately characterize the change in lung stress. Therefore, the clinical equivalent of deforming stress is the product of elastic recoil pressure and transpulmonary pressure ( $P_{TP}$ ).

*Strain* characterizes the relative distortion of the shape (size and form) of airways (alveoli) resulting from the force applied and is related to *stress* via Hooke’s law. This parameter reflects the ratio of  $V_T$  to the functional residual capacity (FRC). Strain is directly proportional to the  $V_T$  adjusted for body weight and includes a static PEEP-related component and a dynamic tidal component related to inflation pressure, with both components carrying dissipated and undissipated energy.

Simply stated, stress determines the risk of barotrauma and

strain is related to volumotrauma, while the most important ‘bridge’ between them is represented by the specific lung elastance. Beyond the stress–strain interplay, it is important to recognize any dynamic (cycled) injury due to the dynamic energy load applied to the specific (functional) lung volume and static strain or static energy load. The dynamic energy load is proportional to the ratio of  $V_T$  and FRC, while the static energy load is related to PEEP and PEEP-induced changes in volume ( $V_{PEEP}$ ) [14,15] (Fig. 3, Table 2). Under the real conditions of manually adjusted ventilator settings, the inspiratory flow will affect the strain rate, changes in  $V_T$  will modify the strain amplitude, and pressures such as  $P_{PLAT}$  and PEEP will characterize maximum and minimal stress values, respectively. However, neither stress–strain values nor dynamic or static energy loads can be accurately measured at the bedside.

Every positive pressure inspiration delivered by the respirator transfers a certain amount of energy to the respiratory system of the ventilated patient. The work involved should overcome the re-



**Fig. 2.** Target groups of patients for protective ventilation. Potential ‘target groups’ for protective ventilation include patients receiving perioperative mechanical ventilation, those with medical conditions requiring respiratory support in ICU, and patients with ARDS. In perioperative patients, it is important to assess pulmonary comorbidities and to determine the risk of complications and ARDS using appropriate prognostic scores. Thereafter, the optimal strategy of respiratory management during anesthesia should be chosen. In ICU patients both with and without ARDS, the protective approach to ventilation has the potential to be personalized based on the presence of common risk factors associated with ARDS, its origin and severity, as well as on patient sub-phenotype (hypo- or hyper-inflammatory). Pulmonary disorders other than ARDS as well as the risk of P-SILI should also be considered, and their recommendations on prevention should be followed, if necessary.

\*Direct and indirect mechanisms; hyperinflammatory and hypoinflammatory phenotypes. ICU: intensive care unit, ARDS: acute respiratory distress syndrome, VALI: ventilator-associated lung injury, P-SILI: patient self-inflicted lung injury,  $PaO_2$ : arterial partial oxygen pressure,  $FiO_2$ : fraction of inspired oxygen, COPD: chronic obstructive pulmonary disease.

**Table 1.** Key Mechanisms and Definitions of Ventilator-associated Lung Injury

Subtype	Mechanism	Process	Prevention
Volumotrauma	Stretch-induced cyclic or static injury	Excessive $V_T$ of the restricted pulmonary tissue ('baby lung') Inflammation	Low protective $V_T$ ( $6 \pm 2$ ml/kg PBW) or ultraproductive $V_T$ (3–4 ml/kg PBW) Neuromuscular blockade and prone positioning in moderate-to-severe ARDS Personalized PEEP
P-SILI	Vigorous spontaneous effort-induced lung injury	Vigorous diaphragmatic efforts with wide pleural pressure swings due to asynchrony and/or increased respiratory drive	Higher PEEP levels to suppress asynchrony Sedation, neuromuscular blockade, correction of acidosis, suppressing asynchrony and excessive respiratory drive
Barotrauma	Stress-induced cyclic or static injury	Alveolar and small airways micro- or macro-tears and extra-alveolar gas leakage	Lower airway pressures $P_{PLAT}$ , $P_{DRIVE}$ , $P_{PEAK}$ , and PEEP to avoid overdistension of aerated parenchyma
Atelectotrauma	Cyclic lung deflation injury	Abrupt disconnections, Low PEEP (?), Pulmonary edema	Avoidance of disconnections, correction of pulmonary edema, personalized PEEP
Biotrauma	Involvement of extrapulmonary pathways due to primary VALI	Multiple organ failure High proinflammatory cytokines Adverse cardiopulmonary interactions	Low $V_T$ and limitation of damaging power Personalized PEEP to suppress P-SILI

$V_T$ : tidal volume, PBW: predicted body weight, ARDS: acute respiratory distress syndrome, PEEP: positive end-expiratory pressure, P-SILI: patient self-inflicted lung injury,  $P_{DRIVE}$ : driving pressure,  $P_{PLAT}$ : plateau (pause) pressure,  $P_{PEAK}$ : peak pressure, VALI: ventilator-associated lung injury.

sistance of the airways and increase the 'viscoelastic' volumes of the lungs and chest wall. A certain part of the energy is spent to deform the ultrastructure of cells and the intercellular matrix, and each breath results in conservation or absorption of some miniscule portions of energy within lung parenchyma. In other words, the amount of energy delivered to the lungs during the mechanical inspiration is not equal to the amount returning during the expiration by means of the elastic recoil of the respiratory system. This 'cumulative dissipation' of mechanical energy produces an inflammatory response and heat production that can increase the risk of VALI over time. The amount of energy delivered per unit of time (joules per minute, J/min) is referred to as the mechanical power, and it can be estimated at the bedside using a number of equations, both in assist-control ventilation and, less accurately, in assisted spontaneous breathing.

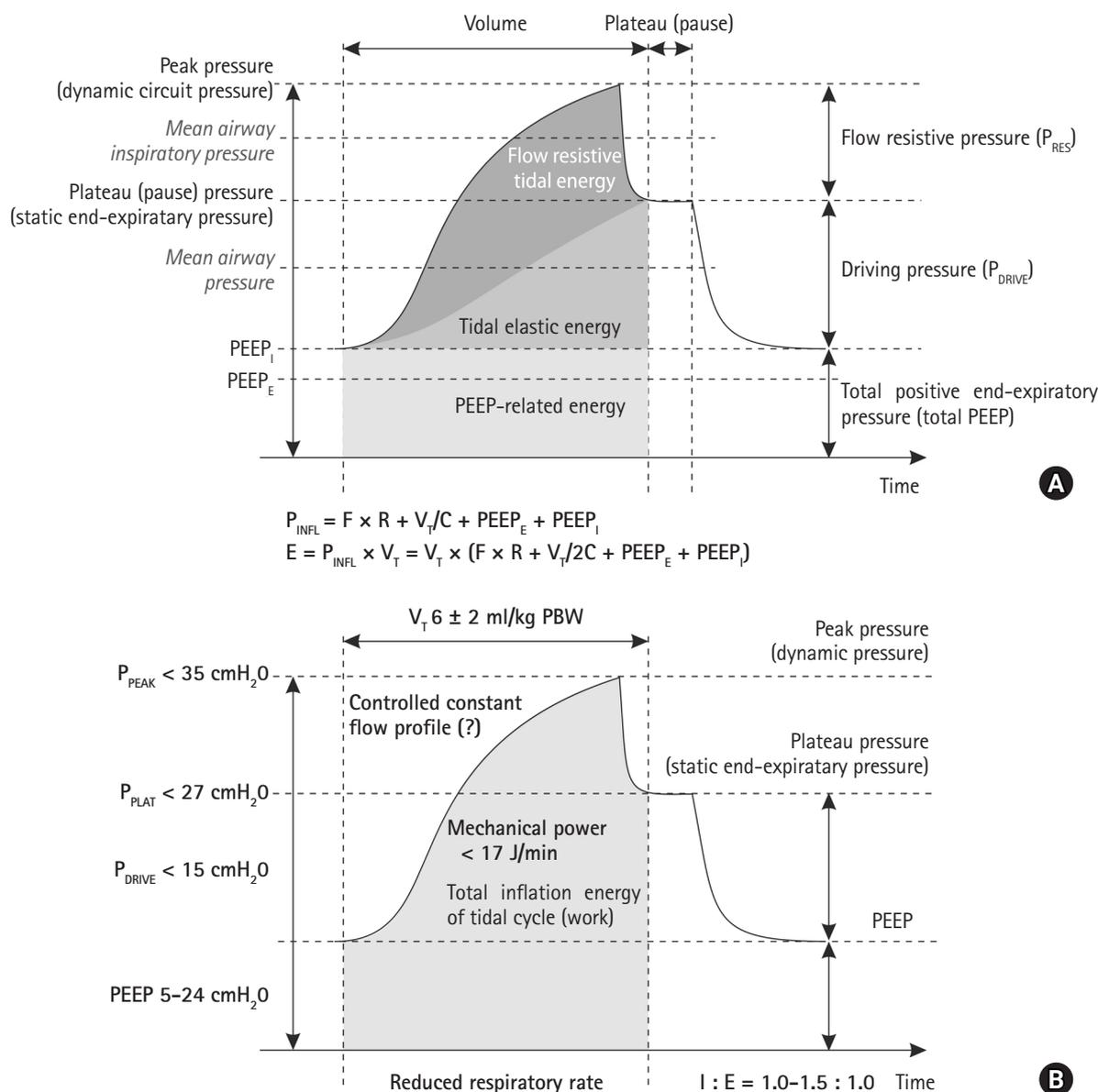
Until now, the energy-, work-, or power-dependent concepts have improved our understanding of the constellation of multiple VALI determinants and individual titration of the ventilation setting, opening new perspectives in the prevention of VALI [9,14,16]. Ventilation is expected to transfer potentially injurious energy per each tidal cycle, and its damaging characteristics involve both set or resulting parameters ( $V_T$ , PEEP, respiratory rate, inspiration to expiration times (I : E) ratio, and inspiratory and expiratory peak flow magnitude and shape) and resulting 'patient-specific' or patient-dependent parameters (peak pressure [ $P_{PEAK}$ ],  $P_{PLAT}$ ,  $P_{DRIVE}$ ,  $P_{TP}$ , etc.) [14,17–19]. The damaging energy

can be modified by the spatial mechanical heterogeneity of the lung tissue, viscoelastic properties of edematous tissue, and, finally, restricted specific pulmonary volume (i.e., 'baby lung') [20]. The threshold of VALI is based on multiple patient-specific factors, including baseline activity of lung inflammation (particularly hyperinflammatory and hypoinflammatory ARDS sub-phenotypes), the mechanism of lung injury (direct or indirect), pulmonary blood flow, and respiratory drive. The power ultimately being transferred to the lungs and eventually resulting in VALI is dependent on the magnitude of the damaging energy and on its exposition time related to the volume and duration of mechanical ventilation [14,16,17]. The proposed upper limit of safe mechanical power varies between 12 J/min and 17 J/min [7,21].

Therefore, beyond  $V_T$ , many respiratory settings can be directly or indirectly involved in the development of VALI: flow magnitude and shape, respiratory rate, PEEP (I : E) ratio, and type of triggering [9,14,17]. The monitoring of resulting pressures, volumes, and mechanical lung properties (compliance) is paramount for assessing the risk of VALI. The safe parameters for protective ventilation are presented in Table 3 and Fig. 3.

## Protective ventilation in ARDS

Low protective and ultra-protective  $V_T$  are the key components in the concept of PPV, both during surgery and in the ICU [4,5,10,22]. Indeed,  $V_T$  is a determinant of the interplay between



**Fig. 3.** Concept of energy in ventilator-associated lung injury (A) and proposed protective ventilation settings (B). Panel A demonstrates the characteristics of the tidal cycle associated with VALI and potentially injurious mechanical energy delivered, accumulated, and 'dissipated' over the respiratory system. During constant inspiratory flow and assist-control ventilation, the sum of the total PEEP driving pressure, and flow-resistive pressure represents the total inflation or 'peak' pressure. The total tidal inspiratory energy (power) consists of three potentially injurious and adjustable components: PEEP-related, total elastic, and flow-resistive tidal energies. The elastic energy dissipates during expiration through both pulmonary tissue (cell deformation and heat) and through the circuit and valves of the respirator. Panel B provides an overview of thresholds and interventions to prevent VALI, including low tidal volume, limited peak, plateau, driving and PEEP, respiratory rate, duration of tidal cycle, flow profile, and inflation power. P<sub>RES</sub>: flow-resistive pressure, P<sub>PEAK</sub>: peak pressure, P<sub>PLAT</sub>: plateau (pause) pressure, P<sub>DRIVE</sub>: driving pressure, PEEP<sub>I</sub>: intrinsic (auto-) positive end-expiratory pressure, PEEP<sub>E</sub>: extrinsic (set) positive end-expiratory pressure, I : E: ratio of inspiration to expiration times, P<sub>INFL</sub>: total inflation pressure, F: flow, R: resistance, V<sub>T</sub>: tidal volume, C: compliance, E: energy, PBW: predicted body weight.

stress and strain (i.e., force/power) applied to restricted functional lung tissue volume. Therefore, along with airway pressures, V<sub>T</sub> is a surrogate of pulmonary stress and strain characteristics. The latter are important determinants of VALI associated with the energy or

power delivered by a ventilator or created by the spontaneously breathing patient [13,23].

ARDS is associated with atelectases and protein-rich edema resulting from the spatial heterogeneity of the mechanical proper-

**Table 2.** Key Definitions of the Physical Mechanisms of Ventilator-associated Lung Injury

Value	Definition
Stress	Force (pressure) applied to alveoli, resulting in change of their resting condition ( $P_{TP}$ )
Strain	Dynamic ( $V_T$ ) or static (end-expiratory lung volume) distortion of the alveoli or change in volume resulting from stress
Energy/work	Work during breathing: $\int P \Delta V dt$ . Force $\times$ Length: $P (F/A) \times V (A \times L)$
Power	Energy applied per unit of time (tidal energy $\times$ RR) Specific power = power to specific aerated volume ratio (i.e., 'baby lung' specific volume)
Injury threshold	The level of specific stress–strain associated with the initiation of VALI

$P_{TP}$ : transpulmonary pressure,  $V_T$ : tidal volume, P: pressure, V: volume, F: force, A: area, L: length, RR: respiratory rate, VALI: ventilator-associated lung injury.

**Table 3.** Settings of Positive Pressure Ventilation during Perioperative Period and in ICU Patients without and with ARDS

Settings	Subset		
	Perioperative patients	ICU patients	
		Low risk of VALI (no ARDS or no common risk factor)	High risk of VALI (ARDS or common risk factor of ARDS, P-SILI)
$V_T$ (ml/kg PBW)	6–8	6–8	4–8 (3–4)*
$P_{DRIVE}$ (cmH <sub>2</sub> O)	$\leq 13$	$\leq 15$	$\leq 10$ (?)
$P_{PLAT}$ (cmH <sub>2</sub> O)	$< 16$	$< 30$	$< 27$
RR (/min)	8–18	15–35	5–35
PEEP (cmH <sub>2</sub> O)	0–5	5–15	10–24
SpO <sub>2</sub> (%)	92–100	92–97	92–97
PaCO <sub>2</sub> (mmHg)	35–45	35–45	45–70*
Prone position	Depends on surgery	No	Recommended*
NMB	Monitored	No	Recommended*

\*Optional in moderate-to-severe ARDS cases only (PaO<sub>2</sub>/FiO<sub>2</sub> below 100–150 mmHg). ICU: intensive care unit,  $V_T$ : tidal volume,  $P_{DRIVE}$ : driving pressure,  $P_{PLAT}$ : plateau (pause) pressure, RR: respiratory rate, PEEP: positive end-expiratory pressure, SpO<sub>2</sub>: pulsatile blood oxygen saturation, PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide, NMB: neuromuscular blockade, VALI: ventilator-associated lung injury, ARDS: acute respiratory distress syndrome, P-SILI: patient self-inflicted lung injury.

ties of the lungs, notably compliance. The reduction of well-aerated volume of functional pulmonary tissue surrounded or mixed with collapsed, surfactant deficient, or flooded alveoli has been widely recognized as a 'baby lung' phenomenon [20]. However, the true value of a safe  $V_T$  is personal and is determined by the functional (residual or specific) lung volume and regional mechanics [10]. Owing to the dramatically reduced volume of aerated functional lung parenchyma, even a low  $V_T$  can be injurious in some lung areas, causing severe overdistension of the alveoli while the compliance remains relatively unchanged.

Prone positioning is an effective approach to increase the functional pulmonary volume by reopening the gravity-dependent dorsal atelectatic areas, reducing ventilation-perfusion mismatch, and increasing the aeration homogeneity. To improve survival in ARDS, the exposition to prone positioning requires at least 12–16 h. Notably, prone positioning is commonly applied in parallel with sedation and neuromuscular blockade in moderate-to-severe ARDS patients [24,25].

Neuromuscular blockade has the clear potential to reduce VALI, as it guarantees precise low  $V_T$  settings and can reduce bio-

trauma via the direct anti-inflammatory effects of muscular relaxants [26]. However, this approach for prevention of VALI is controversial and can increase the risk of serious adverse events, namely, ICU-acquired weakness, diaphragm disuse atrophy, prolonged ICU stay, ventilator dependency, and hemodynamic instability associated with deep sedation [27]. Despite these negative effects, in cases involving severe ARDS and ventilator asynchrony, resulting in excessively high  $V_T$  and P-SILI, neuromuscular blockade prevents any spontaneous breathing activity and can be beneficial when it is not possible to synchronize the patient to a ventilator using adjustment of respiratory parameters or conventional sedation techniques.

### Patient self-inflicted lung injury

Early restoration of spontaneous breathing activity can bring potential benefits, including improved gas exchange, reduced requirements in sedation, and prevention of diaphragm atrophy and ICU-acquired polyneuromyopathy. However, both experimental

and clinical studies have shown that excessively vigorous spontaneous efforts can lead to aggravation of VALI [28–31]. The risk of a condition coined as P-SILI or effort-induced lung injury is strongly associated with moderate-to-severe ARDS. Typically, P-SILI results from the unsuppressed overcoming of a safe  $V_T$  in cases of high ventilation demand [12,26,32]. The risk of P-SILI is often associated with multiple factors, including excessive ventilator settings, asynchrony, pain, anxiety, delirium and neurologic injury, high metabolic demand and hyperthermia, hypercapnia, and acidosis [22,33]. A systemic inflammatory response can trigger most of these conditions, resulting in increased respiratory drive and a compromised Hering–Breuer reflex to depress tidal pulmonary stretch [34]. A too vigorous respiratory drive due to patient respiratory efforts and excessive  $P_{TP}$  will result in global and local overdistension of lung tissue [30,33]. Thus, there are three primary mechanisms associated with P-SILI: pulmonary overdistension, increased lung blood flow, and patient ventilator asynchrony (double and reverse triggering) [31].

Excessive respiratory efforts are difficult to control, while volume-controlled PPV is not capable of preventing P-SILI in ARDS [35]. In 2019, Moss et al. [27] (the ROSE trial) demonstrated that application of a higher PEEP strategy using light sedation vs. neuromuscular blockade and deep sedation can maintain safe spontaneous breathing and does not result in either barotrauma or in increased 90-day mortality. In fact, a higher PEEP level in moderate-to-severe ARDS cases suppresses lung inflammation; decreases diaphragmatic activity; gradient of pleural pressure, and lung distension and stress; improves gas exchange; and prevents the development of P-SILI [35,36].

## Advantages of low tidal volumes and controversy regarding positive end-expiratory pressure

### Low tidal volume

No doubt that ventilation with low  $V_T$  is a cornerstone of the current approach to lung protection. It can prevent VALI in a variety of clinical scenarios, including patients manifesting ARDS, ICU patients without ARDS, and in perioperative surgical settings. Despite potential worsening of oxygenation, accumulation of  $CO_2$ , and increased sedation requirements, low  $V_T$  decreases the harmful effects of PPV [37]. The key mechanism regarding the protective effect of low  $V_T$  consists of the counteracting trigger factors of VALI: increased dynamic strain (i.e.,  $V_T$ ) and PEEP-related static strain (FRC). Thus, researchers began to develop a modern profile of protective ventilation by decreasing the  $P_{PLAT}$

considering the open lung approach and permissive hypercapnia [38,39], and then comparing low  $V_T$  to conventional ventilation [37,40]. In 2000, the NIH ARDS Network enrolled 861 patients with ARDS in a randomized trial and showed that in comparison with the ‘traditional’  $V_T$  of 12 ml/kg and  $P_{PLAT} < 40$  cmH<sub>2</sub>O, positive pressure ventilation with  $V_T$  of 6 ml/kg and  $P_{PLAT} < 30$  cmH<sub>2</sub>O resulted in a striking increase in survival rate [37].

Therefore, considering the profound decrease in functional pulmonary volume due to heterogeneity of the lungs in ARDS (i.e., ‘baby lung’) [20], it would seem reasonable to titrate protective  $V_T$  using the true volume of functional lung capacity. However, measuring the functional lung volume is not an easy task. Thus, at the bedside, we can use its surrogate parameters, such as static respiratory compliance and the derived difference between  $P_{PLAT}$  and PEEP (the so-called  $P_{DRIVE}$ ). This approach was confirmed by a number of studies showing that  $P_{DRIVE}$  can be more accurate for predicting survival compared to PEEP,  $P_{PLAT}$ , and  $V_T$  itself [21,23,41].

Until now, the universal recommendation is to maintain the  $V_T$  at  $6 \pm 2$  ml/kg of the predicted body weight (4–8 ml/kg PBW) in a vast majority of ARDS patients to maintain  $P_{PLAT}$  below 30 cmH<sub>2</sub>O [22,42]. However, ICU practice remains inexplicably far from this standard. The recent LUNG SAFE study has shown that ICU patients with ARDS had  $V_T$  values above 8 ml/kg and 10 ml/kg of PBW in more than 30% and 10% of cases, respectively. In addition,  $P_{PLAT}$  above 30 cmH<sub>2</sub>O was registered in 10% of cases, while  $P_{DRIVE}$  values above 15 cmH<sub>2</sub>O were observed in almost half of the ARDS patients [43].

### Ultralow tidal volume

In severe ARDS cases, the volume of the functional (aerated) lung parenchyma can fall beyond the size of the ‘baby lung’ of a 6-year-old child [20]. In these settings, even a protective  $V_T$  of 6–8 ml/kg can be excessive, associated with  $P_{DRIVE}$  above 15–19 cmH<sub>2</sub>O [42,44]. Currently, ultralow  $V_T$ , referred to as a volume below 6 ml/kg of PBW, may be used. The application of ultralow  $V_T$  ventilation in patients with severe ARDS requires a neuromuscular block and deep sedation to prevent asynchrony and P-SILI; this strategy can also be used during extracorporeal membrane oxygenation to allow the lungs to rest as well as to prevent them from de-aeration and collapse. The recent study of Richard et al. [45] demonstrated that ultraprotective  $V_T$  could be safely set in almost two-third of patients with severe ARDS, which resulted in a mean decrease of 4 cmH<sub>2</sub>O in the  $P_{DRIVE}$ , but it was accompanied by transient respiratory acidosis in one-third of patients. Therefore, permissive hypercapnia should be limited to the range of 60–70

mmHg to avoid severe acidosis. Further investigations into this approach are strongly warranted.

### Controversy involving positive end-expiratory pressure

PEEP is perhaps the most controversial approach used to prevent VALI because its possible benefits for arterial oxygenation should be carefully weighed against potential static lung injury and negative hemodynamic effects [14,16]. The rationales to set the PEEP for prevention of VALI include inflation of consolidated lung areas and improvement of respiratory compliance. Therefore, PEEP has the potential to reduce  $P_{\text{DRIVE}}$  and achieve low  $V_T$  while simultaneously preserving adequate oxygenation by recruiting responding alveoli and by counteracting atelectotrauma [46].

Until now, the optimal PEEP for ARDS patients remains unsettled. It has been shown in several studies that during protective ventilation, PEEP alone does not improve survival [47–50]. The personalized control of PEEP using esophageal monitoring of  $P_{\text{TP}}$  and a combination of PEEP with alveolar recruitment maneuvers (RM) also have not resulted in any survival benefits [51–53]. In a large meta-analysis, including more than 2000 patients, Briel et al. [54] demonstrated that a high PEEP level could decrease mortality in moderate and severe ARDS cases only [54]. Despite the controversy of these findings compared to a more recent meta-analysis by Walkey et al. [55], the recommendation to use higher PEEP in moderate and severe ARDS is implemented in current international guidelines [42]. Moreover, the ART multicenter study revealed increased mortality after high PEEP and alveolar recruitment in moderate-to-severe ARDS cases [52]. However, the methodology of this study is questionable, as patients were subjected to long-lasting periods of excessive intrathoracic pressures. In a more recent PHARLAP investigation, high PEEP and recruitment did not reduce the duration of ventilation-free days or decrease mortality, but it did decrease the use of new hypoxemic adjuvant therapies for moderate-to-severe ARDS (i.e., inhaled nitric oxide, extracorporeal membrane oxygenation, and prone position) [53].

A triad of high PEEP complications includes hypotension, arrhythmias, and static lung injury, usually manifesting as barotrauma. Thus, despite previous major multicenter trials having shown that high PEEP does not increase the risks of these adverse events compared to low PEEP [47,49], the ART trial demonstrated a three-fold rise in incidences of barotrauma and pneumothorax [52] and the PHARLAP study revealed a two-fold rise in arrhythmia rates using a high PEEP approach [53].

In summary, a high PEEP level (10–24 cmH<sub>2</sub>O; Table 2) should be considered only for patients with moderate-to-severe ARDS with low risk of arrhythmias and barotrauma in parallel with thor-

ough hemodynamic and respiratory monitoring. Increased PEEP can also be useful to reduce the risk of P-SILI and avoid the need for neuromuscular blockade [27,31]. The increase in PEEP should be titrated and gradual (by 2 cmH<sub>2</sub>O per several minutes) and should not result in  $V_T$  exceeding 8 ml/kg,  $P_{\text{PLAT}}$  above 30 cmH<sub>2</sub>O, and  $P_{\text{DRIVE}}$  above 15 cmH<sub>2</sub>O [1,47]. Personalization of PEEP settings to attenuate VALI can also include the assessment of  $P_{\text{TP}}$ , intra-abdominal pressure, and dead space volume [51,56] (Table 3).

### Additional evidence-based protective interventions

Evidence-based interventions in ARDS patients with high risk of VALI are not limited exclusively to low  $V_T$ . ‘Adjuvant’ therapies, including prone positioning and/or neuromuscular blockade have substantial potential for improving outcomes in ARDS. However, it is important to remember that any lung protective intervention should not increase the risk of extrapulmonary life-threatening complications.

#### Prone position

Prone positioning was introduced into ICU practice 50 years ago to counteract severe hypoxemia in mechanically ventilated patients. In contrast to the supine position, the prone position changes the vertical gradient of intrapleural pressure and decreases stress in posterior lung regions. In addition, the prone position attenuates the influence of intrathoracic and intraabdominal pressures on lower portions of pulmonary tissue, thus increasing effective lung volume and compliance. As pulmonary perfusion persists in dorsal regions, the prone position can change the ventilation-perfusion ratio and dramatically improve arterial oxygenation. Moreover, it predisposes the lungs to the gravitational recruitment of collapsed dorsal regions and increases the homogeneity of lung ventilation. It has been shown that in severe ARDS, the prone position can mitigate VALI by improving the distribution of a specific  $V_T$  and pulmonary blood flow and has the potential to improve gas exchange and compliance. In severe ARDS, this technique should be initiated as early as possible and becomes more effective when combined with low  $V_T$  higher PEEP, RM, and additive vasodilator therapies (e.g., inhaled nitric oxide) [57–60].

The PROSEVA trial has demonstrated a significant increase in survival in moderate-to-severe ARDS after prone positioning. Neuromuscular blockade was maintained in 85% of the 466 patients enrolled [57]. It is important to emphasize that prone positioning is only beneficial if four criteria are fulfilled: low  $V_T$ , severe hypoxemia (partial oxygen pressure in arterial blood to inspired oxygen fraction ratio ( $\text{PaO}_2/\text{FiO}_2$ )) less than 100–150 mmHg, ex-

position of 12–16 h per day, and early application [58–60]. Specific risks of prone positioning include endotracheal tube dislodgement and/or occlusion as well as pressure sores on the skin and soft tissues [59]. Therefore, prone positioning for at least 12 h per day can be implemented to mitigate VALI in ARDS patients with refractory hypoxemia and high airway pressures, not responding to neuromuscular blockade, and low or ultralow  $V_T$ , and requires careful monitoring [25,42].

### Neuromuscular blockade

Neuromuscular blockade can decrease the risk of VALI and P-SILI by the suppression of asynchrony, guaranteed maintenance of protective  $V_T$ , and reduced work and power of spontaneous breathing. In patients with moderate-to-severe ARDS, muscle relaxants (such as cisatracurium) improve oxygenation, may exert a direct anti-inflammatory effect, and have the potential to decrease mortality [26,61]. In 2010, Papazian et al. [26] showed in an ACURASYS randomized study of moderate-to-severe ARDS that neuromuscular blockade and deep sedation for 48 h are associated with improved survival, shorter duration of mechanical ventilation, and reduced incidence of barotrauma. The results were confirmed in the meta-analysis of Alhazzani et al. [61] which included three studies of prolonged cisatracurium infusion, although the more recent ROSE trial did not reveal any survival benefits for patients receiving muscle relaxants [27]. The adverse effects of neuromuscular blockade include ICU-acquired weakness (not reported in the ACURASYS trial), particularly in patients receiving glucocorticoids, and complications associated with deep sedation, including hemodynamic instability [27,61].

Therefore, early neuromuscular blockade should be considered in ARDS patients with refractory hypoxemia ( $\text{PaO}_2/\text{FiO}_2$  less than 100–150 mmHg) and increased  $P_{\text{PLAT}}$  to guarantee protective  $V_T$  and to decrease P-SILI only when sedation and respiratory settings are unable to synchronize the patient to a ventilator.

### Alveolar recruitment and open lung approach: not for everyone?

Alveolar RM combined with titrated high PEEP settings constitutes the ‘open lung’ concept [48,50]. Successful RM requires the transient increase of airway pressures to re-open collapsed alveoli and, subsequently, to prevent atelectotrauma with stepwise adjusted PEEP. In 2016, Pirrone et al. [62] in a prospective interventional study involving medical and surgical ICUs, demonstrated that RM followed by PEEP titration (12  $\text{cmH}_2\text{O}$ ) can improve respiratory mechanics in morbidly obese patients (body mass index > 35

$\text{kg/m}^2$ ) [62]. However, multiple meta-analyses have failed to show substantial survival benefits in patients receiving RM [53,63,64], and the ART trial involving an aggressive methodology of RM even increased mortality [52]. Adverse effects of recruitment are similar to those of high PEEP and, in some cases, can potentially overcome the potential protective effects. These adverse effects can include transient hypotension, decreased cardiac output, arrhythmias, hypoxia, and overdistension of the aerated specific volume, as well as barotrauma (pneumothorax) [52,64,65].

It would appear reasonable to personalize the application of RM to prevent VALI by focusing this approach on patients without hypovolemia, arrhythmias, severe cardiac comorbidities, refractory shock, and risk of barotrauma. The optimal methodology of RM is arguable and, probably, as in the case of PEEP, should be associated with the decrease of both pulmonary pressures and  $V_T$ ; otherwise, despite improved oxygenation, increased pressures can contribute to static lung injury [14]. The conflicts between the potential benefits of RM and high PEEP versus increased risk of ‘static’ lung injury resulting in VALI prompted Pelosi et al. [66] to declare a new striking motto: ‘Close down the lungs and keep them resting’ 25 years after the original concept by Lachmann [67] (1992): ‘Open up the lung and keep the lung open.’ The controversial effects of RM and high PEEP on pulmonary edema and systemic hemodynamics, the evidence of reduced injury and inflammation in the collapsed regions, the risk of static strain and overdistension, and even the emerging concept of ‘permissive atelectases’ support the position that we should personalize an ‘open lung approach’ only to the subsets of responders with significant and proven recruitment potential [68,69].

### Personalized approach to VALI prevention in ARDS

In the future, priorities in the prevention of VALI and improvement of outcomes may shift to limiting the injurious power or energy associated with breathing [6–9]. The assessment of lung capacity, heterogeneity of lung injury, pulmonary edema, transpulmonary pressure, and gas exchange are vital requirements for personalized respiratory settings. Attempts to reduce respiratory rate and  $V_T$  result in a decrease in minute volume and damaging power; however, they can be associated with permissive hypercapnia ( $\text{PaCO}_2$  45–70 mmHg). The damaging effects of excessive spontaneous efforts to breathe can be suppressed by deep sedation and/or neuromuscular blockade and high PEEP to decrease swings in PTP, the work of spontaneous breathing, the response to permissive hypercapnia, and, finally, the risk of P-SILI [26,31]. All determinants of power and energy should be optimized, including

gradual changes in PEEP (controlled to produce specific  $P_{\text{DRIVE}}$  and  $V_T$ ), minute ventilation, respiratory rate, flow magnitude and profile, and the I : E ratio. It has been shown that the I : E ratio. It has been shown that the I : E ratio varying from 1 : 1 to 1.5 : 1 can be associated with decreased inspiratory flow, providing a safer controlled constant flow profile [8,9].

## Protective ventilation in ICU patients without ARDS

In contrast to manifesting ARDS, the subset of ICU patients without ARDS requiring positive pressure ventilation can be much more heterogeneous in terms of risk of VALI (Fig. 2). This category of critically ill can be subdivided into patients with intact lungs without common risk factors involving ARDS, intact lungs with some risk factors of ARDS (e.g., septic shock, aspiration) and, finally, other lung disorders and hypoxemia that do not meet ARDS criteria. Although there is no strong consensus concerning lung protective ventilation patterns and settings in this scenario, it has been demonstrated that low  $V_T$  ventilation can prevent VALI in the patients with initially intact lungs, and multiple studies have confirmed the benefits of protective ventilation in patients without ARDS [4,70,71]. A further meta-analysis revealed that the implementation of low  $V_T$  resulted in decreased risk of pulmonary complications, including atelectases and pneumonia, reduced ICU and hospital length of stay, and increased number of ventilator-free days, but did not influence the survival rate [72]. Therefore, in this subset of ICU patients, low  $V_T$  is prudent, safe, and is associated with better outcomes [73,74]. Furthermore, use of a high PEEP level is more controversial and should perhaps be used only in situations where the risk of P-SILI exists, when it can decrease  $V_T$  to normal values and attenuate static strain injury [15, 30,31].

## Protective ventilation during perioperative period

Annually, more than 310 million surgical interventions are performed and most require general anesthesia with neuromuscular blockade and positive pressure ventilation [75,76]. Many operations last longer than 2–3 h and are accompanied by increased risk of respiratory complications (Fig. 2). Postoperative pulmonary complications (PPC) in patients with intact lungs are quite common (3%–8%) and represent a heterogeneous group of events: atelectases, pulmonary edema, postoperative pneumonia, pleuritis, re-intubation, requirement for postoperative supplemental oxygen, and ARDS [77,78]. It is well-recognized that PPC

increase the risk of infectious and surgical complications, length of ICU and hospital stay, healthcare costs, and personnel workload, and are a target for primary and secondary prevention (Fig. 1) [5,79]. The influence of PPC on mortality remains is still not well defined and warrants further analysis [80]. Thus, the problem of PPC requires better understanding among anesthesiologists and the implementation of interventions with proven effects to prevent these complications [81,82].

Although the most common PPC are atelectases, one of the most severe PPC is ARDS, whose cumulative incidence may outweigh the incidence of ‘medical’ ARDS in the ICU. The important determinant of perioperative VALI is volumotrauma. Therefore, low  $V_T$  ventilation is of paramount importance to prevent PPC; however, despite its clear advantages, intraoperative protective ventilation is still not widely implemented in current anesthesia practice [83]. There is a wide variety of studies in the different areas of perioperative care showing the benefits of low  $V_T$  for protective ventilation [84–86]. Along with ICU settings, an implementation of lower  $V_T$  and moderate, but not zero-PEEP can dramatically reduce the injurious effects of ventilation during surgery [3,5].

Large-scale studies have been mainly performed on the population of abdominal surgical patients. The IMPROVE trial has shown that ventilation with ‘traditional’  $V_T$  of 10–12 ml/kg and zero PEEP increases the risk of PPC and prolongs hospital stay compared with a  $V_T$  of 6–8 ml/kg and PEEP of 6–8 cmH<sub>2</sub>O [87]. An extended meta-analysis by Serpa Neto et al. [5] found a close relationship among PPC, incidence of postoperative respiratory failure, and  $V_T$ .

Higher levels of PEEP during the perioperative period do not provide any additional benefits [5]. In another study, the PROVHILO trial (2014) demonstrated that a strategy consisting of a high level of PEEP combined with RM during open abdominal surgery does not protect against PPC; the authors conclude that the perioperative protective ventilation strategy should include low  $V_T$  and low PEEP without RM [88]. The recent multi-center PROBESE trial (2019) also demonstrated that setting a high PEEP of 12 cmH<sub>2</sub>O and using RM in obese patients (body mass index > 35 kg/m<sup>2</sup>) is not associated with any reduction of PPC compared to a low level of PEEP (4 cmH<sub>2</sub>O) [89]. The rationale for higher intraoperative PEEP and RM in thoracic surgery with one-lung ventilation is being explored in the ongoing PROTHOR trial (NCT02963025) [90].

Before surgical intervention, patients should be carefully assessed for the risk of PPC using specific scoring systems (LIPS, ARISCAT, and/or SPORC) to personalize a perioperative lung protective strategy [91–93]. The group with high risk of PPC

should prompt targeted management consisting of a bundle of preventive measures that are not limited to ventilation alone. Thus, compared with open abdominal surgery, the risk of respiratory failure, ARDS, pulmonary infections, and pulmonary embolism can be reduced by applying a laparoscopic approach [94]. Perioperative fluid therapy and transfusion can also trigger postoperative ARDS; therefore, a restrictive goal-directed fluid strategy should be considered for patients with high risk of PPC [95,96]. Volatile anesthetics have lung-protective potential and can improve the surgical outcome as well [97]. It appears reasonable to avoid high doses of muscle relaxants and opioids, use selective reversal agents, and give preference to neuraxial methods instead of using general anesthesia [98,99]. Postoperative continuous positive airway pressure, upright positioning and sitting posture, and early mobilization can all reduce the incidence of PPC [100–102].

The consensus approaches for protective ventilation settings in surgical patients are presented in Table 3 and Fig. 2. Note that in the LAS VEGAS study, only the peak pressure (without the plateau or driving pressures) was used as an independent predictor in PPC; however, the  $P_{DRIVE}$  should also be minimized in the process of PEEP personalization [19,88]. Because high  $FiO_2$  levels during perioperative period can be accompanied by hyperoxia and several undesirable effects, and as robust evidence is lacking indicating a beneficial effect of  $FiO_2$  levels above 60% on surgical site infection, the routine use of an  $FiO_2$  level > 60% during anesthesia and surgery is not recommended [103]. Furthermore, using an  $FiO_2$  level of 80% during pre- and post-oxygenation to prevent atelectases appears to be risky in difficult airway situations. The potential benefits of decreased respiratory rate, inspiratory flow, and  $FiO_2$  as well as perioperative RM warrant new studies in different subpopulations of surgical patients. During the early postoperative period, automated weaning from mechanical ventilation systems can reduce the number and duration of deviations from the safe ventilation zone, decrease the workload on medical staff, and provide additional protective parameters as compared to conventional modes [104]. Thus, these systems have the potential for further integration in postoperative respiratory care.

## Conclusions

Today, protective respiratory support with reduced  $V_T$  and pressures is the gold standard for prevention of VALI and PPC, both in perioperative settings and for ICU patients. We have observed a shift in paradigm from ‘normalizing’ blood gases, early restoration of spontaneous breathing, and the ‘open lung’ approach to a balanced strategy of personalized lung protection based on a set of interventions aiming to limit lung stress and

strain. The ‘less is more’ and ‘choosing wisely’ strategies should be implemented by ICU physicians and anesthesiologists in all subsets of ventilated patients by considering individual patient risk, pulmonary comorbidity, risk factors of ARDS, respiratory mechanics, and gas exchange. Finally, the concept of injurious energy load and power can help to reconsider the effects of PEEP and alveolar recruitment.

## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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