Ventilation Strategies: Tidal Volume and PEEP

3

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3.1 Introduction

Acute respiratory distress syndrome (ARDS), defined as an increment in the lung alveolar-capillary membrane permeability causing a pulmonary edema rich in proteins, has been recently reclassified as mild, moderate, and severe according to Berlin definition [1]. It occurred in 1.8–10% of ICU admissions [1–3] and presents a progressively higher mortality ratio from its mild (34.9%) to the more severe form of presentation (46.1%) [3].

3.2 Respiratory System Structural Dysfunction After ARDS

After the initial lung insult, resulting from the exposition of a genetic predisposing patient to a risk factor (pulmonary infection, sepsis, acid-gastric lung aspiration, etc.), epithelial and endothelial lung barriers can be disrupted liberating, respectively, receptors for advanced glycation end products (RAGE) and angiopoietin-2. The extravasation of plasma inside the alveolar space turns an air-filled lung into a heavy high-osmotic pressure liquid-filled lungs. As a consequence, the higher weight of the lungs under the action of the gravity force predisposes the lowermost lung regions to collapse (Fig. 3.1) provoking a higher intrapulmonary shunt, a refractory hypoxemia, and a decrease in lung compliance. The functional alterations of the respiratory system are expressed by a decrease in the functional residual capacity (FRC) and a shift of the respiratory system pressure-volume curve down and to the right. The clinical manifestations are a dyspneic and hypoxemic patient with a high work of breathing that needs a high nasal flow oxygen system,

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D. Chiumello (ed.), *Acute Respiratory Distress Syndrome (ARDS)*,
DOI 10.1007/978-3-319-41852-0_3

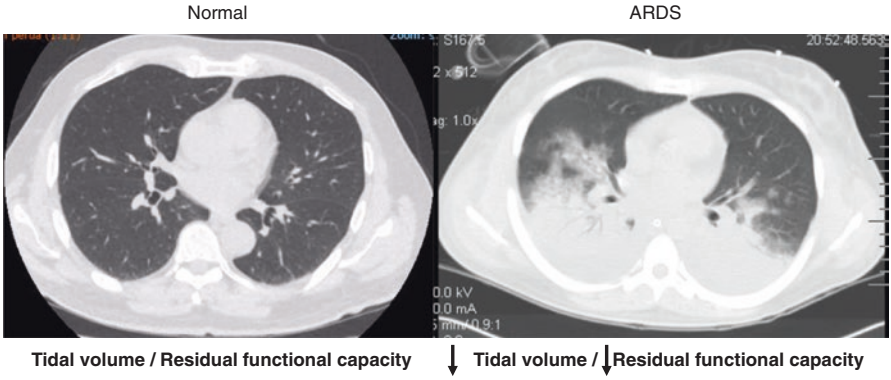

Fig. 3.1 Normal thoracic tomography versus ARDS thoracic tomography (Reprinted with permission from Medical Evidence Percorso Formativo 2015, yr. 8, n. 104, www.ati14.it)

noninvasive ventilation or intubation, and invasive mechanical ventilation to support the patient's gas exchange and respiratory system mechanics while the clinical treatment and avoidance of the risk factors start [4, 5].

3.3 Tidal Volume and PEEP During Spontaneous Ventilatory Support in ARDS Patients

Recently, Frat and colleagues [6] showed that high-flow oxygen through nasal cannula (HFNC= 48 ± 11 L/min) can be used in hypoxemic respiratory failure (PaO_2/FiO_2 ratio less than 300, 79% of these patients with bilateral pulmonary infiltrates) with an intubation rate of 38% in the high-flow oxygen group, 47% in the standard oxygen group, and 50% in the noninvasive ventilation group (p = 0.18; p = 0.17 by the log-rank test). Ventilator-free days at day 28 was significantly lower in high-flow oxygen group as well as crude in ICU and 90-day mortality. One of the hypothesis generated by this study was that the high tidal volume of 9 mL/kg/predicted body weight achieved by the NIV group could be responsible for its poor result. At 1 h after enrollment, the intensity of respiratory discomfort was reduced, and the dyspnea score was improved with the use of high-flow oxygen nasal cannula, as compared with standard oxygen group and NIV generating the hypothesis that HFNC could decrease the patient's inspiratory efforts and their transpulmonary pressures and possibly decreasing their induced lung injury.

Messica and colleagues [7] studied in a 1-year observational study 87 patients with ARDS that received HFNC at least once during their ICU stay. Of those, 45 subjects received HFNC as first-line treatment for respiratory failure, and intubation was needed in 40% of the patients. In the multivariate analysis, SAPS II was significantly associated with intubation requirement.

The role of spontaneous inspiratory effort, intensity of inspiratory muscle activity, and size of tidal volume achieved during spontaneous ventilatory support (Standard oxygen, HFNC or NIV) and their association with ARDS patient outcomes must be better studied in the future. Most of the studies of ARDS patients that needed NIV used low EPAP/PEEP levels (from 0 to 10 cmH_2O). The role of higher PEEP levels or individual PEEP titration in this ARDS population are still not elucidated.

3.4 Invasive Mechanical Ventilation in ARDS Patients: Role of Tidal Volume

It is well documented that lower tidal volumes (6 mL/kg of predicted body weight) compared to higher tidal volumes (12 mL/kg of predicted body weight) associated with PEEP levels titrated by a PEEP/FiO_2 table reduced mortality in a randomized, clinical trial that analyzed 861 ARDS patients (ARMA trial) [8]. In the ARMA trial, lower tidal volumes led to lower levels of plasma IL-6, IL-8 ,and TNFR1 over the subsequent 1–3 days [9].

So, low tidal ventilation (≤6 mL/kg of predicted body weight) must be initiated as soon as the ARDS patient is intubated and mechanically ventilated. The predicted body weight (PBW) can be calculated as follows: for women, PBW= 45.5 + 0.91 (height in centimeters – 152.4) and, for men, PBW = 50.0 + 0.91 (height in centimeters −152.4). It is important to adjust tidal volume to lung size that depends on the height and sex but, more importantly, to adjust the tidal volume to functional lung size that depends on the ARDS severity (lung compliance), sex, height, and chest wall compliance. It also depends where in the pressure-volume curve of the respiratory system the tidal ventilation takes place, even more, the interaction between the FRC (functional residual capacity) and tidal ventilation inside the thoracic cage during controlled ventilation. During assisted ventilation other two factors must be added to the interaction between the FRC and above tidal ventilation inside the thoracic cage: the patient's negative inspiratory efforts, and the pressures that resulted from the desynchronization between the patient and the mechanical ventilator. Recent evidences showed that in severe ARDS, patients' inspiratory efforts during assisted ventilation could worsen ventilator lung injury induced by the mechanical ventilation during the ventilatory support of the ARDS patients [10]. This associated and added injury could explain the results of a phase IV randomized controlled trial in moderate/severe ARDS patients (PaO_2/FiO_2 < 150); comparing cisatracurium to placebo for 48 h showed an improved adjusted 90-day survival rate and increased ventilator-free in the cisatracurium group without a significant increase in muscle weakness. Short-term paralysis may facilitate patient-ventilator synchrony in the setting of lung-protective ventilation. Short-term paralysis would eliminate patient triggering and expiratory muscle activity. In combination, these effects may serve to limit regional overdistention and cyclic alveolar collapse. Paralysis may also act to lower metabolism and overall ventilatory demand [11].

At the same time that a low tidal volume is set, an adequate respiratory rate must be concurrently set in order to keep a minute ventilation around 7–8 L/min and a $PaCO_2$ around 40–60 mmHg and a pH above 7.2. In the more severe ARDS patients, sometimes after the adjustment of a minute ventilation around 8 L/min with tidal volumes lesser than 6 mL/kg of predicted body weight, the $PaCO_2$ levels stay above 80 mmHg and pH less than 7.2 (specially patients with septic shock and metabolic acidosis). In these cases, the VCO_2 must be assessed and be kept as least as possible (fever control, low carbohydrate intake), and hemodialysis can be initiated (specially in ARDS patients with concomitant acute renal failure) in order to help control the metabolic acidosis. Efforts must be taken to decrease the pulmonary death space by means of recruitment maneuvers and PEEP titration, tidal volume and respiratory rate adjustments, or even the initiation of prone ventilation. In the most difficult cases, tracheal gas insufflation or extracorporeal CO_2 removal or extracorporeal oxygenation should be started in order to keep the protective low tidal volume ventilation [4].

Potentially harmful consequences of permissive hypercapnia include pulmonary vasoconstriction and pulmonary hypertension, proarrythmic effects of increased discharge of catecholamines, and cerebral vasodilation yielding increased intracranial pressure. Special attention should be given to patients with pulmonary hypertension and right ventricular dysfunction secondary to ARDS that could not tolerate high $PaCO_2$ and low pH levels [4].

Nonetheless, permissive hypercapnia should probably be used with caution in patients with heart disease and is relatively contraindicated in those with elevated intracranial pressure. In ARDS cases with pulmonary hypertension and right ventricular dysfunction, prone position ventilation should be preferred [4].

Recent evidence showed that prolonged prone position ventilation (16 h) must be used in early ARDS with PaO_2/FiO_2 <150 with PEEP levels of or more than 5 cmH_2O in order to significantly improve 90-day mortality compared to supine ventilation [12]. Recent meta-analysis also showed that in the era of low tidal ventilation, the prone position use improved mortality of moderate/severe ARDS patients that needed invasive mechanical ventilatory support [13]. If PEEP titration during prone position ventilation should improve survival of ARDS patients is still a matter of debate [14].

Another recent approach for application of extracorporeal carbon dioxide removal new devices (ECMO-R) in ARDS patients is the demonstration that in severe ARDS, even the low tidal volume ventilation with 6 mL/kg of predicted body weight can cause tidal hyperdistension in the nondependent regions of the lungs accompanied by plateau airway pressures greater than 28 cmH_2O and elevated plasma markers of inflammation. In this group application of ECMO-R could allow the authors to decrease the tidal volume to less than 6 mL/kg with a consequent plateau pressure less than 25 cmH_2O that was associated with a lower radiographic index of lung injury and lower levels of lung-derived inflammatory cytokines [15]. However, prognostic implication of this new ECMO-R devices application in clinical practice is still under investigation [16].

Pumpless interventional lung assist (iLA) is also used in patients with ARDS and is aimed at improving extracorporeal gas exchange with a membrane integrated in a passive arteriovenous shunt. iLA serves as an extracorporeal assist to support mechanical ventilation by enabling low tidal volume and a reduced inspiratory plateau pressure in extremely severe ARDS patients. Zimmermann and colleagues used iLA in 51 severe ARDS patients and observed a decrease in $PaCO_2$ allowing the decrease in tidal volume and plateau pressure (ultraprotective ventilation) with a hospital mortality rate of 49% [17]. Recently, Fanelli and colleagues described the feasibility and safety of use of an ultraprotective strategy using 4 mL/kg of predicted body weight associated with low-flow extracorporeal carbon removal in 15 moderate ARDS patients [18].

3.5 Limiting the Tidal Volumes in ARDS with Modern Ventilators

Recently, Wing and colleagues [19] showed that modern ventilators have an increasing number of optional settings that can change the size of the delivered tidal volume. These settings may increase the delivered tidal volume and disrupt a low tidal volume strategy. Recognizing how each setting within a mode affects the type of breath delivered is critical when caring for ventilator-dependent patients. The AVEA has two options in volume A/C: demand breaths and V-sync. When activated, these options allow the patient to exceed the set tidal volume. When using the Evita XL, the option Auto-Flow can be turned *on* or *off*, and when this option is *on*, the tidal volume may vary. The PB 840 does not have any additional options that affect volume delivery, and it maintains the set tidal volume regardless of patient effort. The SERVO-i's demand valve allows additional flow if the patient's inspiratory flow rate exceeds the set flow rate, increasing the delivered tidal volume; this option can be turned *off* with the latest software upgrade. The continuous monitoring of the low tidal volumes during the ARDS ventlatory support must be implemented in our ICUs in order to guarantee that a protective ventilation is continuously offered to our ARDS patients.

3.6 Low Tidal Volumes Must Generate Low Driving Pressures to Assure It Is Really Protective to ARDS Patients

Recently, Amato and colleagues [20] hypothesized that driving pressure ($\Delta P = VT/CRS$), in which VT is intrinsically normalized to functional lung size (instead of predicted lung size in healthy persons), would be an index more strongly associated with survival than VT or PEEP in patients who are not actively breathing. Using a statistical tool known as multilevel mediation analysis to analyze individual data from 3562 patients with ARDS enrolled in nine

previously reported randomized trials, they examined Δp as an independent variable associated with survival. In the mediation analysis, they estimated the isolated effects of changes in Δp resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease. The authors observed that among ventilation variables, Δp was most strongly associated with survival. A 1-SD increment in Δp (approximately 7 cm of water) was associated with increased mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31–1.51; $p < 0.001$), even in patients receiving "protective" plateau pressures and VT (relative risk, 1.36; 95% CI, 1.17–1.58; $p < 0.001$). Individual changes in VT or PEEP after randomization were not independently associated with survival; they were associated only if they were among the changes that led to reductions in Δp (mediation effects of Δp, $p = 0.004$ and $p = 0.001$, respectively). They concluded that Δp was the ventilation variable that best stratified risk. Decreases in Δp owing to changes in ventilator settings were strongly associated with increased survival.

3.7 Invasive Mechanical Ventilation in ARDS Patients: Role of End-Positive Expiratory Pressure (PEEP) Levels

Recently, three large clinical trials [21–23], including acute lung injury/ARDS patients ventilated with low tidal volume, have compared different PEEP strategies (high vs. low), but none of them could show a significant difference in mortality. Moreover, a recent meta-analysis has pooled those trials [24], revealing some combined benefit of the high PEEP strategy; still, the survival benefit was modest and limited to the subgroup of ARDS patients with $PaO_2/FiO_2 < 200$. Conceptually, one could argue that none of the "high PEEP" strategies was designed to test the "open-lung hypothesis" postulated by Lachmann [25–28], that is, the hypothesis that most of the collapsed lung tissue observed in early ARDS can be reversed at an acceptable clinical cost, potentially resulting in better lung protection. According to a recent study by Borges and colleagues [29], a straight test of the "open-lung hypothesis" would certainly require more aggressive recruiting maneuvers in association with individualized, decremental PEEP titration. Thus, one can speculate that the limited results reported above were related to suboptimal ventilatory strategy. Recently, de Matos and colleagues [30] reported the experience with maximal recruitment rtrategy (MRS) in 51 patients with ARDS. MRS consisted of 2-min steps of tidal ventilation with pressure-controlled ventilation, fixed driving pressure of 15 cmH_2O, respiratory rate of 10 breaths/minute, inspiratory/expiratory ratio of 1:1, and stepwise increments in PEEP levels from 10 to 45 cmH_2O (recruitment phase). After that, PEEP was decreased to 25 cmH_2O and, then, from 25 to 10 cmH_2O (PEEP titration phase) in steps of 5 cmH_2O, each one lasting 4 min. At each of the steps, computer tomography image sequences from the carina to the diaphragm were acquired during an expiratory pause of 6–10 s. Lung collapse was assessed online by visual inspection, for immediate clinical decision, and offline for quantitative measurements.

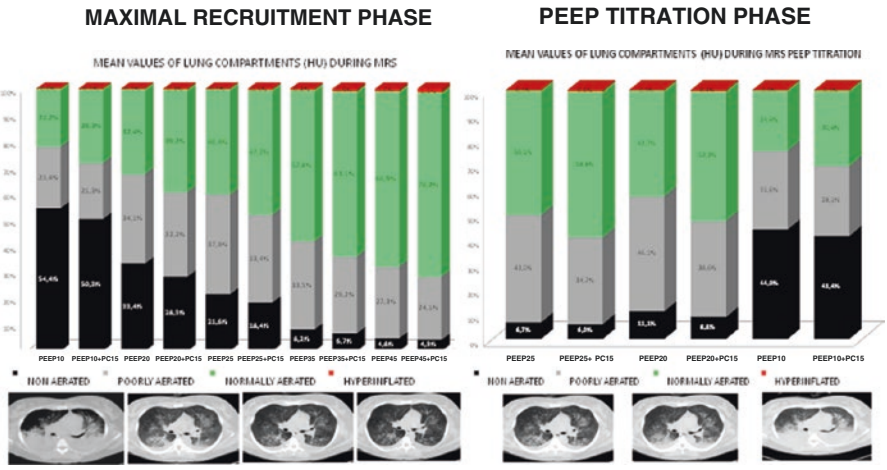

Fig. 3.2 Detailed thoracic Tomographic analysis of nonaerated (HU from −100 to +100U), poorly aerated (HU form −100 to −500 U), normally aerated (HU from −500 to −900U), and hyperinflated (HU more than −900U) in 12 patients with moderate/severe ARDS during maximal recruitment manuevers and PEEP titration (Reprinted with permission from Medical Evidence Percorso Formativo 2015, yr. 8, n. 104, www.ati14.it)

MRS showed a statistically significant decrease in nonaerated areas of the ARDS lungs that was accompanied by a significant increment in oxygenation. The opening plateau pressure observed during the recruitment protocol was 59.6 (±5.9 cmH_2O), and the mean PEEP titrated after MRS was 24.6 (±2.9 cmH_2O). Mean PaO_2/FiO_2 ratio increased from 125 (±43) to 300 (±103; $p < 0.0001$) after MRS and was sustained above 300 throughout 7 days. Nonaerated parenchyma decreased significantly from 53.6% (interquartile range (IQR): 42.5–62.4) to 12.7% (IQR: 4.9–24.2) ($p < 0.0001$) after MRS. The potentially recruitable lung was estimated at 45% (IQR: 25–53). ICU mortality was 28% and hospital mortality was 32%. The independent risk factors associated with mortality were older age and higher driving pressures (or higher delta pressure control). There were no significant clinical complications with MRS or barotrauma. A better evolution of these ARDS patients with less necessity of oxygen supplementation in the recovery phase of the disease and a better quality of life must be tested in prospective, controlled clinical trials. A recent meta-analysis [23] showing beneficial effects on mortality using higher PEEP levels compared with lower PEEP in ARDS patients corroborates the results of our clinical case series of ARDS patients submitted to MRS. A detailed thoracic tomographic analysis performed in 12 of these ARDS patient thoracic computed tomographies during recruitment phase and PEEP titration phase showed a significant increment in normal aerated lungs and decrement of nonaerated during maximal recruitment maneuvers and PEEP titration (Fig. 3.2). These results demonstrated that keep sufficient PEEP levels after recruitment is crucial in ARDS patients (Fig. 3.3).

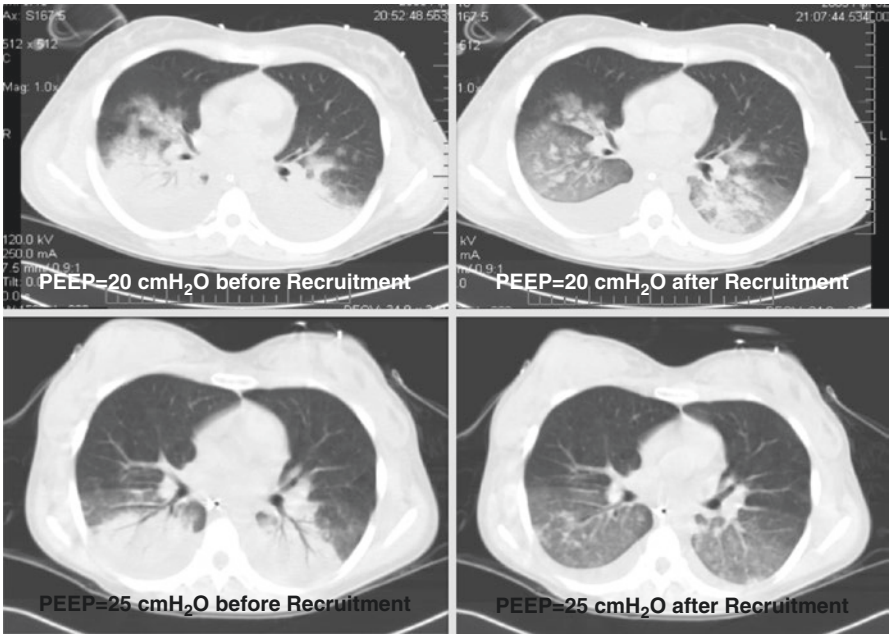

Fig. 3.3 Maximal recruitment manuevers can open up the collapsed lung in ARDS, and high PEEP levels are crucial to keep the lungs open (Reprinted with permission from Medical Evidence Percorso Formativo 2015, yr. 8, n. 104, www.ati14.it)

3.8 Interaction Between Low Tidal Volume and High PEEP Levels During Invasive Mechanical Ventilation in ARDS Patients

Amato and colleagues [31] demonstrated reduction in 28-day mortality in 53 ARDS patients submitted to recruitment maneuver (CPAP 40 cmH_2O) PEEP titrated by static Pressure × Volume ($P \times V$) curve associated with low tidal volume (VT = 6 mL/kg), compared to those ventilated with high VT (12 mL/kg) and low PEEP strategy. Villar and colleagues [32] found congruent results in a similar protocol in 103 ARDS patients. These two clinical, prospective, and control trials showed significant results in improving ARDS mortality with a relatively small number of patients indicating that should be an interaction between high PEEP and low tidal volume during invasive mechanical ventilation in ARDS patients, and static pressure-volume curve of the respiratory system of ARDS patients should be the best window to ventilate our ARDS patients.

Finally, perhaps, it would be important to optimize PEEP in each patient based on the respiratory characteristics. In ARDS, we have to deal with the transpulmonary pressure (airway pressure minus pleural pressure) at both end inspiration and end expiration. If we consider end inspiration, due to the high variability of chest wall to lung elastance ratio across the patients, similar pressure applied to the

airway opening can generate different changes in transpulmonary pressure. Consequently, the application of similar tidal volume and PEEP may have harmful or not harmful effects on the lung stress/strain depending on the patient's respiratory characteristics. In addition, for the same tidal volume, different PEEP levels may result in different degrees of ventilator-associated lung injury [33]. Talmor and colleagues [34], in a small single-center randomized controlled trial, individualized PEEP in order to achieve end expiratory transpulmonary pressure between 0 and 10 cmH_2O in ARDS patients for 3 days. They found higher PEEP levels, better oxygenation, and greater compliance of the respiratory system in the esophageal pressure PEEP-guided group as compared to the control group (gas exchange-based PEEP). End inspiratory transpulmonary pressure and mortality rate at 28 days were similar in the two groups.

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