Intensive Care Med (2014) 40:1731–1733
DOI 10.1007/s00134-014-3457-7

Nuttapol Rittayamai
Laurent Brochard

What's new in ARDS (clinical studies)

Received: 14 August 2014
Accepted: 16 August 2014
Published online: 3 September 2014

N. Rittayamai · L. Brochard (✉)
Keenan Research Centre and Critical Care Department,
St Michael's Hospital, 30 Bond Street, Toronto M5B 1W8,
ON, Canada
e-mail: brochardl@smh.ca
Tel.: +1-416-864-5686

N. Rittayamai
Division of Respiratory Diseases and Tuberculosis, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

L. Brochard
Interdepartmental Division of Critical Care Medicine,
University of Toronto, Toronto, Canada

New definition

The definition of the acute respiratory distress syndrome (ARDS) has been revised using a conceptual model of acute, diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability and lung weight, and loss of aerated lung tissue. The definition, however, was primarily based on feasibility, reliability, and validity [1]. The term "acute lung injury (ALI)" has been removed and ARDS is now categorized into mild, moderate, and severe, based on the degree of hypoxemia (*P*/*F* ratio) with a positive end-expiratory pressure (PEEP) of at least 5 cmH_2O. The accuracy of the new criteria has been evaluated from autopsy in 352 patients who met clinical criteria for ARDS at time of death, by specifically looking for the presence of diffuse alveolar damage (DAD). Sensitivity and specificity of the new criteria were 89 and 63 %, respectively, and DAD was significantly related to ARDS severity [2]. A prospective study in ten ICUs in France failed to validate the new definition, since neither the stratification by severity nor the P/F ratio at baseline was associated with 28-day mortality [3]. In this study, like in others, however, the numbers studied were relatively small for testing the predictive validity. In addition, the primarily goal of the definition is not to predict mortality at an individual level. The optimal timing of P/F ratio determination to diagnose ARDS is also still debated. A prospective, multicenter study in Spain found that using P/F ratio at 24 h with standard ventilatory setting (PEEP $\geq$ 10 cmH_2O and $FiO_2 \geq 0.5$) had the best correlation to ICU mortality [4]. Costa et al. [5] also suggested that P/F ratio after 24 h could be more representative of severity and outcome of ARDS than using P/F ratio at baseline. The major problem with requiring a 24-h delay for the definition, discussed by the task force of the Berlin definition, is the risk of an additional delay for enrollment into trials.

Prone position

The rational for using prone position is to improve alveolar recruitment, improve ventilation–perfusion matching and oxygenation, and prevent ventilator-induced lung injury (VILI). In the past decade, several studies failed to demonstrate the benefit of prone position on outcome, although two meta-analyses had suggested a favorable prognosis when used in the sickest ARDS. A recent large randomized study recently demonstrated that prolonged sessions of proning in "severe" ARDS patients (*P*/*F* ratio <150 with $FiO_2 \geq 0.6$) significantly decreased mortality with relative risk reduction of 50 % over supine

position [6]. Two recent meta-analyses found that prone position significantly improved survival when using with low tidal volume strategy and all-cause mortality decreased when the duration of prone was prolonged (>16 h per day), particularly in patients with severe ARDS [7, 8]. Prone position might also have a synergistic effect with PEEP in reducing the risk of VILI [9]. Last, favorable hemodynamic effects of proning were recently confirmed, decreasing right ventricular afterload and increasing cardiac index in patients with preload reserve [10]. The use of prone position, however, is also associated with a higher risk of pressure ulcers than the supine position [11].

Extracorporeal life support

Extracorporeal membrane oxygenation (ECMO) has been increasingly used since the 2009 pandemic influenza (H1N1). In addition, the CESAR study demonstrated a mortality or severe disability benefit of being transferred to a specialized center offering ECMO over conventional treatment in patients with severe acute respiratory failure [12]. Some debate arose, however, about a limited use of lung protective ventilation strategy in the conventional treatment group in this study. Pham et al. prospectively analyzed factors associated with death and influence of ECMO on ICU mortality in a large cohort of patients with severe influenza A(H1N1)-related ARDS. After multiple adjustments, higher lactate and plateau pressure under ECMO were significantly associated with death, but not plateau pressure before ECMO. No difference in mortality was found between ECMO patients and matched non-ECMO patients [13]. Selecting a good candidate patient who may benefit from ECMO is important. Schmidt et al. proposed the PRESERVE mortality risk score by using 8 pre-ECMO parameters and demonstrated that this scoring system correlated with the probability of survival in severe ARDS patients [14]. Recently, the RESP score was developed using 12 pre-ECMO variables which associated with hospital survival on logistic regression using a database of 2,355 severe ARF patients treated with ECMO and having a 57 % survival rate [15].

Extracorporeal carbon dioxide removal ($ECCO_2R$) with low blood flow rates has been proposed to facilitate the use of ultra protective ventilation strategy [tidal volume (V_T) < 4 mL/kg PBW] and reduce VILI. A randomized trial assigned 79 ARDS patients to receive a low V_T ventilation ($V_T \approx 3$ mL/kg PBW) combined with arterio-venous $ECCO_2R$ or to the ARDSNet strategy. The results found that very low V_T was feasible to use with $ECCO_2R$. No difference in ventilator-free days existed but a post hoc analysis suggested benefits in severely hypoxemic patients (P/F ratio ≤150) [16]. Larger trials are needed to determine the benefit of $ECCO_2R$ with ultraprotective ventilation.

Prevention of ARDS

Identifying patient at risk and implementing a preventive strategy for ARDS may be considered in all mechanically ventilated patients in the ICU. A recent population-based, nested, matched case-control study demonstrated that inadequate antimicrobial therapy, ventilation with injurious volume, hospital-acquired aspiration, and volume of blood transfusion and fluid administration were associated with the development of ARDS [17]. The use of lung protective strategy might be of benefit in patients without ARDS. A randomized study comparing V_T 10 versus 6 ml/kg PBW was performed in mechanically ventilated patients without ALI at onset. The trial was stopped early because the occurrence of ALI was significantly higher in the conventional V_T as compared with lower V_T (13.5 vs. 2.6 %, $p = 0.01$) [18]. A meta-analysis also found that a lower V_T (≤6 ml/kg PBW) could be associated with shorter duration of ventilation without affecting sedation or analgesia needs [19].

Long-term outcome

There are few but important publications on long-term outcomes in ARDS survivors. Survivors tend to return to quasi normal pulmonary function at 1 year but continue to have functional impairment and compromised health-related quality of life for up to 5 years after discharge from the ICU, particularly muscle wasting and weakness [20]. Fan et al. conducted a 2-year prospective follow-up study to evaluate the epidemiology of muscle weakness in 222 survivors of ALI. The results demonstrated that 36 % of survivors had evidence of ICU-acquired muscle weakness at hospital discharge. The proportion of patients with weakness declined over time, and 9 % of ALI survivors still had weakness at 24 months, associated with impaired physical activity and quality of life that persisted at 24 months [21]. Thus, prevention of muscle weakness and early rehabilitation may be useful to reduce the long-term physical impairment in ARDS survivors.

Conflicts of interest L.B.'s research laboratory has received or is receiving research grants from Covidien, Maquet, General Electric, Vygon and Draeger. L.B. has been a consultant for Draeger and Covidien.

References

1. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD et al (2012) Acute respiratory distress syndrome: the Berlin definition. J Am Med Assoc 307:2526–2533. doi: 10.1001/jama.2012.5669
2. Thille AW, Esteban A, Fernández-Segoviano P et al (2013) Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med 187:761–767. doi: 10.1164/rccm.201211-1981OC
3. Hernu R, Wallet F, Thiollière F et al (2013) An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. Intensive Care Med 39:2161–2170. doi: 10.1007/s00134-013-3122-6
4. Villar J, Pérez-Méndez L, Blanco J et al (2013) A universal definition of ARDS: the PaO_2/FiO_2 ratio under a standard ventilatory setting–a prospective, multicenter validation study. Intensive Care Med 39:583–592. doi: 10.1007/s00134-012-2803-x
5. Costa ELV, Amato MBP (2013) The new definition for acute lung injury and acute respiratory distress syndrome: is there room for improvement? Curr Opin Crit Care 19:16–23. doi: 10.1097/MCC.0b013e32835c50b1
6. Guérin C, Reignier J, Richard J-C et al (2013) Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368:2159–2168. doi: 10.1056/NEJMoa1214103
7. Beitler JR, Shaefi S, Montesi SB et al (2014) Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. Intensive Care Med 40:332–341. doi: 10.1007/s00134-013-3194-3
8. Sud S, Friedrich JO, Adhikari NKJ et al (2014) Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Can Med Assoc J 186:E381–390. doi: 10.1503/cmaj.140081
9. Cornejo RA, Díaz JC, Tobar EA et al (2013) Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 188:440–448. doi:10.1164/rccm.201207-1279OC
10. Jozwiak M, Teboul J-L, Anguel N et al (2013) Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 188:1428–1433. doi:10.1164/rccm.201303-0593OC
11. Girard R, Baboi L, Ayzac L et al (2014) The impact of patient positioning on pressure ulcers in patients with severe ARDS: results from a multicentre randomised controlled trial on prone positioning. Intensive Care Med 40:397–403. doi: 10.1007/s00134-013-3188-1
12. Peek GJ, Mugford M, Tiruvoipati R et al (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374:1351–1363. doi: 10.1016/S0140-6736(09)61069-2
13. Pham T, Combes A, Rozé H et al (2013) Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 187:276–285. doi:10.1164/rccm.201205-0815OC
14. Schmidt M, Zogheib E, Rozé H et al (2013) The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 39:1704–1713. doi: 10.1007/s00134-013-3037-2
15. Schmidt M, Bailey M, Sheldrake J et al (2014) Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score. Am J Respir Crit Care Med 189:1374–1382. doi: 10.1164/rccm.201311-2023OC
16. Bein T, Weber-Carstens S, Goldmann A et al (2013) Lower tidal volume strategy ($\approx$3 ml/kg) combined with extracorporeal CO_2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 39:847–856. doi: 10.1007/s00134-012-2787-6
17. Ahmed AH, Litell JM, Malinchoc M et al (2014) The role of potentially preventable hospital exposures in the development of acute respiratory distress syndrome: a population-based study. Crit Care Med 42:31–39. doi: 10.1097/CCM.0b013e318298a6db
18. Determann RM, Royakkers A, Wolthuis EK et al (2010) Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care Lond Engl 14:R1. doi: 10.1186/cc8230
19. Serpa Neto A, Simonis FD, Barbas CSV et al (2014) Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med 40:950–957. doi: 10.1007/s00134-014-3318-4
20. Herridge MS, Tansey CM, Matté A et al (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304. doi: 10.1056/NEJMoa1011802
21. Fan E, Dowdy DW, Colantuoni E et al (2014) Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med 42:849–859. doi: 10.1097/CCM.0000000000000040