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REVIEW

New insights in mechanical ventilation and adjunctive therapies in ARDS

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Abstract

Patients with acute respiratory distress syndrome (ARDS) often require mechanical ventilation (MV) and may experience high morbidity and mortality. The ventilatory management of ARDS patients has changed over the years to mitigate the risk of ventilator-induced lung injury (VILI) and improve outcomes. Current recommended MV strategies include the use of low tidal volume (V_T) at 4–6 mL/kg of predicted body weight (PBW) and plateau pressure (P_{PLAT}) below 27 cmH_2O. Some patients achieve better outcomes with low V_T than others, and several strategies have been proposed to individualize V_T, including standardization for end-expiratory lung volume or inspiratory capacity. To date, no strategy for individualizing positive-end expiratory pressure (PEEP) based on oxygenation, recruitment, respiratory mechanics, or hemodynamics has proven superior for improving survival. Driving pressure, transpulmonary pressure, and mechanical power have been proposed as markers to quantify risk of VILI and optimize ventilator settings. Several rescue therapies, including neuromuscular blockade, prone positioning, recruitment maneuvers (RMs), vasodilators, and extracorporeal membrane oxygenation (ECMO), may be considered in severe ARDS. New ventilator strategies such as airway pressure release ventilation (APRV) and time-controlled adaptive ventilation (TCAV) have demonstrated potential benefits to reduce VILI, but further studies are required to evaluate their clinical relevance. This review aims to discuss the cornerstones of MV and new insights in ARDS ventilatory management, as well as their rationales, to guide the physician in an individually tailored rather than a fixed, sub-physiological approach. We recommend that MV be individualized based on physiological targets to achieve optimal ventilatory settings for each patient.

Keywords

Mechanical ventilation; ARDS; COVID-19; Mechanical power; APRV

1. Background

The definition of acute respiratory distress syndrome (ARDS) dates back to 1967 [1]. Despite 55 years of research and clinical experience, ARDS management remains challenging, and the syndrome is associated with a high mortality rate [2], requiring intensive care unit (ICU) admission and mechanical ventilation (MV) [3]. In recent decades, a huge effort has been made to investigate the impact of lung-protective ventilation on ARDS outcome and to modify ventilatory management strategies to reduce the risk of ventilator induced lung injury (VILI). Although several ventilatory strategies are now recognized as the standard of care in the management of ARDS patients, an individualized approach, which takes into account the limits of physiological gain and the uncertainty concerning ventilatory manipulation on outcome, is now under consideration [4] (Fig. 1). This review aims to discuss the cornerstones of MV and new insights in ARDS ventilatory management, as well as their rationale, to guide the physician in an individually tailored rather than a fixed, less physiological approach.

2. Standard of care

2.1 Low tidal volume

The current standard of care of MV in ARDS includes lung-protective ventilation targeting a low tidal volume (V_T) of 4–6 mL/kg of predicted body weight (PBW), and plateau pressure (P_{PLAT}) below 27 cmH_2O [5]. The introduction of these targets dates back to the 2000 ARMA trial, where a traditional approach of V_T = 12 mL/kg of PBW with a P_{PLAT} less than 50 cmH_2O was compared with a lung protective approach of V_T = 6 mL/kg with a P_{PLAT} below 27 cmH_2O, showing that ARDS patients with low V_T had significant reductions in mortality [6]. Although these large trials established that lung-protective ventilation using low V_T should be pursued in ARDS, research

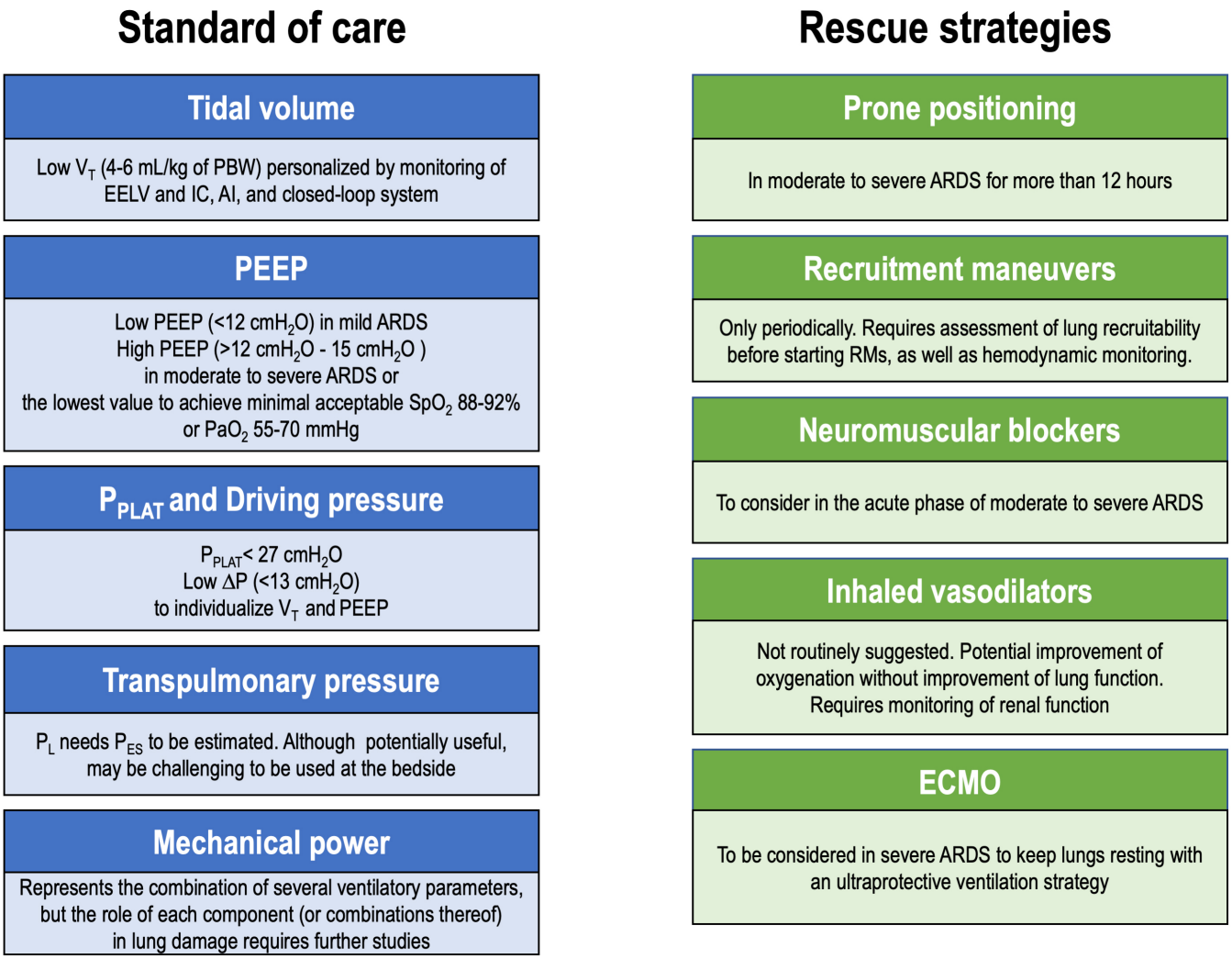

FIGURE 1. Mechanical ventilation in ARDS: standard of care and rescue strategies. On the left, the cornerstones of mechanical ventilation in acute respiratory distress syndrome (ARDS). On the right, possible rescue strategies in case of moderate to severe ARDS refractory to conventional strategies. V_T, tidal volume; PBW, predicted body weight; EELV, end-expiratory lung volume; IC, inspiratory capacity; AI, artificial intelligence; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; P_{PLAT}, plateau pressure; ΔP, driving pressure; P_L, pleural pressure; P_{ES}, esophageal pressure; RMs, recruitment maneuvers.

regarding the use of low V_T in ARDS continued over the next 20 years [7]. A large multinational prospective cohort study, LUNG SAFE, identified a frequent underdiagnosis of ARDS at ICU admission and noncompliance with lung-protective ventilation strategies, resulting in a strong association with mortality [8]. The detrimental sequelae of MV with high V_T have been clearly demonstrated [9]. Current approaches suggest individualizing MV according to patient and disease characteristics [4]. Given that V_T has been strongly associated with mortality in patients with lower respiratory system compliance (C_{RS}) [10], it should ideally be set according to the amount of aeration, using inspiratory capacity (IC), or end-expiratory lung volume (EELV) measured at 30 cmH_2O. This could be considered the approach of choice since, in heterogenous ARDS-affected lungs, lung volumes do not correlate well with PBW. However, V_T can be set according to EELV only if positive end-expiratory pressure (PEEP) is reduced, since it may change with C_{RS} [11]. Therefore, IC seems to be a more reliable technique at bedside, V_T being easily achieved with automated systems and artificial intelligence (AI) support [4].

2.2 Positive end-expiratory pressure

PEEP represents an essential component in ARDS management. PEEP allows alveolar recruitment to potentially open collapsed or edematous and inhomogeneously distributed areas of the ARDS "baby lung" [12]. A recruitment maneuver (RM) to open the collapsed alveoli is commonly followed by the application of PEEP to keep recruited alveoli open and improve gas exchange [4]. The use of high PEEP levels and RMs has been questioned, however. Two meta-analyses of randomized controlled trials (RCTs) concluded that low V_T combined with high PEEP improves survival in patients with ARDS [13, 14]. A secondary analysis of the Open Lung Ventilation Study showed improvement in oxygenation with high PEEP, associated with lower risk of death [15]. On the contrary, in the

ART trial, a PEEP higher than 15 cmH_2O was associated with increased risk of mortality in patients who were hemodynamically unstable [16], while in the PHARLAP trial an aggressive recruitment strategy was associated with cardiac arrhythmias [17]. In a third scenario, three RCTs of lung-protective ventilation in ARDS patients found no differences in mortality with high and moderate PEEP levels [18–20]. Benefits of PEEP application include alveolar recruitment, reduction of intrapulmonary shunting, and improvement of oxygenation, while harms include increased EELV, possible volutrauma, and VILI [3, 21]. High PEEP is associated with increased static stress, even though a meta-analysis concluded that neither RMs nor higher PEEP affect mortality in ARDS patients [22]. Current recommendations suggest adopting high PEEP (>12 cmH_2O) only for patients with moderate or severe ARDS [23]. However, individualization of PEEP according to the potential for alveolar recruitment should be considered [24]. Indeed, it is important to distinguish recruitable and non-recruitable ARDS patients. In the latter, the airway pressure tends to increase, causing hemodynamic impairment and lung overdistension, whereas when the collapsed areas are recruitable, the lung can benefit from reduction of pressures. Unfortunately, monitoring alveolar recruitment at the bedside remains challenging and, to date, no definitive recommendations on how to set PEEP are available. A possible strategy could be to set PEEP according to transpulmonary pressure (P_L) or a low PEEP/arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) table, which does not seem to influence mortality [16, 25]. A possible, relatively new strategy to estimate PEEP at bedside expects to appraise the recruitment volume by performing two pressure/volume (P/V) curves (at high and low PEEP) and measuring the difference between the expired volume and the volume predicted by the compliance of the respiratory system above the airway opening pressure: $\frac{\Delta Vrec}{\Delta Prec}$ where $\Delta Prec = PEEP_{high} - PEEP_{low}$.

The compliance of the recruited lung can be estimated by the ratio: $\frac{\frac{\Delta Vrec}{(PEEP_{high} - PEEP_{low})}}{Crs\ above\ airway\ opening\ pressure\ or\ at\ PEEP_{low}}$ [26]. When this ratio is equal to or greater than 0.5, patients are more likely to be recruitable, and might need higher levels of PEEP. In any case, from a clinical point of view, PEEP should be set at the lowest level to achieve a minimal acceptable peripheral saturation of oxygen (SpO_2) (88–92%) or PaO_2 (55–70 mmHg) [27, 28], but keeping in mind possible detrimental clinical effects on right ventricular function, cardiac output, and lymphatic flow drainage [29, 30]. In addition to the aforementioned methods for PEEP titration, electrical impedance tomography (EIT), lung ultrasound (LUS), and computed tomography (CT) should be mentioned. As compared with pressure/volume curve, PEEP titration using EIT was associated with improved oxygenation, compliance, driving pressure, and weaning success rate [31]. However, "optimal" PEEP levels determined by EIT may differ significantly among ARDS patients (of around 10%) due to the presence of non-recruitable lungs and heterogeneity of ventilation. The advantage of using EIT at the bedside to individualize PEEP is the possibility of identifying lung heterogeneity, thus avoiding alveolar cycling and regional overdistension and minimizing the risk of VILI in a personalized manner. Despite this potential advantage, the literature on possible optimization of mechanical ventilation using EIT in ARDS is still scarce, and further implementation is needed [32]. LUS demonstrated good estimation of lung recruitment at the bedside, with the limitation of not assessing PEEP-induced lung hyperinflation [33], but ability to distinguish between different ARDS morphologies (focal *vs.* non-focal) [34]. The use of LUS to individualize PEEP in patients with ARDS has several advantages, including bedside availability, low cost, no ionizing radiation, and relatively little dependence on operator skills. LUS provides the possibility of observing changes in ultrasound patterns during PEEP implementation and successfully selecting an appropriate level of PEEP, and can detect response to the application of RMs, helping the clinician distinguish between recruiters and non-recruiters [35]. Other methods such as CT could help in titration of PEEP in case of limitations of noninvasive methods [36], allowing a visual, anatomical analysis of lung recruitability [37]. However, CT has potential disadvantages, including the impossibility to be performed routinely and repeated due to the limitations of patient transportability and ionizing radiations exposure, as well as the need for possible increased sedation and neuromuscular blockade. For this reason, CT cannot be considered for routine use in individualizing PEEP at the bedside [35].

2.3 Driving pressure

Driving pressure (ΔP) represents the ratio between V_T and C_{RS} or the airway plateau pressure minus PEEP (P_{PLAT}–PEEP). In other terms, since C_{RS} correlates with aeration of the lung, ΔP represents an easy estimator of strain (V_T/aeration of the lung at end expiration) for that particular V_T. ΔP was first considered a component of lung protective ventilation in 1998 by Amato et al. in a small RCT [38]. Since then, ΔP has been adopted as a method to set PEEP, but the benefits of this strategy are counterbalanced by potential harms, including the fact that ΔP depends on the different V_T used as well as C_{RS}. At high C_{RS}, lower ΔP may help achieve higher PEEP. ΔP may also be affected by changes in chest wall compliance, and airway closure may confound the relationship between PEEP and ΔP [4]. Decreases in ΔP have been associated with survival benefit even when the patient received protective plateau pressure and V_T [39], while ΔP higher than 13 cmH_2O was associated with mortality [40]. A meta-analysis of 7 RCTs and 2 observational studies also confirmed that ΔP above 15 cmH_2O is associated with significantly higher mortality [41]. In short, maintaining ΔP below 13 cmH_2O and P_{PLAT} below 27 cmH_2O is the best suggested approach, although an individualized tailored strategy according to V_T and PEEP is preferable [42]. It is our opinion that the beneficial effects of reduced ΔP on outcome are because of lower V_T, and not to the reduction of ΔP with higher PEEP, mostly associated with increased P_{PLAT}.

2.4 Transpulmonary pressure

Transpulmonary pressure (P_L) represents the distending force of the lung determined by the equation $P_{AW} - P_{PL}$ (where P_{AW} is airway pressure and P_{PL} is the pleural pressure), and

it is estimated by esophageal pressure (P_{ES}) [43]. In ARDS, both lung and chest wall elastance (E_{CW}) are often impaired. To induce alveolar recruitment, PEEP needs to overcome P_L [44, 45]. P_{AW} is not injurious at tidal ventilation, provided E_{CW} is increased. P_{PL} allows differentiation of lungs *vs.* chest-wall mechanics [43]. In the supine position, P_L acts as the pressure that works on alveoli and airways due to the pressure gradient between nondependent and dependent areas [46]. Using P_{ES} to interpret P_L, the difference between P_{AW} − P_{ES} at end-expiration or end-inspiration can reflect the P_L in the middle lung, while the difference in P_L (ΔP_L) between end-inspiration and end-expiration estimates the ΔP_{ES} [4]. Further, one should consider that P_{ES} overestimates the pleural pressure by + 5 cmH_2O in nondependent lung regions (near the sternum), while underestimating by −5 cmH_2O the pleural pressure in dependent lung regions (near the vertebrae). For these reasons, the absolute P_L in the dependent lung regions at end-expiration should be calculated as PEEP − P_{ES} − 5 cmH_2O, while in the nondependent lung regions at end-inspiration, it should be calculated as P_{PLAT} − P_{ES} + 5 cmH_2O. Several trials targeting mechanical ventilation by using P_L have found no beneficial effects on outcome [45, 47]. However, none of them appropriately corrected for appropriate absolute P_L. Preliminary data regarding the use of transpulmonary pressure to tailor ventilator settings are encouraging, but further, adequately powered studies are warranted. Therefore, although this technique represents an appealing "precision medicine" approach to individualized mechanical ventilation parameters, the routine use of transpulmonary pressure is limited and should be reserved only for selected cases (*e.g.* obese patients, to assess the impact of the chest wall; patients in whom ventilatory pressures are too high to be explained by other, easier methods). Indeed, the assessment of transpulmonary pressure with continuous monitoring of P_{ES} at the bedside is often challenging because of the need to insert an esophageal catheter connected to a computer running dedicated software [43, 45, 47]. Furthermore, as explained elsewhere in this review, other, more suitable, and accessible methods to personalize mechanical ventilation in ARDS are available.

2.5 Mechanical power

Mechanical power (MP) is the product of mechanical energy and respiratory rate [48], also defined as the amount of energy per unit of time. Lung damage can be directly explained by using some parameters that are set on the ventilator by the clinician (V_T, ΔP, airflow, respiratory rate, and PEEP). The mechanisms associated with these variables alone or different combinations thereof cause direct damage to epithelial/endothelial cells and extracellular matrix [48]. MP calculation is based on the following formulas, according to the type of ventilation that is applied:

$$MP_{VCV} = 0.098 \times V_T \times (P_{PEAK} - \frac{\Delta P}{2}) \times RR$$

$$MP_{PCV} = 0.098 \times V_T \times (\Delta P + PEEP) \times RR$$

where VCV is volume-controlled mode, PCV is pressure-controlled mode [49, 50], and RR represents the respiratory rate in breaths per minute. In general, these MP formulas are based on the basic equation of motion, $P_{RS} = E_{RS} \times V_T + V'_{INSP} \times R_{AW}$, which considers changes in pressure as well as elastic and resistive components (V'_{INSP} is the inspiratory flow and R_{AW} is the airway resistance). The same equation can be computed for the "absolute" level of respiratory system energy as $P_{RS} = E_{RS} \times V_T + V'_{INSP} \times R_{AW} + PEEP$. However, to date, controversies remain regarding the best equation to evaluate MP at bedside [51]. MP has been associated with increased mortality and worse oxygenation in ARDS and non-ARDS populations [52, 53], although in another report this was true only if normalized to compliance as well as to aerated tissue [54]. More studies are needed to better understand the association between MP and survival in ARDS patients. For this reason, although MP represents an appealing and easily available method that integrates several ventilatory parameter in a unique equation which can be calculated at the bedside, the lack of literature confirming the impact of this parameter on hard outcomes limits its routine use as a potential target to individualize mechanical ventilation in ARDS [4].

3. Other ventilation modes

3.1 Airway pressure release ventilation and time-controlled adaptive ventilation

Airway pressure release ventilation (APRV) is a ventilatory strategy first developed by Downs *et al.* [55] for patients with reduced compliance. This ventilatory mode uses a continuous positive airway pressure combined with a partial and short release phase for ventilation, allowing the patient to breathe spontaneously. A high pressure (P_{high}) around 20–30 cmH_2O is applied and maintained for a certain time (T1) during which the patient can breathe spontaneously. At the end of T1, the pressure decreases to low pressure (P_{low}) according to lung elastic recoil. T2 is obtained with an expiratory flow around 25–50% of the maximum value. However, $P_{high}$and P_{low} should be set according to the higher and lower inflection points of the P/V loop [56]. The efficacy of APRV in ARDS has been recently demonstrated in a meta-analysis of 6 clinical trials and 375 patients, showing an improvement in oxygenation with shorter ICU stay [57]. Regarding hemodynamic stability, another meta-analysis found an increase in the mean arterial pressure and reductions in peak pressure and 28-day mortality [58]. APRV, compared to lung-protective ventilation, increased compliance and oxygenation and improved hemodynamics, thus resulting in reduced mortality, duration of MV, and ICU stay [59, 60]. The use of time-controlled adaptive ventilation (TCAV) during APRV showed improvement of lung recruitment, more homogeneous ventilation, and reduction in alveolar strain and stress [61]. In experimental ARDS, TCAV, compared to lung-protective MV, reduced lung damage and inflammation [62], making this strategy a possible valuable alternative to classic APRV. These two ventilatory techniques are implemented for the management of patients with ARDS for all the above-mentioned reasons. However, when targeting patients who might benefit from this techniques to individualize therapy, several potential situations should be

considered, including the fact that spontaneous breathing effort can result in increased oxygen consumption by the respiratory muscles; that vigorous breathing efforts may increase the transcapillary pressure gradient, enhancing pulmonary edema formation; and large tidal volumes and transpulmonary pressure swings can be achieved because APRV is also a type of pressure-controlled ventilation, thus potentially contributing to volutrauma [63].

3.2 High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) is a conceptually appealing method of MV to reduce VILI in ARDS patients, using V_T equal or lower than dead space (0.1–3 mL/kg) but respiratory rates >150 breaths/min or 3–15 Hz and a bias flow of gas set at 5–60 L/min [64]. The equation of Fredberg explains how alveolar ventilation is obtained with HFOV: $(f)^x \times (V_T)^y$, where x is between 0.5 and 1 and y between 1.5 and 2.2, which can be written as follows: $(f) \times (V_T)^2$. Based on this equation, it can be noted that V_T has a greater influence than respiratory rate in determining alveolar ventilation. HFOV maintains a continuous distending pressure and facilitates elimination of carbon dioxide, mainly by accelerating the molecular diffusion process [64]. In experimental ARDS, HFOV reduced lung injury, hyaline membrane formation, airway epithelial cell damage, and biomarkers of inflammation (interleukin (IL)-1β, IL-6, IL-8, IL-10, transforming growth factor and adhesion molecules, as well as tumor necrosis factor (TNF)) when compared to conventional MV [64, 65]. In ARDS patients, HFOV, when used as a rescue therapy, improved oxygenation [66]. However, other studies found it resulted in higher mortality rates in patients whose oxygenation failed to improve [67], or a nonsignificant trend towards reduced 30-day mortality when compared to conventional MV [68]. In 2017, a meta-analysis by Meade *et al.* [69] reported that HFOV increases mortality in patients with ARDS, but not in case of severe hypoxemia on conventional MV. A previous Cochrane review concluded that there is not enough evidence to demonstrate superiority of HFOV in adult ARDS patients when compared with lung-protective conventional MV, but benefits of HFOV were seen regarding survival and treatment failure (*i.e.*, refractory hypoxemia, hypercapnia, hypotension, or barotrauma) [70]. In summary, the use of HFOV in adult ARDS remains controversial, especially regarding survival outcomes. HFOV can be considered as rescue therapy in ARDS if potential harms (higher intrathoracic pressure, interference with right ventricular preload, pneumothorax, displacement of the endotracheal tube, airway obstruction from mucus plug, refractory acidosis, cellular injury) and benefits (improved oxygenation, reduced VILI, failed conventional ventilation, lower V_T, lungs inflation avoiding repeated opening and closing of alveoli) are weighed carefully with respect to individual patient characteristics and needs [71]. Patients who can benefit from HFOV as a rescue strategy are those with severe ARDS whose lungs cannot tolerate high tidal distending pressure.

4. Adjunctive therapies

4.1 Prone positioning

Prone positioning represents a rescue therapy in severe ARDS. In ARDS lungs, dependent areas are commonly more perfused than the nondependent due to gravitational gradient, resulting in hypoxia associated with ventilation/perfusion mismatch. Prone positioning allows a more homogenous distribution of ventilation/perfusion with diminished intrapulmonary shunt [72]. Nevertheless, some conflicting results were published in the clinical setting regarding ARDS patient outcomes. The prone-supine RCT found no differences in survival when comparing prone with supine positioning, but more complications [73]; in contrast, the PROSEVA trial showed reduced mortality in prone compared to supine groups, and similar rates of complications [74]. A meta-analysis of RCTs confirmed the benefits of reduced mortality using prone positioning [75]. Particularly, in a sub-analysis, mortality rate was further reduced when prone positioning was applied for more than 12 hours [76]. Finally, two recent meta-analyses supported the use of prone positioning and venous-venous extracorporeal membrane oxygenation (VV-ECMO) in adjunction to lung-protective ventilation in ARDS patients, demonstrating survival benefits [77, 78]. Prone positioning has also become one of the cornerstones of mechanical ventilation in COVID-19 patients with ARDS, as briefly explained in the appropriate section below "5. Mechanical ventilation in COVID-19".

4.2 Recruitment maneuvers

Recruitment maneuvers (RMs) are considered part of the "open lung approach", reducing repeated opening and closing of collapsed alveoli and intrapulmonary shunt, thus improving oxygenation [79]. However, RMs may lead to VILI and hemodynamic impairment. The ART trial reported that high-pressure stepwise lung RMs (up to P_{PLAT} of 50–60 cmH_2O) combined with higher PEEP titration increased patient mortality [16], while the PHARLAP trial [17], assessing RMs up to a P_{PLAT} of 28 cmH_2O, was interrupted as several patients experienced hemodynamic issues. Meta-analyses of RCTs, despite supporting the use of RMs in combination with PEEP or alone, did not describe which type of RMs was performed in each trial, thus leading to poor accuracy. RMs are usually adopted in cases of severe hypoxemia, but there is no evidence regarding their optimal frequency or exact timing. Some studies report systematic application of RMs, while others report the application of RMs when the lung is de-recruited, as a rescue measure. Regardless, RMs appear to be safe if used periodically (*i.e.*, not systematically), since they improve oxygenation and seem not to lead to barotrauma or hemodynamic compromise [22, 80, 81]. Additionally, it is important to identify lung recruitability at bedside to individualize the use of RM strategies in ARDS patients. An approach which targets at the need of the patient by assessing lung recruitability at the bedside before applying potentially harmful maneuvers is suggested. A potentially recruitable lung consists of some areas of open alveoli and others of collapsed alveoli, which can be opened, thus decreasing shunt, pulmonary vascular resistance, and edema, as well as improving oxygenation. Conversely, a potentially non-recruitable or poorly recruitable lung is mainly constituted of already open alveoli, carrying a high risk of

VILI from excessive stress and strain, increased dead space, shunting, and potentially high pulmonary vascular resistances [82]. Methods to assess lung recruitability have been explained in paragraph 2.2 "Positive end-expiratory pressure".

4.3 Sedation, analgesia and neuromuscular blockers

In the acute phase, patients with severe ARDS remain deeply sedated and require the use of neuromuscular blocking agents (NMBAs) to improve gas exchange. On the other hand, early active breathing has the advantage of reducing respiratory muscle wasting, improving oxygenation, and increasing compliance [83]. Analgesia and sedation with or without the use of NMBAs is challenging in patients with ARDS. The primary objective of analgesia and sedation in patients with ARDS is to provide safety and comfort, to help the patient interact with the ventilator and the staff, to facilitate critical interventions, and to promote physical and cognitive recovery to minimize the risk of delirium and agitation [84]. Sedation and analgesia should be set according to individual patient requirements, without rigid adherence to a single strategy—*i.e.*, accepting short intervals of moderate sedation to reduce patient-ventilator asynchronies and discomfort, occasional deep sedation (especially in case of need for invasive mechanical ventilation with high pressures and neuromuscular blockade), or mild sedation with adequate analgesia, such as during ventilator weaning. In any case, sedation and analgesia should be individualized to patient requirements and ventilation needs [84]. Monitoring of sedation and pain levels with validated tools (*i.e.*, Richmond Agitation Sedation Scale (RASS), Sedation Agitation Scale (SAS), Behavioral Pain Scale (BPS), etcetera) should be encouraged. Analgesic and sedative infusions should be continued unless NMBAs are stopped [84]. It is important to distinguish which ARDS patients will benefit from the use of NMBAs, including those with higher The Acute Physiology and Chronic Health Evaluation (APACHE) II score, alveolar-arterial oxygen gradient, and P_{PLAT}, or those who are critical and require rescue therapies like VV-ECMO or prone positioning [85]. In 2010, Papazian *et al.* [86] found that a strategy of early administration of NMBAs improved 90-day survival and liberation from MV without increasing muscle weakness from disuse. In the ROSE trial, which included patients with moderate to severe ARDS, no significant differences in mortality were found between patients who received an early and continuous infusion of NMBAs *vs.* those who received usual care and lighter sedation [87]. A recent meta-analysis excluding the ROSE trial concluded that NMBAs did not reduce the overall risk of death at 28 days and 90 days, while ICU mortality was significantly reduced [88]. The reasons for excluding the ROSE trial were (1) the use of different PEEP titration strategies and (2) different degrees of sedation (light sedation compared to deep sedation strategy used in the other trials) [88]. Considering the differing results obtained from RCTs including severe ARDS patients, NMBAs appear to improve oxygenation and reduce the risk of barotrauma, but do not decrease mortality risk, ventilator-free days, or duration of MV.

4.4 Vasodilators

Selective pulmonary vasodilators, like inhaled nitric oxide (iNO), are an another rescue therapy for ARDS patients unresponsive to conventional therapies [89]. iNO improves oxygenation through a selective vasodilatation of capillary vessels in well-aerated alveoli, thus reducing ventilation/perfusion mismatch and pulmonary vascular resistance as well as increasing right ventricular output [89]. However, a meta-analysis of RCTs did not support routine use of iNO in ARDS, since no significant changes in survival were observed and a risk of renal dysfunction was detected [90]. As an alternative to iNO, inhaled epoprostenol has been suggested. The advantages of inhaled epoprostenol compared to iNO are (1) reduced potential side effects, (2) easier administration, and (3) lower costs. However, there are few studies regarding the use of inhaled epoprostenol in ARDS targeting mortality as a primary outcome [91].

4.5 Venous-venous (VV)-ECMO

VV-ECMO is often adopted as a rescue strategy for severe ARDS patients. The risk of VILI is reduced as an ultra-protective ventilatory strategy is provided [92]. The suggested criteria for VV-ECMO initiation in ARDS are: (1) mortality risk $>50\%$ and PaO_2/FiO_2 <150 with FiO_2 $>90\%$ and/or a Murray score of 2–3, an Age-Adjusted Oxygenation Index (AOI) score of 60; (2) mortality risk $\geq 80\%$ and PaO_2/FiO_2 <100 with FiO_2 $>90\%$, and/or Murray score 3–4, AOI score >80 or Acute Physiology of Stroke Score (APSS) (Age, PaO_2/FiO_2, Plateau Pressure) of 8; (3) hypercapnia despite protective mechanical ventilation and rescue therapies (*e.g.* prone positioning, recruitment maneuver); (4) severe air leak syndrome; (5) need for lung transplantation; or (6) acute severe heart or pulmonary failure that is potentially reversible but unresponsive to conventional management [93–95]. A meta-analysis of 2 RCTs and 5 observational studies concluded that ARDS patients undergoing VV-ECMO and MV exhibited a significantly lower mortality rate than those receiving MV alone at 30, 60, and 90 days [96]. However, a recent reanalysis of the data presented by Munshi *et al.* [97] using both traditional and Bayesian models to estimate the treatment effect concluded no certainty regarding the efficacy of VV-ECMO in ARDS on mortality. Compared with conventional MV, VV-ECMO showed lower 60-day, 90-day, and 1-year mortality in patients with ARDS, as demonstrated by both conventional and individual-patient-data meta-analyses [98, 99]. Hence, the latest evidence does not clearly support the use of VV-ECMO for patients who are critical and cannot obtain other benefits from conventional therapies. Therefore, patients with ARDS who might benefit from VV-ECMO are those needing complete pulmonary support to allow adequate oxygenation and carbon dioxide removal, while limiting the risk of VILI due to conventional ventilator strategies. However, given that VV-ECMO is commonly adopted as a rescue strategy, the decision to start VV-ECMO is difficult to place into the context of personalized ARDS therapy. The decision to initiate ECMO should also weigh the patients' possibility of recovery, family expectations, odds of survival, potential life-threatening complications, and ethical considerations [100].

5. Mechanical ventilation in COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has called into question several cornerstones of MV in ARDS, mainly because at the onset of the pandemic ARDS and COVID-19 were considered very similar; thus, there was an attempt to employ the same MV strategies for both conditions. The main driver of MV strategies in COVID-19 ARDS is actually the identification of pathophysiological differences and similarities between COVID-19 ARDS and non-COVID-19 ARDS, although both are characterized by severe refractory hypoxemia and high mortality [101]. Severe COVID-19 and typical ARDS are usually characterized by respiratory compromise and multiorgan failure. Biological markers have been identified as exacerbating factors for severe disease in both cases [102]. Particularly, variations in the immune and inflammatory response, including cytokine release (*e.g.* interleukin-6 and 10), endothelial dysfunction, microthrombus formation with an altered coagulation cascade, have led to the identification of several serum biomarkers (lactate dehydrogenase, D-dimer, among others) able to provide early detection of progression to severe disease, although their potential association with outcomes is unclear [103]. This concept has been previously raised in non-COVID-19 ARDS, with the identification of sub-phenotypes (*i.e.*, hyperinflammatory and hypoinflammatory), which may represent a shift toward a more targeted "precision medicine" approach [104]. In COVID-19 ARDS, unlike in typical ARDS, nondependent aerated regions show mostly perfusion over ventilation, with a certain degree of hypoxic vasoconstriction in the dependent lung regions that results in a non-gravitational distribution of regional blood flow [105]. The identification of COVID-19 phenotypes (1 or L and 2 or H) through chest CT could be a valid strategy to select patients who would benefit from early intubation and those who would not [106]. In COVID-19 phenotype 1, lung compliance typically is not markedly affected, whereas gas exchange and hypoxia deteriorate rapidly due to microthrombosis, with increased wasted ventilation, and reduced ventilation/perfusion mismatch, while lung weight is lower [107]. On the other hand, in COVID-19 phenotype 2, lung weight is increased, with reduced compliance, increased wasted ventilation, and true shunting, whereas ventilation/perfusion mismatch is less compromised [106]. Indeed, COVID-19 patients receiving invasive MV show a decrease in lung volume and increase in poorly aerated or non-aerated lung tissue areas compared to patients receiving noninvasive respiratory support (NIRS) [108].

Therefore, the use of NIRS as a first-line strategy should be put within the context of COVID-19 phenotypes and considered especially for COVID-19 phenotype 1. In general, current recommendations moved from an early intubation approach at the onset of the pandemic to a more conservative one [109], distinguishing between COVID-19 phenotypes 1 and 2 in order to intubate early only those patients who clearly present with COVID-19 phenotype 2 or deterioration of phenotype 1 after NIRS. The recognition of patients who are at higher risk of NIRS failure is challenging [109] and should consider possible patient self-inflicted lung injury (P-SILI). NIRS methods include high-flow nasal oxygen (HFNO), noninvasive continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV). An initial strategy using non-invasive CPAP was found to reduce the risk of tracheal intubation or mortality compared to conventional oxygen therapy, while this was not confirmed for HFNO [110]. A brief period of awake prone positioning during NIRS can also be considered before moving forward to intubation [111]. In the presence of clinical deterioration or if patients already present with phenotype 2 (or H) on admission, intubation and invasive mechanical ventilation can be considered. This mode of ventilation should be set using a low VT of 4–6 mL/kg of PBW, low plateau pressure <28–30 cmH_2O, and moderate levels of PEEP (10 to 15 cmH_2O) according to individual patient response and requirements [111]. When lung compliance is preserved and areas of atelectasis are few, low to moderate rather than high PEEP levels might be indicated [111]. Hence, a strategy for the early phase (with predominance of low ventilation/perfusion areas) would comprise higher oxygen fraction and moderate levels of PEEP, while in the late stage (predominance of shunt), higher PEEP levels (but not exceeding 15 cmH_2O) might be suggested, given that poor response to oxygen is expected [111]. Regarding the use of prone positioning during invasive mechanical ventilation in patients with COVID-19 ARDS, there is no agreement in the literature as to which patients may benefit from this strategy. In general, more severe patients with COVID-19 phenotype 2 are considered eligible. The main rationale is that the improvement in oxygenation achieved with prone positioning allows a more homogeneous distribution of ventilation and perfusion, reducing the risk of VILI. This improvement in oxygenation is often associated with redistribution of perfusion (anti-gravitational as compared with non-COVID-19 ARDS) rather than effective alveolar recruitment in COVID-19 [28, 112]. Although prone positioning led to an improvement in oxygenation, this improvement was not always associated with better survival [113–115]. Moreover, the identification of "responders" to prone positioning among patients with COVID-19 is highly heterogeneous by definition [113, 115, 116], due to such factors as the use of different thresholds for defining an improvement in oxygenation. Some studies also identified a higher mortality in "non-responders" [114]. APRV and RMs could be considered in patients with COVID-19 and ARDS who do not improve despite optimization of mechanical ventilation. The use of VV-ECMO in patients with COVID-19 ARDS should be considered individually, based on a careful evaluation of risks, benefits, and available resources (*i.e.*, ECMO center, ICU beds and staff). Indications for initiation of VV-ECMO in COVID-19 overlap with those for non-COVID-19 ARDS. The main difference between these two entities of ARDS is represented by the constrained availability of resources within the context of a pandemic, as patients with COVID-19 exhibit mortality rates similar to those of historical VV-ECMO cohorts [117].

6. Summary

Mechanical ventilation in patients with ARDS has changed markedly over the last decades. A recommended approach is that of keeping V_T, P_{PLAT}, ΔP, and MP low. Several rescue

therapies, including neuromuscular blocking agents, vasodilators, prone positioning, RMs, and VV-ECMO, may be used in severe ARDS. An individually tailored mechanical ventilation strategy based on each patient's characteristics might be the cornerstone of future enhancement of MV in ARDS and may represent a promising approach for respiratory diseases with presentations like ARDS, such as COVID-19.

AUTHOR CONTRIBUTIONS

DB designed and wrote the manuscript; PRMR designed, wrote, edited, and approved the manuscript; PP edited and approved the manuscript. All authors read and approved the submitted manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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