

The forgotten sides of acute lung injury and acute respiratory distress syndrome

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Acute respiratory distress syndrome (ARDS) is defined as acute hypoxemic respiratory failure combined with bilateral pulmonary infiltrates that are associated with both pulmonary and non-pulmonary risk factors and are not primarily due to left atrial hypertension [1].

Despite recent advances in our understanding of the syndrome's pathophysiology and treatment, the long term outcome of ARDS patients is not always favorable, with mortality rates remaining high [2].

Diagnosis of ARDS is not always easy [3], especially in emergency situations, and current American-European Consensus Conference definitions for acute lung injury (ALI) and ARDS have come under question. The definitions are considered inadequate for inclusion into clinical trials due to the lack of standardization for measuring the oxygenation defect [4].

Mechanical ventilation is an essential component of patient care with ALI/ARDS. A large number of randomized controlled clinical trials have now been conducted evaluating the efficacy and safety of various methods of mechanical ventilation for the treatment of ARDS.

Low tidal volume ventilation (≤ 6 ml/kg predicted body weight) should be utilized in all patients with ALI/ARDS, as it is the only method of mechanical ventilation that has been shown to improve survival, to date [5]. High positive end-expiratory pressure with alveolar recruitment maneuvers [6], and prone positioning [7] may also be useful as rescue therapies in patients with severe hypoxemia, but these methods do not improve survival for the wide population of patients.

A study by the National Institutes of Health's ARDS Network on low tidal volume, showed improved survival rates, which may suggest that their PEEP/FIO₂ titration tables represent the best method for adjusting these variables [5]. Based upon an extensive literature review of PEEP and respiratory system mechanics in ARDS, it is possible to reach three conclusions. Firstly, for most patients the therapeutic range of PEEP is relatively

narrow, so the ARDS Network PEEP/FIO₂ strategy is reasonable and supported by high-level evidence. Secondly, how best to adjust PEEP to prevent or ameliorate ventilator-associated lung injury is still unknown and under investigation. Thirdly, in a small subset of patients with severe lung injury and/or abnormal chest wall compliance, highly individualized titration of PEEP (based upon the respiratory-system pressure-volume curve, PEEP/tidal-volume titration grids, or a recruitment maneuver and a PEEP decrement trial) is a reasonable alternative.

Although not specific to the treatment of ARDS, protocol-driven weaning, that utilizes a daily spontaneous breathing trial and ventilation in the semirecumbent position, has proven benefits and should be used in the management of ARDS patients [8].

More recently, it has been found that fluid management, and in particular supporting a restrictive fluid management, can be also beneficial in ALI/ARDS patients [9].

In this issue of *Current Opinion in Critical Care*, we will discuss the relevant issues relating to ALI/ARDS – from basic pathophysiology, to clinical assessment and management – which are not usually considered in detail.

Some articles discuss the role of the endothelium, epithelium and extracellular matrix, as well as the lymphatics in the pathogenesis and development of ALI/ARDS. While the endothelium and epithelium have been extensively investigated, scientific knowledge about their role in the process of ALI/ARDS is continuously increasing. In particular, the role of extracellular matrix and lymphatics in the development of ALI/ARDS has now been studied during different pathogenetic processes and ventilatory settings. Recent data suggest that they can play a relevant role in the development of ventilator-induced lung injury, influencing the hydrostatic balance in the lung.

Inflammatory mediators have also been extensively studied. In recent years, the role of molecular biology has played a more extensive role in the better understanding of the inflammatory process leading to ALI/ARDS. Few published articles, however, are easily understandable to physicians not expert in the field. Despite this, it is likely that in the future molecular biology will play a relevant role both in the clinical practice and in the development of new pharmacological treatments.

2 Respiratory system

The role of peripheral airways has also been partially ignored, especially in relation to the optimal selection of PEEP. Generally considered as a therapeutic treatment to improve oxygenation and respiratory mechanics, PEEP avoids atelectasis and reduces ventilator-induced lung injury by limiting the opening and closing of alveoli. Recent studies, however, report that application of PEEP may also reduce the injury of peripheral airways independently from the presence of atelectasis per se. In addition, further investigations have focused on possible new methods, which can be applied at the bedside for early detection of peripheral airways lung injury, like the analysis and measurement of exhaled NO. In this context, mucus should be considered, especially in relation to the ventilatory setting and for its possible influence on changes in the peripheral airways and lung mechanics alterations. The possible differences in pulmonary and extrapulmonary ALI/ARDS are also discussed, in particular in relation to the possibility of different diagnostic and therapeutic approaches.

The chest wall has been recently considered to play a relevant role to determine the real transpulmonary pressure during mechanical ventilation. As transpulmonary pressure is the main determinant for ventilator-induced lung injury, a better understanding of the chest wall's mechanical properties is essential to optimize ventilatory treatment in this type of patient. In addition, chest wall mechanics may deeply affect hemodynamics and its correct interpretation.

Anatomopathology plays a central role to the better understanding of the basic mechanisms leading to ALI/ARDS, and in particular to the better understanding of possible etiologies not commonly detectable in clinical practice (e.g. possible presence of viruses or interstitial alterations). An increased knowledge of these mechanisms may dramatically contribute to an improvement in diagnostic sensitivity and treatment. In this context, the role of open lung biopsy is examined.

Both new and old aspects related to respiratory mechanics are discussed. Focusing on this important and essential

tool at the bedside will increase our understanding of the clinical status of the patient, and improve our ventilatory and clinical management in general.

Finally, recent findings from CT analysis are presented, which may increase understanding of ALI/ARDS pathophysiology, improve its definition, the application of PEEP and recruitment maneuvers, and the future design of clinical trials.

We hope that this issue of Current Opinion in Critical Care may contribute to a better understanding and discussion of these neglected issues. Despite their often complex nature, especially to those outside of their specific field, I firmly believe they are of extreme importance – not only to improving our scientific knowledge of the pathogenesis of ALI/ARDS, but also to the diagnosis and treatment of these difficult-to-treat patients.

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