Recruitment maneuvers in acute respiratory distress syndrome: The safe way is the best way

Raquel S Santos, Pedro L Silva, Paolo Pelosi, Patricia RM Rocco

Recruitment maneuvers (RMs) are a simple, low-cost, feasible intervention that can be performed at the bedside in patients with ARDS. RMs are characterized by the application of airway pressure to increase transpulmonary pressure transiently. Once non-aerated lung units are reopened, improvements are observed in respiratory system mechanics, alveolar reaeration on computed tomography, and improvements in gas exchange (functional recruitment). However, the reopening process could lead to vascular compression, which can be associated with overinflation, and gas exchange may not improve as expected (anatomical recruitment). The purpose of this review was to discuss the effects of different RM strategies - sustained inflation, intermittent sighs, and stepwise increases of positive end-expiratory pressure (PEEP) and/or airway inspiratory pressure - on the following parameters: hemodynamics, oxygenation, barotrauma episodes, and lung recruitability through physiological variables and imaging techniques. RMs and PEEP titration are interdependent events for the success of ventilatory management. PEEP should be adjusted on the basis of respiratory system mechanics and oxygenation. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (i.e., that providing the best balance of benefit and harm) and
the effects of RMs on clinical outcome are still under discussion, and further evidence is needed.

**Key words:** Recruitment maneuvers; Acute respiratory distress syndrome; Positive end-expiratory pressure; Transpulmonary pressure; Lung ultrasonography

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Core tip: Experimental and clinical studies show that stepwise recruitment maneuvers (RMs) improve oxygenation and lung aeration and are associated with less hemodynamic instability and inflammatory impact on lung tissue compared to traditional abrupt maneuvers. Patients with severe acute respiratory distress syndrome, characterized by increased edema and atelectasis, are good candidates for RMs. Patients whose oxygenation improves with increased pressure are at lower risk of death. Post-recruitment positive end-expiratory pressure (PEEP) titration is critical to maintaining stabilization of alveolar units and avoiding derecruitment. The use of individualized PEEP based on lung compliance might move clinical management forward.


**INTRODUCTION**

The acute respiratory distress syndrome (ARDS) is clinically characterized by severe hypoxemia, reduced lung compliance, and bilateral radiographic infiltrates[1]. Protective mechanical ventilation strategies, which are characterized by protective tidal volumes \( V_T = 6 \text{ mL/kg, predicted body weight (PBW)} \) and end-inspiratory (plateau) airway pressures lower than 28 cm H\(_2\)O, have been associated with improved survival in randomized clinical trials[2,3]. However, the use of protective \( V_T \) alone seems to be not enough to maintain homogeneous distribution of ventilation across different alveolar units[4]. In this line, \( V_T \) titrated to 6 mL/kg (PBW) may result in repetitive opening and closing of such units, which may result in atelectrauma unless sufficient positive end-expiratory pressure (PEEP) is applied. On the other hand, overdistension and disruption of alveolar units may develop if high PEEP values are used[5].

General anesthesia and neuromuscular blockade may potentiate the generation of atelectatic areas[6]. In a normal homeostatic condition, the sigh reflex maintains lung compliance and decreases atelectasis[7]. However, during mechanical ventilation, there is no sigh reflex. One possibly way to maintain oxygenation, functional residual capacity, and respiratory system elastance is the application of recruitment maneuvers (RMs), which have become a component of lung-protective ventilation strategies[6,9]. A recent systematic review suggested that, when included in ventilatory strategies, RMs reduced mortality by 6% in patients with moderate to severe ARDS[10]. Since this is only a slight improvement in mortality and no major differences in length of intensive care unit or hospital stay were observed, subsequent studies raised concerns regarding the beneficial effects and the safety of RMs.

This review sought to discuss: (1) the physiologic effects of RMs; (2) describe different types of RMs and their safety; (3) techniques of positive end-expiratory pressure titration; and (4) the future perspectives of RMs in the presence of protective ventilation strategies.

**PHYSIOLOGICAL EFFECTS OF RMS**

A RM is a dynamic, transient increase in transpulmonary pressure (difference between airway pressure and pleural pressure) which is directly proportional to the reopening of lung units. Its success and/or adverse events can be predicted by the magnitude of transpulmonary pressure, balancing the increase in aerated lung areas and the reduction of mechanical stress between the edge of collapsed and aerated areas[11]. Traditionally, RMs usually improve lung mechanics and oxygenation, but whether these are the only positives consequences of RM use remains unknown. Thus far, no randomized clinical trial has aimed to show whether the presence or absence of RM among the constituent elements of a protective ventilator strategy bundle makes a difference. A randomized clinical trial designed to answer this question with sufficient statistical power, the alveolar recruitment for ARDS trial, is ongoing. Nevertheless, important, physiologically based studies have attempted to answer key questions. In a prospective study of 16 mechanically ventilated patients with ARDS by Di Marco et al[12] divided participants into responders and non-responders based on an increase in diffusing capacity for carbon monoxide associated with a higher PEEP. Increasing PEEP from 5 to 15 cm H\(_2\)O has been demonstrated to yield increased lung volume (anatomical recruitment) in half of patients, while in other patients, higher PEEP results in improvement of lung volume and perfusion (functional recruitment). In other words, opening of alveolar units does not necessarily entail restoration of lung perfusion in that specific region. In cases of functional recruitment, an increment in PaO\(_2\)/FiO\(_2\) can be expected (Figure 1).

The viscoelasticity and time-dependent force required to open collapsed areas is a function of both transpulmonary pressure and time[13], known as the pressure-time product. In an attempt to evaluate optimal RM duration and hemodynamic changes, Arnal et al[14] conducted a prospective clinical trial of 12 recruited patients with ARDS. The authors found that most recruitment occurs in the first few seconds of a sustained inflation, suggesting that time is less important as a determinant of RM success. Instead, time plays a critical
role in hemodynamic alterations, which generally occur with a longer duration of inflation.

RMs are largely related to reversal of atelectasis in the context of ARDS. Moreover, their beneficial effects have also been described in patients under general anesthesia, during postoperative ventilation, and in other conditions related to hypoxemia, including heart failure.  

**TYPES OF RMS**

Tables 1 and 2 summarize clinical and experimental studies comparing different RM methods according to Population, Intervention, Comparison, Outcome criteria. Sigh was the first reported RM, applied interposed with monotonous ventilation to mimic physiological breathing as it occurs in healthy subjects. This RM consists of high Vt in controlled mode or high PEEP up to a specific plateau pressure level, for a selected number of cycles. In this line, Pelosi et al., in an observational study, ventilated 10 ARDS patients for 1 h with a lung-protective strategy consisting of three consecutive sighs/minute at 45 cm H2O plateau pressure. These patients exhibited improvement in oxygenation, lung elastance, and functional residual capacity compared to patients who did not receive sighs. Despite the beneficial effects of this maneuver, high sigh frequency (up to 180/h) was associated with hyperinflation and expression of type II procollagen mRNA in lung tissue in experimental models. Lower sigh frequency can protect the lung, mainly when combined with pressure-support ventilation.

The most widely described RM is sustained inflation, in which airway pressure is abruptly raised for a given time interval. A common sustained inflation is 40 cm H2O for 40 s. More recently, RMs with a stepwise increase in airway pressure and/or PEEP (stepwise RM) have been proposed to provide slowly increasing transpulmonary pressure instead of the rapid increase used in sustained inflation, in experimental and clinical studies. Both sustained inflation (fast RM) and stepwise RM (slow RM) have been reported to improve oxygenation and lung function and minimize atelectasis in experimental and clinical scenarios. Since stepwise RMs recruit lung units as effectively as sustained inflation with a lower mean airway pressure, they may lead to less hemodynamic compromise and hyperinflation. In this context, sustained inflation has also been associated with risk of hypotension, barotrauma, and has even been reported to be ineffective in improving oxygenation and reducing intrapulmonary shunting. In an observational study and randomized controlled trial, respectively, stepwise RM improved lung compliance, shunt fraction, and oxygen saturation, and was associated with lower mean airway pressure, they may lead to less hemodynamic effects in an observational clinical study.

In experimental endotoxin-induced mild ARDS, stepwise RM, compared to sustained inflation, was associated with reduced type II epithelial cell damage and decreased expression of markers associated with fibrosis and endothelial cell damage, depending on ARDS etiology.

Despite extensive research into the applications of RMs, definitive guidelines for these maneuvers have not been established. As a step toward standardization, a trial with high methodological quality is being conducted to assess the 28-d survival of ARDS patients subjected to maximum stepwise alveolar recruitment followed by ventilation with PEEP titrated according to best compliance. This multicenter study may represent a valuable contribution to the treatment of patients with ARDS.

Assisted ventilation may be associated with homogeneous lung recruitment. In the presence of lung recruitment, end-expiratory lung volume increases, thus reducing strain, while lung elastance decreases, resulting in lower inspiratory transpulmonary pressure and stress. However, in the absence of lung recruitment, transpulmonary pressure might be higher than during controlled mechanical ventilation and thus,
Table 1  Recruitment maneuver methods and outcomes reported in the literature about clinical studies

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<th>Ref.</th>
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<th>Interventions</th>
<th>Comparison</th>
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<tr>
<td>Pelosi et al[30]</td>
<td>Patients with pulmonary and extrapulmonary ARDS</td>
<td>Observational study</td>
<td>3 sighs/min at Pplat 45 cm H2O, Vt to maintain Pplat ≤ 35 cm H2O, PEEP level to keep the lung open</td>
<td>(1) 1 h of ventilator strategy; (2) 2 h of ventilator strategy; and (3) 1 h of ventilator strategy with three consecutive sighs/min at Pplat 45 cm H2O</td>
<td>Sigh during protective ventilation improved lung recruitment</td>
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<td>Borges et al[31]</td>
<td>Patients with early ARDS</td>
<td>Observational study</td>
<td>Stepwise maximum-recruitment strategy with sequential increments in Paw, in 5-cm H2O steps, until the detection of PaO2 + PaCO2 ≥ 400 mmHg</td>
<td>No comparisons</td>
<td>Stepwise maximum recruitment reverted hypoxemia and fully recruited the lungs</td>
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<td>Meade et al[32]</td>
<td>Patients with ARDS (PaO2/FiO2 ≤ 250 mmHg)</td>
<td>Randomized controlled trial</td>
<td>Low Vt, Pplat ≤ 30 cm H2O or ≥ 40 cm H2O, and lower or higher PEEP levels according to a table</td>
<td>(1) Ventilator strategy with Pplat &lt; 30 cm H2O, and conventional PEEP levels; (2) &quot;open lung&quot; approach with Pplat ≤ 40 cm H2O, RM, and higher PEEP levels</td>
<td>“Open-lung” approach improved oxygenation associated with lower use of rescue therapies</td>
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<td>Hodgson et al[33]</td>
<td>Patients with early ARDS</td>
<td>Observational study</td>
<td>Staircase RM, Paw set to 15 cm H2O above the PEEP, which was increased in a stepwise manner to 17, 20, and 23 cm H2O every 2 min, followed by PEEP titration</td>
<td>No comparisons</td>
<td>Staircase RM improved plasma cytokines, oxygenation and lung function over 7 d</td>
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<tr>
<td>Hodgson et al[34]</td>
<td>Patients with ARDS</td>
<td>Randomized controlled trial</td>
<td>Control ventilation strategy compared to staircase recruitment maneuver</td>
<td>(1) Control group: PCV, Pplat &lt; 30 cm H2O, Vt ≤ 6 mL/kg, FiO2 adjusted to SaO2: 90% to 92%; and (2) Staircase RM: Paw adjusted to 15 cm H2O above PEEP level, which was increased in a stepwise manner to 17, 20 and 23 cm H2O every 2 min, and then reduced in steps of 2.5 cm H2O every 3 min until a decrease in SaO2: ≥ 1%</td>
<td>Staircase RM improved oxygenation but caused hemodynamic instability and transient hypoxemia</td>
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<tr>
<td>Morán et al[35]</td>
<td>Patients with early ARDS</td>
<td>Observational study</td>
<td>Stepwise RM started from plateau pressure/PEEP of 40/25 cm H2O, 5 cm H2O of PEEP was sequentially increased until PaO2/FiO2 of 350 mmHg or plateau pressure/PEEP of 60/40 cm H2O</td>
<td>No comparisons</td>
<td>Stepwise RM improved oxygenation but caused hemodynamic instability and transient hypoxemia</td>
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Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. ARDS: Acute respiratory distress syndrome; FiO2: Inspiratory oxygen fraction; PaO2: Arterial oxygen partial pressure; PaCO2: Arterial carbon dioxide partial pressure; PCV: Pressure-controlled ventilation; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; SaO2: Arterial oxygen saturation; Vt: Tidal volume.
compared to sustained inflation, resulted in greater oxygenation and less hemodynamic impairment as reflected by lower central venous and pulmonary artery pressures, lower right ventricle workload, and higher cardiac output. In addition, the post-RM level of PEEP and lung recruitability should be taken into account to avoid complications related to high intrathoracic pressure during RMs\(^{42,43}\).

Desaturation and barotrauma are less common complications of RMs. Hodgson et al\(^{45}\), demonstrated that although 8 of 20 patients desaturated and exhibited transient circulatory depression during application of RMs, they had improved shunt fraction, oxygenation, and respiratory system compliance 60 min after maneuver application followed by PEEP titration. In a randomized controlled trial by Meade et al\(^{29}\), five patients with ARDS developed ventilator asynchrony, three experienced discomfort during the RM, two had hypotension, and four developed barotrauma. However, some issues should be taken into account, such as the sedation protocol allowing spontaneous cycles during the application of a sustained maneuver for 40 s. In addition, the level of PEEP was returned to the same value as before RM application. On the other hand, in a previous observational study, Borges et al\(^{44}\) demonstrated that two of 26 patients developed barotrauma; one case occurred 24 h and the other 12 h after application of the RM. Despite the preceding reports, recent data confirm that RMs are not associated with an increased risk of barotrauma\(^{10,45}\).

Lung recruitability could provide valuable information before RM application to prevent possible deleterious effects. Oxygenation and respiratory system elastance are often used to evaluate response to RMs.Gattinoni et al\(^{42}\) aimed to establish an estimation of lung recruitability in patients with ARDS based on three physiological variables: Oxygenation, respiratory system compliance, and alveolar dead space in patients exposed to a progressive increase in PEEP. However, these variables had low sensitivity and specificity to predict higher lung recruitability. Static lung compliance (the difference between respiratory system compliance and chest wall compliance) reflects transpulmonary pressure as well as lung recruitment, and could be used instead of respiratory system compliance to measure lung recruitability\(^{46}\). Esophageal pressure monitoring permits measurement of lung compliance, but its implementation in the intensive care unit setting is still a challenge. In research settings, computed tomography can be used to assess recruitment, as well as to individualize ventilation strategies in order to keep the lungs open\(^{45,47,48}\). Additionally, the use of lung ultrasonography (LUS) can be a useful imaging tool to assess lung aeration in critically ill patients\(^{49,50}\). In this context, studies have shown the utility of LUS in the detection and quantification of lung recruitment via a transesophageal approach\(^{51}\), and via a transthoracic approach\(^{50}\). Electrical impedance tomography (EIT) can provide a good estimate of the amount of tidal recruitement and may be useful to individualize ventilatory settings\(^{52,53}\). Even though LUS and EIT offer, at the bedside, an easy, alternative way to evaluate lung recruitement, both are inappropriate to detect hyper-inflation.

Response to RMs and/or lung recruitability cannot be predicted a priori, and require individualized assessment. Recently, Cressoni et al\(^{47}\) showed that extent of lung inhomogeneities increases as poorly aerated tissue increases from mild to severe ARDS (from 14% to 23%). In this study, high lung recruitability was considered in patients in whom the poorly aerated tissue area decreased with increasing PEEP, unlike in patients in whom poorly aerated tissue increased with increasing

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<tr>
<td>Rezinski et al(^{24})</td>
<td>Animals with mild extrapulmonary lung injury</td>
<td>Randomized experimental study</td>
<td>Prolonged RM stepwise increase in PIP of 15-20-25 cm H(_2)O above a PEEP of 15 cm H(_2)O (maximal PIP = 40 cm H(_2)O)</td>
<td>(1) Animals ventilated with V(_t) = 6 mL/kg and PEEP = 5 cm H(_2)O with no RMs; (2) Sustained inflation (40 cm H(_2)O for 40 s); or (3) Stepwise increase in Paw of 15, 20, 25 cm H(_2)O above a PEEP of 15 cm H(_2)O (maximal PIP = 40 cm H(_2)O), with interposed periods of Paw = 10 cm H(_2)O above a PEEP = 15 cm H(_2)O</td>
<td>Prolonged RM improved lung function, with less damage to alveolar epithelium, resulting in reduced pulmonary injury. The reduction in sigh frequency led to a protective effect on the lung and distal organs.</td>
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<tr>
<td>Steimback et al(^{46})</td>
<td>Animals with extrapulmonary lung injury</td>
<td>Randomized experimental study</td>
<td>Sigh with different PIP and frequencies</td>
<td>(1) Animals ventilated with V(_t) = 6 mL/kg and PEEP = 5 cm H(_2)O with no RMs; (2) Sustained inflation (40 cm H(_2)O for 40 s); (3) RM (180 sighs/h) and PIP (40 cm H(_2)O); (4) RM (10 sighs/h) and PIP (40 cm H(_2)O); and (5) RM (10 sighs/h) and PIP (20 cm H(_2)O) after PEEP titration.</td>
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<tr>
<td>Silva et al(^{41})</td>
<td>Animals with pulmonary and extrapulmonary lung injury</td>
<td>Randomized experimental study</td>
<td>Stepwise RM (5 cm H(_2)O/step, 6.5 s at each step during 51 s); Stepwise RM (5 cm H(_2)O/step, 5 s at each step during 30 s)</td>
<td>(1) Sustained inflation (30 cm H(_2)O for 30 s); (2) Stepwise PIP increase 30 cm H(_2)O over 51 s (STEP-51); and (3) Stepwise PIP increase over 30 s with maximum PIP sustained for a further 30 s (STEP-30/30).</td>
<td>Stepwise RM prevented fibrogenesis and endothelial cell damage.</td>
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</table>

Summary of the results of clinical and experimental studies comparing different recruitment maneuver (RM) methods, according to population, intervention, comparison, outcome criteria. PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; V\(_t\): Tidal volume.
pressure. Additionally, poorly aerated tissue areas, i.e., areas of tidal recruitment/derecruitment, are the primary targets of the inflammatory process in ventilator-induced lung injury. In this context, severe ARDS is more recruitable than mild or moderate disease, and extrapulmonary ARDS is more recruitable than cases of pulmonary etiology. Several studies have demonstrated that focal lung injury (pulmonary etiology) is associated with lower recruitability and alveolar overinflation in response to increased PEEP levels. In contrast, within the group of ARDS responders, in those with diffuse loss of aeration (extrapulmonary etiology), alveolar recruitment resulting from PEEP is not accompanied by lung overinflation.

Recently, Caironi et al. retrospectively analyzed a large cohort of patients with ARDS, aiming to describe lung edema and recruitability according to the Berlin definition and elucidate whether assessment of PaO2/FiO2 at standardized PEEP (5 or 15 cm H2O) allows a more accurate description of ARDS severity as compared to its clinical assessment. They reported that the clinical PEEP applied when assessing PaO2/FiO2 may mask the underlying ARDS severity, and that application of the Berlin definition at 5 cm H2O PEEP more accurately matches ARDS lung injury severity and recruitability, providing important information to guide ventilator strategies and to assess mortality risk.

**TITRATION OF POSITIVE END-EXPIRATION PRESSURE**

PEEP is required to recruit or maintain recruitment in the heterogeneous ARDS lung. The most common method for PEEP level selection is the use of PEEP/FiO2 tables, introduced by the ARDS Network and the LOVS study. Although high PEEP values improve oxygenation and decrease alveolar stress, they can sometimes result in lung overdistension and hemodynamic instability. An explanation for this discrepancy may be found in the heterogeneity of ARDS: A subpopulation of non-responders (patients with low recruitability) experience no change in arterial oxygenation with higher PEEP, and may be at greater risk of ventilator-induced lung injury from overdistention. On the other hand, patients with predominantly recruitable lung (severe ARDS; PaO2/FiO2 < 150 mmHg) exhibit an association of oxygenation response and PEEP adjustment, as well as lower risk of death. Recently, a Cochrane review of seven trials concluded that high PEEP levels are unrelated to hospital outcome as compared with low levels. A relationship between higher PEEP and low mortality could be achieved in patients with more severe ARDS, in whom lung recruitability is higher. In the era of identification of PEEP responders and/or high recruitability, attention to prevention of intratidal collapse and decollapse ("open the lung and keep it open") and lung function seems to be more relevant than oxygenation.

In a study of 57 patients with ARDS, Huh et al. compared daily decremental PEEP titration according to the best dynamic compliance performed after an RM vs PEEP selection as suggested by ARDSnet, based on a PEEP/FiO2 table. In this protocol, an initial improvement in oxygenation occurred in patients who received decremental PEEP titration after RM compared to those in whom the PEEP/FiO2 table method was used. This earlier improvement in oxygenation was not related to any advantage in respiratory mechanics within 1 wk, nor with 28-d intensive care unit mortality.

Cressoni et al. reported that, in mechanically ventilated patients in the supine position, collapse occurs first in the most dependent areas and overinflation in the less dependent regions, as observed on computed tomography analysis. This finding calls into question the use of a single pressure parameter to reflect the entire lung structure. Pintado et al., in a randomized controlled pilot study, suggested that PEEP application according to the highest compliance was associated with more organ dysfunction-free days and a trend toward lower mortality at 28 d as compared with FiO2-guided PEEP selection, with no differences in oxygenation ratio or PEEP level among groups.

The new concept of transpulmonary pressure to titrate PEEP during the decremental method has emerged as a measurement of alveolar stability and alveolar stress. Rodriguez et al. showed that high and low transpulmonary pressure values were associated with lung overdistension and with reductions in oxygenation and collapse, respectively. In addition, a positive correlation has been observed between transpulmonary and airway pressures. Transpulmonary pressure reflects pleural pressure surrounding dependent lung regions at a given point, while airway pressure only reflects opened alveolar units. In this context, transpulmonary pressure could be a more representative measure to guide PEEP selection and prevent alveolar unit instability.

"Open-lung PEEP", first described more than 2 decades ago by Lachmann et al., represents the level of PEEP that combines the minimal tidal recruitment/derecruitment, overinflation, and dead space with optimal oxygenation and lung compliance. Open-lung PEEP should be achieved after an application of RM, which may open collapsed alveolar units, and should then be titrated gradually toward the minimum value that can stabilize the previously recruited lung. RM and PEEP titration are interdependent events for the success of ventilatory management.

**CONCLUSION**

RMs are a simple, low-cost, feasible intervention that can be performed at bedside in intensive care units. A wealth of experimental and clinical data has demonstrated improvements in oxygenation, lung mechanics, and lung re-aeration after application of RMs. Recent systematic reviews and meta-analyses suggest that RMs are associated with lower mortality in patients with ARDS. However, the optimal RM method (i.e., that with the
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