Mechanical Ventilation in ARDS

5

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Contents

5.1 General Principles

Since its first description in 1967, many aspects of acute respiratory distress syndrome (ARDS) have changed, including understanding of its pathophysiology, diagnostic criteria and definitions (see Table 5.1), therapeutic strategies, and even the meaning of the "A" within the acronym "ARDS" (which initially stood for

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Table 5.1 Acute Respiratory Distress Syndrome (ARDS) diagnostic criteria according to the current (Berlin) definition [4] and to the early American-European Consensus Conference [5].*PaO_2* Arterial oxygen partial pressure, *FiO_2*Inspiratory oxygen fraction, *PEEP* Positive end-expiratory pressure, *CPAP* Continuous positive airway pressure, *ALI* Acute Lung Injury

Berlin ARDS definition (2012)	American-European Consensus Conference ARDS definition (1994)
Impaired oxygenation:[a] • *Mild ARDS.* $PaO_2/FiO_2 \leq 300$ (but >200) mmHg with PEEP/CPAP ≥5 cm H_2O • *Moderate ARDS.* $PaO_2/FiO_2 \leq 200$ (but >100) mmHg with PEEP ≥5 cm H_2O • *Severe ARDS.* $PaO_2/FiO_2 \leq 100$, with PEEP ≥5 cm H_2O	Impaired oxygenation:[a] • *ALI.* $PaO_2/FiO_2 \leq 300$ (but >200) mmHg • *ARDS.* $PaO_2/FiO_2 \leq 200$ mmHg

[a]In association (in summary) with acute onset, bilateral pulmonary infiltrates at chest imaging, and no cardiac disease as the leading cause

"adult") [1–6]. However, ARDS remains a major critical care issue, accounting for about 10% of intensive care unit (ICU) admissions, with an in-hospital/ICU mortality still around 40% [2, 6].

Both pathophysiology and clinical management of ARDS are linked to the mechanisms of ventilator-induced lung injury (VILI), firstly, because the risk of VILI is increased in ARDS patients due to a disruption of lung architecture, which leads to poorly compliant and heterogeneously aerated lungs [2, 3, 7], and, secondly, because mechanical ventilation itself may act as a second "hit" that causes ARDS in the presence of pulmonary (e.g., pneumonia, aspiration of gastric content, toxic inhalation, lung contusion, near-drowning) or extra-pulmonary (e.g., sepsis, trauma, burns, pancreatitis, blood transfusion, cardiopulmonary bypass) predisposing inflammatory insults [8, 9].

Lung-protective ventilation (LPV) and prone positioning (PP) are currently the two cornerstones of ARDS treatment. LPV with low tidal volumes (V_T), moderate-to-high levels of positive end-expiratory pressure (PEEP) and, possibly, recruitment maneuvers (i.e., a transitory increase in transpulmonary pressure aimed at opening atelectatic alveoli) may prevent or attenuate VILI [2, 7, 8] and has been widely shown in randomized controlled trials (RCTs) to reduce mortality in ARDS patients [10–13]. However, evidence about the favorable effects in terms of survival of PEEP and recruitment maneuvers is not as conclusive as that about low V_T [14, 15]; on the contrary, a recent investigation suggested possible harm from lung recruitment and PEEP titration strategies [16].

Mechanical ventilation in the prone position has been shown for over 40 years to improve oxygenation in ARDS patients [17, 18], but only in recent years a large multicenter RCT [19] (as well as several meta-analyses [20–22]) succeeded in demonstrating a reduced mortality with this intervention.

In this chapter, we discuss the main evidences about the role of LPV and PP in reducing mortality among ARDS patients, the pathophysiological mechanisms through which these interventions are believed to improve survival, and their use in

clinical practice. Moreover, other therapeutic strategies related to mechanical ventilation which have been investigated for a possible role in improving outcomes (including mortality) in ARDS patients, such as pressure-controlled ventilation as compared with volume-controlled ventilation, high-frequency oscillatory ventilation (HFOV), use of esophageal pressure for PEEP titration, and targeting mechanical ventilation according to driving pressure, are briefly discussed.

5.2 Main Evidences

5.2.1 Lung-Protective Ventilation

LPV is one of the interventions best proven to affect mortality in critically ill patients [23]. In fact, as many as three multicenter RCTs found a significant reduction in mortality with LPV in ARDS patients [11–13].

In 1998, Amato et al. [11] randomly assigned 53 patients with early ARDS to receive conventional ventilation or LPV. Conventional ventilation consisted in V_T = 12 mL/kg of body weight with a target arterial partial pressure of carbon dioxide (P_aCO_2) of 35–38 mmHg and the lowest PEEP allowing acceptable oxygenation while LPV was intended as V_T < 6 mL/kg with permissive hypercapnia (P_aCO_2 up to 80 mmHg) and PEEP above the lower inflection point (P_{flex}) on the static pressure-volume curve. A dramatic reduction in 28-day mortality in the latter group (38 vs 71%, $p < 0.001$) was reported, together with significantly lower rates of barotrauma (7 vs 42%, $p = 0.02$).

The ARDS Network trial [12], published 2 years later, enrolled 861 patients (from ten ICUs) with acute lung injury (ALI) or ARDS (according to the definitions at that time, see Table 5.1). Patients were randomized to receive either low-V_T ventilation or "traditional" ventilation. In the former group, V_T was initially set at 6 mL/kg of predicted body weight (PBW) (Fig. 5.1) [2, 12, 13] and was subsequently reduced, if necessary, in order to maintain a plateau pressure (P_{PLAT}; i.e., the airway pressure measured after a 0.5 s inspiratory pause) ≤ 30 cm H_2O. The control

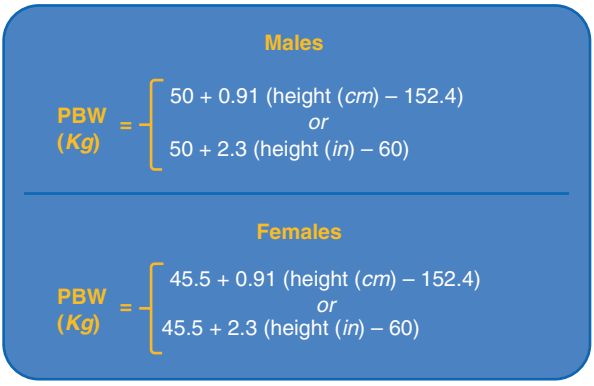

Fig. 5.1 Calculation of predicted body weight (PBW). *Cm* Centimeters, *in* Inches. Modified from Silversides and Ferguson [2] Copyright © 2013 BioMed Central Ltd.

group received an initial V_T of 12 mL/kg PBW, subsequently reduced if necessary, to maintain a $P_{PLAT} \leq 50$ cm H_2O. Unlike the previous study, PEEP was similar in the two groups. Mortality before home discharge without ventilatory assistance was significantly less in the low-V_T group (31 vs 39.8%, $p = 0.007$). No differences in the incidence of barotrauma were found.

Finally, Villar and colleagues [13] enrolled 103 ARDS patients (from eight ICUs) and showed a significant reduction in mortality (32 vs 53.3%, $p = 0.04$) among patients ventilated with $V_T = 5–8$ mL/kg PBW and initial PEEP 2 cm H_2O above P_{flex} as compared with those ventilated with higher V_T (9–11 mL/kg PBW) and lower PEEP (≥5 cmH_2O). No difference in the incidence of barotrauma was found in this study as well.

Although two of the three above-mentioned investigations included higher levels of PEEP as part of an LPV strategy, two subsequent meta-analyses of multicenter RCTs comparing higher PEEP (with or without recruitment maneuvers) versus lower PEEP, with similar (low) V_T between groups, failed to show a clear benefit of higher PEEP on survival in ARDS patients [14, 15]. Most remarkably, the recent Alveolar Recruitment for ARDS (ART) trial [16] randomized 1010 patients with moderate-to-severe ARDS (see Table 5.1) from 120 ICUs to either an open lung strategy involving recruitment maneuvers and PEEP titration according to the best respiratory system compliance or to a conventional low-PEEP strategy: both 28-day and 6-month mortality were higher in the experimental group as compared with the conventional control group (55.3 vs 49.3%, hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.01–1.42, $p = 0.04$ and 65.3 vs 59.9%, HR1.18, 95%CI 1.01–1.38, $p = 0.04$, respectively). Moreover, patients in the experimental group had significantly fewer mean ventilator-free days and an increased risk of barotrauma and pneumothorax requiring drainage, while no differences were found in ICU and hospital length of stay (LOS) as well as in ICU and in-hospital mortality.

5.2.2 Prone Positioning

After a series of major investigations yielding neutral results with regard to a possible role of PP in reducing mortality among ARDS patients [24–27], the PROSEVA trial by Guérin et al. [19] was the first (and it remains the only) RCT which reported a significant reduction in mortality with PP in ARDS patients. Nonetheless, the evidence provided acquires strength when considering the progressive refinements that the study design has undergone over time, especially as compared with the earliest large RCTs. In particular, the duration of PP was far higher (17–18 h per day, on average) in the newer studies [26, 27] than in the two older studies (<10 h per day) [24, 25]. Moreover, only the most recent of the previous RCTs [27] limited enrollment to the most severe ARDS patients ($PaO_2/FiO_2 \leq 200$ mmHg with PEEP ≥5 cm H_2O) and employed a strict LPV protocol. Finally, the PROSEVA trial [19] featured a more homogeneous population, in terms of ARDS severity, and a longer duration of PP, which can both explain the differences in the results compared to the older trials [28–30].

The PROSEVA trial [19] included 466 patients (from 27 ICUs) with "severe" ARDS, defined as $PaO_2/FiO_2 < 150$ mmHg in patients receiving LPV with $V_T \approx 6$ mL/kg PBW, PEEP ≥5 cm H_2O and $FiO_2 \geq 0.6$ (with these criteria persisting after a stabilization period of 12–24 h, in order to select the most severe cases) [30]. Patients were randomized to either undergo early PP (within 1 h after randomization) or to be left supine. Additionally, the study included, among others [30] PP sessions of at least 16 h per day with prefixed criteria to stop them (on average, 17 h per day for 4 days), an experience >5 years with PP management in all centers involved, a minimized crossover between the two groups and more time spent on prone position, as compared with the investigation by Taccone et al. [27]. Mortality at 28 days was 16% in the prone group and 32.8% in the supine group ($p < 0.001$). A significant reduction in 90-day mortality (23.6 vs 41%, $p < 0.001$) was also found in the prone group.

These results are consistent with those of both patient-level [20] and study-level [21] meta-analyses of the previous RCTs. In addition, all the updated meta-analyses which included the PROSEVA trial have confirmed these findings [17, 29, 31].

5.2.3 Other Mechanical Ventilation Strategies

There is currently no clear evidence that pressure-controlled ventilation (PCV) may provide advantages in terms of survival over volume-controlled ventilation (VCV) in ARDS patients [32]. In the only RCT showing a significantly increased in-hospital mortality with VCV as compared with PCV, multivariate analysis suggested that such difference could not be attributable to the ventilatory mode [33].

High-frequency oscillatory ventilation (HFOV), consisting in delivering very low V_T at very high rates, is theoretically the perfect LPV strategy and has been suggested to provide potential benefits in ARDS patients [6]. However, the large multicenter OSCILLATE trial [34], which was stopped after randomization of 548 patients due to safety concerns, found a significantly increased in-hospital mortality in patients with moderate-to-severe ARDS randomized to early HFOV as compared with those receiving conventional LPV with low V_T and high PEEP (47 vs 35%, relative risk [RR] 1.33, 95% CI 1.09–1.64, $p = 0.005$). Routine use of HFOV is currently strongly discouraged [6].

The use of esophageal pressure (P_{ES}) to titrate PEEP in ARDS patients seemed to be a promising approach until recently [35], but the lately published EPVent-2 study [36], which included 200 patients (from 14 ICUs) with moderate-to-severe ARDS randomized to either P_{ES}-guided PEEP titration or empirical PEEP-FiO_2 setting, failed to show any difference between groups in 28-day mortality, days free from mechanical ventilation, or any other planned clinical endpoint.

Finally, a recent multilevel mediation analysis of nine previous RCTs suggested that driving pressure (i.e., the difference between P_{PLAT} and PEEP) rather than other ventilatory parameters is strongly associated with mortality in ARDS patients [37]. However, currently available evidence does not support targeting driving pressure when setting mechanical ventilation in ARDS patients, particularly if this means increasing PEEP [6, 38].

5.3 Pathophysiological Principles: Mechanisms of Reduced Mortality

ARDS is characterized by diffuse alveolar-capillary membrane disruption that results in increased permeability and subsequent pulmonary edema and atelectasis. Alveolar damage however is not homogeneously distributed, as atelectasis mainly affects the dependent lung regions (namely, those most subjected to hydrostatic pressure) while non-dependent regions remain better aerated [2, 3, 7]. For these reasons, also the volume that needs to be ventilated decreases (hence the term "baby lung") [3].

Although barotrauma (e.g., pneumothorax) may occur as a consequence of mechanical ventilation with high volumes, the main determinant of VILI is thought to be alveolar overdistension (volutrauma) rather than airway pressure [7]. Therefore, it is reasonable that low-V_T ventilation prevents or minimizes VILI in ARDS patients, by avoiding overinflation of the decreased normally aerated regions. However, VILI can occur even during a low-V_T ventilation, due to cyclic alveolar opening and closure (atelectrauma), which leads to epithelial sloughing, hyaline membranes, and pulmonary edema [2, 7]. Since atelectrauma is intensified in the presence of broad heterogeneities in ventilation [7], as in ARDS, higher levels of PEEP may contribute to minimize VILI by reducing alveolar collapse during expiration [2, 7].

Prone positioning improves oxygenation, often considerably, due to a reduction in intrapulmonary shunt: while blood flow distribution remains essentially unchanged (thus prevailing into dorsal regions), the conversion from the supine to prone position induces an increase in aeration in dorsal regions that exceeds ventral derecruitment [18, 28, 30]. As a consequence, in addition to lung ventilation and ventilation-to-perfusion ratio [39], also transpulmonary pressure and lung densities are more homogeneously distributed along the ventral-to-dorsal axis.

The primary determinant of these effects is the shape matching between the conically shaped lungs and the cylindrically shaped chest wall (see Fig. 5.2) [28] that implies a greater distention in the ventral lung regions [18]. Since the hydrostatic pressure (i.e., the forces due to gravity) is always greater in the regions that lie below (the so-called dependent regions), in the prone position it mainly acts on ventral regions, where it is counteracted by regional expansion. In other words, there is a larger volume of dependent lung in supine position as compared to prone [39]. Other factors, such as the reduced compression of lung tissue by the heart, contribute to the more homogeneous distribution of lung density/inflation in the prone position [18, 28, 39].

Improvement in oxygenation however does not seem to be the primary mechanism of mortality reduction by PP. Indeed, a retrospective analysis of data from the PROSEVA trial showed that the reduction in mortality observed in ARDS patients receiving prone ventilation was not dependent on whether PP improved gas exchange [40].

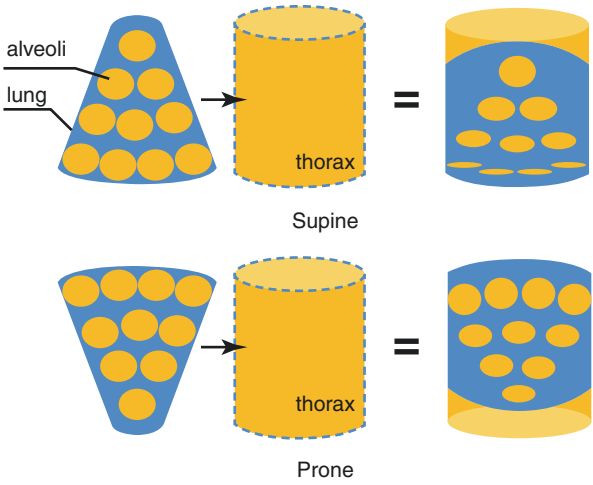

Fig. 5.2 The greater lung expansion in ventral regions, due to shape matching between lung and thorax, counteracts hydrostatic pressure, which acts mostly on those ventral regions in the prone position. This leads to a more homogeneous inflation of alveoli along the ventral-to-dorsal axis in the prone position, as compared to supine. Adapted from Gattinoni et al. [18] with permission

The survival benefit may be rather attributed, also for PP, to the prevention of VILI [18, 28, 30, 40, 41], whose major determinants are, as mentioned, volutrauma (pertaining to lung stress, namely the increase in transpulmonary pressure), and atelectrauma [2, 30]. The more uniform distribution of the gravitational transpulmonary pressure gradient, as well as of both V_T and end-expiratory lung volume, results in a homogenization of the strain (i.e., the V_T to end-expiratory lung volume ratio) imposed by mechanical ventilation and, consequently, in a reduction of the resulting stress [18, 28, 30]. Finally, a more uniformly distributed V_T translates into a reduced atelectrauma [40], and improvements in PaO_2/FiO_2 ratio resulting from PP may itself indirectly contribute to the prevention of VILI by reducing the need for iatrogenic interventions to sustain oxygenation [18].

5.4 Therapeutic Use

Low-V_T ventilation (with $P_{PLAT} \leq 30$ cm H_2O) is indicated in patients with ARDS of any severity [42, 43]. However, probably not all ARDS patients (e.g., those with stiff chest wall and, consequently, high pleural pressure) really need a so low P_{PLAT} (and V_T) in order to avoid alveolar overdistension [7].

Low-V_T ventilation often results in hypercapnia and acidosis, with possible metabolic complications such as acute hyperkalemia [2, 9]. These abnormalities can be counteracted by increasing respiratory rate (RR), but it should be considered that high RR (usually >30 breaths/min) may lead to dynamic hyperinflation and auto-PEEP [9]. However, since low-V_T ventilation was shown to reduce mortality despite hypercapnia [11, 12], it may be speculated that the latter itself may be beneficial due to rightward shift of the oxy-hemoglobin dissociation curve, systemic and microcirculatory vasodilation, and inhibitory effects on inflammatory cells. Moreover, mean

pCO_2 levels of 66.5 mmHg or higher and a pH up to 7.15 can be tolerated unless specific contraindications exist, such as increased intracranial pressure [2].

A discussion of the use of "ultraprotective" ventilator strategies ($V_T \approx 3$ mL/kg PBW) in association with extracorporeal arteriovenous CO_2 removal or extracorporeal membrane oxygenation (ECMO) is beyond the scope of this chapter.

As mentioned, the role of PEEP and recruitment maneuvers in the treatment of ARDS is not as definite as that of low V_T. Higher levels of PEEP should be reserved for moderate-to-severe forms of ARDS [43]. Maybe, in patients with mild ARDS (and possibly in a proportion of patients with a more severe disease), the potential adverse effects of higher PEEP levels (e.g., impairment of venous return, circulatory depression, lung overdistension) may overcome the advantages [7, 14]. Clinical trials could have failed to show clear benefits of high PEEP levels [14, 15], or even highlighted possible harms [16], due to the difficult in tailoring PEEP on the single patient. In fact, lung inflation is strictly dependent on transpulmonary pressure (P_{TP}), that is the difference between alveolar and pleural pressure: since pleural pressure is broadly and unpredictably variable among ARDS patients, it is difficult to determine which level of PEEP is needed to prevent alveolar collapse and, therefore, atelectrauma in the individual patient [7]. Finally, some concerns exist about the possible complications of recruitment maneuvers, including transient desaturation, hemodynamic impairment, pneumothorax, and even worsening of VILI [2, 7].

Prone positioning is strongly recommended in patients with severe ARDS [43]. In order to be effective in reducing mortality, PP should be initiated early and maintained for at least 12 h per day (even if maybe >16 is better) until stable improvement in oxygenation is achieved (optimal duration of PP has yet to be established [29]). Contraindications are few and not well defined: conditions such as pelvic/spinal instability, severe facial or neck trauma, open wounds/burns on the ventral body surface, non-stabilized fractures, increased intracranial pressure, hemodynamic instability, serious cardiac arrhythmias and pregnancy should preclude PP or, at least, impose a careful evaluation of the risks/benefits balance [18, 41, 44].

A skilled and well-coordinated team is pivotal in order to avoid potentially serious complications, including endotracheal tube displacement, kinking or obstruction, and vascular lines kinking/removal [17–19, 29, 41, 44]. Finally, although a higher risk of pressure ulcers was reported by previous trials and meta-analyses [17, 29], and also confirmed in an ancillary study of the PROSEVA trial [45], it is not clear whether such findings are related to PP itself or to the greater survival which results from it [30, 45].

Clinical summary					
Technique	Indications	Cautions	Side-Effects	Dose	Notes
Protective ventilation (low tidal volume with or without high PEEP and recruitment maneuvers)	All ARDS patients (low V_T) Moderate-to-severe ARDS patients (low V_T + high PEEP)	Hypercapnia may be hazardous in patients with increased intracranial pressure Excessive respiratory rate may lead to dynamic hyperinflation and auto-PEEP	Low V_T: • hypercapnia • acidemia • acute hyperkalemia High PEEP and recruitment maneuvers: • hemodynamic impairment • lung overdistension • pneumothorax • possible increase in mortality	Initial $V_T$of 6 mL/kg of predicted body weight (adjusted to maintain $P_{PLAT} \leq 30$ cm H_2O) Initial PEEP 2 cm H_2O above P_{flex} (adjusted according to oxygenation)	The role of PEEP and recruitment maneuvers has to be further clarified PEEP titration guided by esophageal pressure does not seem to affect outcomes High-frequency oscillatory ventilation may increase mortality No clear differences between volume-controlled and pressure-controlled ventilation
Prone positioning	Severe ARDS Moderate-to-severe ARDS (PaO_2/FiO_2 < 150 mmHg)	Possible contraindications: • pelvic/spinal instability • severe facial or neck trauma • increased intracranial pressure • open wounds/burns on the ventral body surface • non-stabilized fractures • hemodynamic instability/serious arrhythmias • pregnancy	Major airway problems: • endotracheal tube kinking/obstruction • endotracheal tube displacement (unplanned extubation or selective main stem bronchus intubation) Pressure ulcers (debated)	At least 12 h per day (maybe >16 h/day could be better, but the optimal daily duration is unknown)	Must be associated with protective ventilatory strategies Requires high experience and specifically trained personnel Feasible during ECMO

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