Clinical Study

Increased Extravascular Lung Water Reduces the Efficacy of Alveolar Recruitment Maneuver in Acute Respiratory Distress Syndrome

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1. Introduction

The consolidation of pulmonary tissue and, in particular, the formation of atelectases is a key component in the pathogenesis of acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS) [1]. Loss of pulmonary tissue aeration resulting from decreased production of surfactant, evolution of lung edema, and denudation of alveolar basal membrane, is one of the crucial mechanisms of intrapulmonary shunting and arterial hypoxemia [2]. The formation of atelectases can also be triggered by gravity forces related to the increased weight of the edematous parts of the lungs resulting in a fall in functional residual capacity and compression of dependent lung areas in the supine patient [1].

The accumulation of interstitial, alveolar, and migrating cellular fluid in the lungs may also play an important role in the pathogenesis of ARDS, although its importance is often underestimated [3, 4]. Obviously, in severe lung edema the lung fluid content, which is reflected by extravascular lung water, can increase 2-3-fold prior to a significant decrease in arterial oxygenation [5]. Increments in extravascular lung water content of 500–700 mL up to 1000–1800 mL, corresponding to increments in extravascular lung water index (EVLWI) of from 7–10 mL/kg to 14–25 mL/kg may be seen. An experimental study from our group demonstrated that
such an increase in EVLWI is not necessarily accompanied by a substantial expansion of the pulmonary parenchyma, as assessed by spiral computer tomography (CT) [6]. The expansion of the extravascular fluid volume may take place at the expense of a compression in the conducting airways and alveoli, and, to a minor extent, of the vascular bed, since severe pulmonary hypertension is not a prerequisite for the evolution of ARDS [7]. Most likely accumulation of extravascular lung water in the early edematous phase of ARDS may result in destabilization of alveolar tissue requiring higher PEEP values to counteract gravity-related lung collapse and consolidation.

The aim of the alveolar recruitment maneuver (RM) is to expand and reopen collapsed lung tissue by intermittent short-acting increase in airway pressure. In the general ICU population, RM may improve the oxygenation ratio (PaO2/FiO2) by 29–50% of ARDS patients [8–10]. However, this method also has a number of side-effects and complications, the most severe being barotrauma and compromised cardiac preload [11, 12]. Notably, these adverse effects are more pronounced in nonresponders with a considerable decrease in the individual benefit-to-risk ratio [13].

Therefore, an active search for predicting an individual’s response to RM seems to be reasonable. Assuming there is a potential propensity of edematous pulmonary tissue to consolidate, or vice versa, a resistance of injured parenchyma to reopen, we hypothesized that EVLWI may influence the efficacy of the recruitment maneuver in ARDS patients. Thus, the aim of our study was to evaluate the response to RM, as assessed by EVLWI, in patients with ARDS.

2. Materials and Methods

The study was approved by the Medical Ethics Committee of Northern State Medical University, Arkhangelsk, Russian Federation. Written informed consent was obtained from every patient or his/her next of kin.

This prospective pilot study was performed in a 900-bed university hospital. From 2007 to 2010, we enrolled 17 adult patients who met the ALI/ARDS criteria according to the American European Consensus Conference [14]. Exclusion criteria were duration of ALI/ARDS >24 hrs, hypovolemia, severe COPD, and/or severe cerebral or cardiac diseases.

Patients were sedated with fentanyl (1 mcg/kg/hr) and midazolam (0.05 mg/kg/hr) and ventilated using pressure-controlled ventilation (PCV) (Avea, Viasys, USA) with the following initial settings: FiO2 0.5, positive end-expiratory pressure (PEEP) 5 cm H2O, driving pressure to a targeted tidal volume of 7 mL/kg of predicted body weight (PBW), and a respiratory rate providing a PaCO2 of 35–45 mm Hg. For males, PBW (kg) was calculated as = 50 + 2.3 (height (cm)/2.54–60), and correspondingly for females PBW (kg) = 45 + 2.3 (height (cm)/2.54–60). If the initial ventilator settings did not result in a SaO2 ≥94% and/or PaO2 ≥70 mm Hg, FiO2 was increased in steps of 0.1 up to 0.8 and remained unchanged during the study.

Hemodynamic monitoring was performed using the single transpulmonary thermodilution technique. In all patients the femoral artery was cannulated with a 5F thermodilution artery catheter (Pulsiocath PV2015L20, Pulsion). The catheter was connected to a PiCCOplus (Pulsion Medical Systems, Germany) monitor for measurements of cardiac index (CI), extravascular lung water index (EVLWI, which was adjusted to PBW), global end-diastolic volume index (GEDVI), systemic vascular resistance index (SVRI), mean systemic arterial pressure (MAP), and heart rate (HR).

The thermodilution measurements were performed in triplicate with injections of ice-cold (<8°C) 5% dextrose solution via a preinserted jugular central venous catheter (8.5F triple-lumen 20 cm catheter).

After initial measurements and muscular relaxation with pipercuronium (0.06 mg/kg), RM was performed by subjecting the patients to a continuous positive airway pressure of 40 cm H2O for a period of 40 seconds [10]. The RM was discontinued in case of hypotension (MAP <50 mm Hg or a decrease in MAP of more than 30 mm Hg from the initial value), or hypoxemia (SpO2 <85% or a decrease of more than 10%). Then PCV was resumed with the same settings as before the RM. PEEP was set at 2 cm H2O above the lower inflection point (LIP) of the pressure-volume (P-V) curve determined by an inflection point maneuver by the ventilator (Avea, Viasys, USA). The efficacy of the recruitment maneuver was assessed by registering the change in PaO2/FiO2 five minutes later. Patients were identified as responders if PaO2/FiO2 increased by at least 20% [8, 10, 13]. The stability of RM was assessed by following changes in PaO2/FiO2 at 40–60 min after the return to PCV.

For additional analysis of the efficacy of RM, patients were divided by the baseline EVLWI values as low EVLWI (<10 mL/kg) and high EVLWI (≥10 mL/kg) groups [4, 15].

Hemodynamic parameters were evaluated at baseline. Blood gases, lung mechanics, and parameters of mechanical ventilation were registered before RM and at 5 min and 40–60 min after RM.

2.1. Statistical Analysis. For data collection and analysis we used SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). Power analysis was not performed because of the pilot design of the study. The data distribution was assessed with Shapiro-Wilk’s test. Quantitative data were presented as mean ± standard deviation or median (25th–75th percentile) depending on the data distribution. Discrete data were expressed as absolute values or percentages. In case of normal distribution, we used two-tailed Student’s t-test for comparisons between the groups and repeated measures t-test for assessment of intragroup changes. Nonparametrically distributed data were assessed by two-tailed Mann-Whitney’s U-test and Wilcoxon’s test for comparisons between and within the groups, respectively. Discrete data were evaluated using Fisher’s exact test. For all tests a P value <0.05 was considered significant.

3. Results

Fourteen male and three female patients were enrolled into the study. The mean age of the patients was 47 ± 2 yrs.
3.1. The Efficacy of the Recruitment Maneuver: Responders and Nonresponders. The recruitment maneuver was accompanied by an increase in PaO₂/FiO₂ of more than 20% of the baseline value in 5 patients (responders) and did not affect oxygenation significantly in 12 patients (nonresponders). The demographic characteristics of responders and nonresponders are presented in Table 1. The groups did not differ regarding age, weight and height, type of ARDS, and the severity of lung injury or other organ dysfunctions. Baseline PaO₂/FiO₂ values were similar in both groups (Table 2).

The RM increased PaO₂/FiO₂ by a median of 62 (32–91)% in the responders, whereas the nonresponders demonstrated no changes or even decreased PaO₂/FiO₂ compared to the baseline value: 1(13)–(4)% (P = 0.002). Despite improvement in PaO₂/FiO₂ after RM in the responders, the PaO₂/FiO₂ did not differ significantly between responders and nonresponders (Table 2).

The stability of the RM was evaluated in 12 patients including 4 responders and 8 nonresponders. A decrease in PaO₂/FiO₂ of more than 15% compared with values yielded immediately after recruitment was found in 58% of patients including 75% of the responders and 38% of the nonresponders. The average decreases in PaO₂/FiO₂ were 61 (6–102)% and 14 (4–22)% in responders and nonresponders, respectively (P = 0.19). Hemodynamics and ventilatory variables did not differ significantly between responders and nonresponders (Table 2).

In most cases (94%), the baseline PaO₂/FiO₂ was less than 200 mm Hg.
Table 3: General characteristics of patients with low and increased extravascular lung water index.

| Parameter                  | EVLWI <10 mL/kg (n = 5) | EVLWI ≥10 mL/kg (n = 12) | P  
|---------------------------|---------------------------|---------------------------|---
| Age, years                | 40.4 ± 14.9               | 49.2 ± 17.2               | 0.34
| Gender, male/female       | 5/0                       | 9/3                       | 0.52
| Type of ARDS, direct/indirect | 3/2                        | 9/3                       | 0.60
| SAPS II, points           | 38 ± 7                    | 46 ± 16                   | 0.29
| SOFA, points              | 10.4 ± 2.7                | 7.3 ± 2.3                 | 0.03
| Murray score, points      | 2.50 (2.38–2.75)           | 2.25 (2.06–3.12)          | 0.36

Data are presented as mean ± standard deviation, absolute values or median (25th–75th percentile).

(≥10 mL/kg) was found in 12 patients including two responders (40% of all responders) and 10 nonresponders (83% of all nonresponders). EVLWI did not differ between patients with direct and indirect ARDS.

The general characteristics of patients with low and high EVLWI are presented in Table 3. Patients with low EVLWI had higher SOFA score values (Table 3).

The baseline PaO2/FiO2 did not differ between patients with low and high EVLWI. In response to the RM patients in the low EVLWI group demonstrated a 33 (4–65) % increase in PaO2/FiO2. In contrast patients with EVLWI ≥10 mL/kg showed no substantial changes in PaO2/FiO2: −1((−13)–(+5)) (P = 0.035 compared with the low EVLWI group) (Figure 1).

During the assessment of recruitment stability, PaO2/FiO2, PaCO2, and hemodynamic parameters were similar in patients with low and increased EVLWI (Table 4). Baseline tidal volume was higher in the low compared to the high EVLWI group.

4. Discussion

Our study demonstrates that during ALI and ARDS the efficacy of alveolar recruitment depends, at least partly, on the content of extravascular lung water. Pulmonary edema is associated with a reduced capability of 40 cm H2O × 40 sec RM to improve arterial oxygenation, thus, necessitating a search for other interventions to counteract hypoxemia during ARDS.

Alveolar RM is an important component of the open lung strategy in patients with ALI/ARDS of different etiologies. There are multiple modifications of the RM technique with individual adverse effects and benefits [16–18]. One extensively used principle is to increase pressure in the airways related to the consolidated areas over the level of the re-opening pressure [19]. A short-term sustained inflation pressure of up to 40 cm H2O for 40 seconds is the simplest and most well-studied version of RM, commonly used in ARDS patients.

Our study showed that 40 cm H2O × 40 sec RM resulted in a substantial improvement in PaO2/FiO2 in 29% of the patients. This is consistent with the findings of other recent investigators who reported the percentage of responders as 29–50% [8–10]. It is intriguing that the PaO2/FiO2 in responders and nonresponders was similar after the RM but the difference in response can be explained by the tendency to lower baseline PaO2/FiO2 in responders. In 75% of the responders and 38% of the nonresponders PaO2/FiO2 decreased within 40–60 minutes following the RM despite having identified and set an optimal individual PEEP value (2 cm H2O above LIP of the P-V curve). Indeed, the effect of alveolar recruitment is unstable; PaO2/FiO2 may decrease to baseline values as quickly as 30–45 minutes after PEEP has been adjusted [20, 21]. The stability of the alveolar reexpansion may be limited by the technique used to detect the optimal PEEP. The adjustment of an optimal PEEP using the pressure-volume (P-V) curve, as used in this study, is probably one of the most widespread and preferable methods for use at the bedside [22]. However, particularly in patients with “stiff” lungs resulting from severe ARDS, the lower inflection point of the P-V curve may be hard to discern [23].

The response to an RM may be affected by a wide range of factors, including the origin of ALI (direct or indirect), the technique used for the recruitment and the PEEP level used.

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Table 4: Blood gases, hemodynamics, and parameters of mechanical ventilation in patients with low and increased extravascular lung water index.

| Parameter                        | EVLWI <10 mL/kg (n = 5) | EVLWI ≥10 mL/kg (n = 12) | P    |
|----------------------------------|-------------------------|--------------------------|------|
| PaO2/FiO2 at baseline, mm Hg     | 117 ± 34                | 159 ± 47                 | 0.09 |
| PaO2/FiO2 after RM, mm Hg        | 146 (122–177)           | 158 (122–168)            | 0.46 |
| PaO2/FiO2 stability of RM, mm Hg | 134 ± 58                | 149 ± 46                 | 0.58 |
| Changes in PaO2/FiO2 within the period of stability assessment, % | -14((−1)−(−5)) | -18((−37)−(−9)) | 0.68 |
| PaCO2 at baseline, mm Hg         | 45 ± 8                  | 45 ± 8                   | 0.89 |
| PaCO2 after RM, mm Hg            | 49 ± 13                 | 48 ± 9                   | 0.54 |
| PaCO2 stability of RM, mm Hg     | 43 ± 6                  | 48 ± 8                   | 0.29 |
| CI, L/min/m²                     | 3.61 ± 0.98             | 3.65 ± 1.32              | 0.95 |
| MAP, mm Hg                       | 75 (66–106)             | 88 (71–99)               | 0.40 |
| SVRI, dyn sec cm⁻¹/m²            | 1717 (1089–2144)        | 1597 (1285–2238)         | 0.75 |
| HR, beat/min                     | 101 (97–105)            | 103 (84–133)             | 0.92 |
| GEDVI, mL/L/m²                   | 654 ± 92                | 714 ± 140                | 0.39 |
| EVLWI, mL/kg                     | 8.2 (6.0–9.1)           | 15.8 (11.2–17.8)         | 0.002|
| FiO2, %                          | 50 (50–80)              | 50 (50–60)               | 0.51 |
| Tidal volume, mL                 | 504 ± 34                | 439 ± 58                 | 0.04 |
| Minute ventilation, L/min        | 11.6 (11.4–14.6)        | 9.9 (8.4–12.0)           | 0.06 |
| Dynamic respiratory compliance, mL/cm H2O | 29 (26–59)           | 28 (24–35)               | 0.67 |

Data are presented as mean ± standard deviation, absolute values or median (25th–75th percentile).
RM: recruitment maneuver; CI: cardiac index; MAP: mean arterial pressure; SVRI: systemic vascular resistance index; HR: heart rate; GEDVI: global end-diastolic volume index; EVLWI: extravascular lung water index.

Increased interstitial hydrostatic pressure and pulmonary weight have been suggested to be among the key mechanisms of atelectasis formation in ALI/ARDS according to the "sponge theory," postulating a fall in lung compliance combined with compression and collapse of dependent small airways [24, 28, 29]. Studies carried out with the use of spiral CT have revealed that RM can lead to overdistension of intact or minimally injured areas located adjacent to the consolidated foci of lung tissue, resulting in volume- and/or biaxial trauma [30]. In areas of collapsed and consolidated lung tissue, particularly in regions of focal deaeration, a RM of 40 cm H2O does not regularly result in a substantial improvement in aeration [13, 29–31].

In this study, patients with low EVLWI (<10 mL/kg) showed a significant increase in PaO2/FiO2 following RM. In contrast, those with pulmonary edema failed to respond with an improvement in arterial oxygenation. However, we found no significant correlation between EVLWI and the percentage of positive response to RM. The cut-off value for EVLWI of 10 mL/kg was selected according to the results obtained by Chung and coauthors, who demonstrated that EVLWI ≥10 mL/kg predicts mortality with a sensitivity of 94.7% and a specificity of 66.7% [4]. In our study, EVLWI was above 10 mL/kg PBW in 71% of patients. This is in agreement with previously published data from our group [32]. In addition, according to the above definition, EVLWI was increased in 40% of the responders and 83% of the nonresponders. Indeed, pulmonary edema and aeration of lung parenchyma are closely associated. Extravascular lung water index correlates with the CT-reconstructed volume of pulmonary tissue of aqueous density, both in experimental [6] and clinical settings [33]. However, the accuracy of EVLWI measurement might be influenced by pulmonary vascular obstruction and prevalence of focal or regional pulmonary injury [34]. In the absence of lung edema, the atelectatic areas might be more compliant to the transiently increased airway pressure, similar to compression atelectasis where gas remains in the occluded acinar compartment [35].

Our study has several limitations, first of all, a small sample size. Thus, further larger studies of extravascular lung water and alveolar recruitment are warranted. The numerical differences in mean tidal volumes between the groups may be explained by different predicted body weights and dynamic ventilatory properties of the edematous and nonedematous lungs. Surprisingly, in this population of critically ill patients, the SOFA score was higher in the group with low EVLWI. This finding may confirm our assumption that the severity of pulmonary edema rather than dysfunction of other organs is a key factor that might affect the efficacy of the RM in ARDS patients.

5. Conclusions

In ALI and ARDS responses to the lung recruitment maneuver (40 cm H2O × 40 sec) may depend on the severity of
pulmonary edema. In patients with EVLWI above 10 mL/kg, the recruitment maneuver may be less effective and may even be considered as contraindicated.

Conflict of Interests

Mikhail Kirov is a member of the medical advisory board of Pulsion Medical Systems.

References

[1] L. Gattinoni, P. Caironi, P. Pelosi, and L. R. Goodman, "What has computed tomography taught us about the acute respiratory distress syndrome?" *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 9, pp. 1701–1711, 2001.

[2] M. A. Matthay and R. L. Zemans, "The acute respiratory distress syndrome: pathogenesis and treatment," *Annual Review of Pathology*, vol. 6, pp. 147–163, 2011.

[3] A. Davy-Quinn, J. A. Gedney, S. M. Whiteley, and M. C. Bellamy, "Extravascular lung water and acute respiratory distress syndrome—oxygenation and outcome," *Anaesthesia and Intensive Care*, vol. 27, no. 4, pp. 357–362, 1999.

[4] F. T. Chung, S. M. Lin, S. Y. Lin, and H. C. Lin, "Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit," *Respiratory Medicine*, vol. 102, no. 7, pp. 956–961, 2008.

[5] R. Maharaj, "Extravascular lung water and acute lung injury," *Cardiology Research and Practice*, vol. 2012, Article ID 407035, 6 pages, 2012.

[6] V. V. Kuzkov, E. V. Suborov, M. Y. Kirov et al., "Radiographic lung density assessed by computed tomography is associated with extravascular lung water content," *Acta Anaesthesiologica Scandinavica*, vol. 54, no. 8, pp. 1018–1026, 2010.

[7] M. Beiderlinden, H. Kuehl, T. Boes, and J. Peters, "Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography," *Intensive Care Medicine*, vol. 32, no. 6, pp. 852–857, 2006.

[8] A. Villagrá, A. Ochagavia, S. Vatua et al., "Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 165, no. 2, pp. 165–170, 2002.

[9] J. M. Constantin, S. Jaber, E. Futier et al., "Respiratory effects of different recruitment maneuvers in acute respiratory distress syndrome," *Critical Care*, vol. 12, no. 2, article R50, 2008.

[10] S. Grasso, L. Mascia, M. Del Turco et al., "Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy," *Anesthesiology*, vol. 96, no. 4, pp. 795–802, 2002.

[11] I. Morán, E. Zavala, R. Fernández, L. Blanch, and J. Mancebo, "Recruitment manoeuvres in acute lung injury/acute respiratory distress syndrome," *European Respiratory Journal, Supplement*, vol. 22, no. 42, pp. 37s–42s, 2003.

[12] I. Morán, L. Blanch, R. Fernández, E. Fernández-Mondéjar, E. Zavala, and J. Mancebo, "Acute physiologic effects of a stepwise recruitment maneuver in acute respiratory distress syndrome," *Minerva Anestesiologica*, vol. 77, no. 12, pp. 1167–1175, 2011.

[13] J. M. Constantin, S. Cayot-Constantin, L. Roszyk et al., "Response to recruitment maneuver influences net alveolar fluid clearance in acute respiratory distress syndrome," *Anesthesiology*, vol. 106, no. 5, pp. 944–951, 2007.

[14] G. R. Bernard, A. Artigas, K. L. Brigham et al., "The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 3, pp. 818–824, 1994.

[15] S. G. Sakka, M. Kleln, K. Reinhart, and A. Meier-Hellmann, "Prognostic value of extravascular lung water in critically ill patients," *Chest*, vol. 122, no. 6, pp. 2080–2086, 2002.

[16] R. M. Kacmarek and R. H. Kallet, "Should recruitment maneuvers be used in the management of ALI and ARDS?" *Respiratory Care*, vol. 52, no. 3, pp. 622–631, 2007.

[17] J. B. Borges, C. R. R. Carvalho, and M. B. P. Amato, "Lung recruitment in patients with ARDS [6]," *The New England Journal of Medicine*, vol. 355, no. 3, pp. 319–320, 2006.

[18] W. Oczenkski, C. Hörmann, C. Keller et al., "Recruitment maneuvers during prone positioning in patients with acute respiratory distress syndrome," *Critical Care Medicine*, vol. 33, no. 1, pp. 54–63, 2005.

[19] R. M. Kacmarek, S. Dimas, and C. W. Mack, *Essentials of Respiratory Care*, Elsevier Mosby, St. Louis, Mo, USA, 4th edition, 2005.

[20] M. Lichtwarck-Aschoff, J. Guttmann, L. Eberhard, B. Fabry, J. Birle, and M. Adolph, "Delayed derecruitment after removal of PEEP in patients with acute lung injury," *Acta Anaesthesiologica Scandinavica*, vol. 41, no. 6, pp. 675–684, 1997.

[21] W. Oczenkski, C. Hörmann, C. Keller et al., "Recruitment maneuvers after a positive end-expiratory pressure trial do not induce sustained effects in early adult respiratory distress syndrome," *Anesthesiology*, vol. 101, no. 3, pp. 620–625, 2004.

[22] D. Pestaña, C. Hernández-Gancedo, C. Royo et al., "Adjusting positive end-expiratory pressure and tidal volume in acute respiratory distress syndrome according to the pressure-volume curve," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 3, pp. 326–334, 2003.

[23] M. Mergoni, A. Volpi, C. Bricchi, and A. Rossi, "Lower inflection point and recruitment with PEEP in ventilated patients with acute respiratory failure," *Journal of Applied Physiology*, vol. 91, no. 1, pp. 441–450, 2001.

[24] C. Guerin, S. Debord, V. Leray et al., "Efficacy and safety of recruitment maneuvers in acute respiratory distress syndrome," *Annals of Intensive Care*, vol. 1, no. 1, p. 9, 2011.

[25] D. R. Riva, M. B. G. Oliveira, A. F. Rzezinski et al., "Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury," *Critical Care Medicine*, vol. 36, no. 6, pp. 1900–1908, 2008.

[26] P. Pelosi, P. Caironi, and L. Gattinoni, "Pulmonary and extrapulmonary forms of acute respiratory distress syndrome," *Seminars in Respiratory and Critical Care Medicine*, vol. 22, no. 3, pp. 259–268, 2001.

[27] A. W. Thille, J. C. M. Richard, S. M. Maggiore, V. M. Ranieri, and L. Brochard, "Alveolar recruitment in pulmonary and extrapulmonary acute respiratory distress syndrome: comparison using pressure-volume curve or static compliance," *Anesthesiology*, vol. 106, no. 2, pp. 212–217, 2007.

[28] P. Pelosi, L. D’Andrea, G. Vitale, A. Pesenti, and L. Gattinoni, "Vertical gradient of regional lung inflation in adult respiratory distress syndrome," *American Journal of Respiratory and Critical Care Medicine*, vol. 149, no. 1, pp. 8–13, 1994.

[29] J. C. Richard, S. Maggiore, and A. Mercat, "Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome?" *Current Opinion in Critical Care*, vol. 9, no. 1, pp. 22–27, 2003.

[30] L. Gattinoni, P. Caironi, M. Cressoni et al., "Lung recruitment in patients with the acute respiratory distress syndrome," *The
[31] S. Grasso, T. Stripoli, M. De et al., “ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure,” *American Journal of Respiratory and Critical Care Medicine*, vol. 176, no. 8, pp. 761–767, 2007.

[32] V. V. Kuzkov, M. Y. Kirov, M. A. Sovershav et al., “Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury,” *Critical Care Medicine*, vol. 34, no. 6, pp. 1647–1653, 2006.

[33] N. Patroniti, G. Bellani, E. Maggioni, A. Manfio, B. Marcara, and A. Pesenti, “Measurement of pulmonary edema in patients with acute respiratory distress syndrome,” *Critical Care Medicine*, vol. 33, no. 11, pp. 2547–2554, 2005.

[34] F. Michard, “Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls,” *Critical Care Medicine*, vol. 35, pp. 1186–1192, 2007.

[35] P. Pelosi, P. Cadringher, N. Bottino et al., “Sigh in acute respiratory distress syndrome,” *American Journal of Respiratory and Critical Care Medicine*, vol. 159, no. 3, pp. 872–880, 1999.