

## **Acute Respiratory Distress Syndrome (ARDS): New Advances**

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ARDS is the pulmonary component of a generalized inflammatory mostly endothelial injury. The most common cause is pneumonia, but lungs previously injured by ARDS can be later over infected (pneumonia associated to mechanical ventilation, what already can be an object of confusion about what was first). ARDS usually begins during the first 48 of admission and means a significant increase of in-hospital mortality of patients.

Although the list of risk factors for development of ARDS is long (apart from pneumonia sepsis, shock, pancreatitis, aspiration, poly-trauma and/or cranioencephalic trauma, major surgery and multiple transfusion, among others), the best predictors of developing ARDS within patients with sepsis and/or pneumonia are hypoxemia and acidosis, the BAL levels of TNF/leukotrienes and chronic alcohol consume.

The clinical criteria for diagnosis of ARDS have been changed by Berlin definition, though it is not very different from the first criteria established in 1992 in the consensus conference which meant an important step forward, but only for defining the concept of acute lung injury (ALI) as an intermediate level of severity of ARDS based on the level of hypoxemia (the clinical relevance of ALI and the anatomopathological consequences have still to be established, although it seems not to be the most important prediction factor).

ARDS severity is defined by the following criteria:

- Lung compliance < 30 (about less than 30% of ventilated alveoli).
- Elevated ventilatory pressures > 25 over PEEP.
- Systemic complications, mainly hemodynamic and renal.
- CT thoracic infiltrates spread/extension.
- PaO<sub>2</sub>/FiO<sub>2</sub> (low accuracy rate).

Despite of the increasing information and efforts regarding diagnostic accuracy and therapeutic or ventilatory measures, mortality still remains being high, though it could be better if we took in mind the following improvements:

- To avoid inadequate or in necessary antimicrobial treatments, while an adequate antibiotic policy could be beneficial.
- To avoid aspiration pneumonia especially in obnubilated patients.
- To avoid high volumes ventilation or inadequated peep, with high plateau pressures.
- To avoid multiple transfusions or excessive fluids especially after the first 6 h of admission (during the first 6h, the fluid reanimation is permitted).
- To avoid high alcohol consume.

Apart from these complications, there are others that can be associated to worse prognosis:

- Ventilator induced diaphragmatic dysfunction, maybe because of the overuse of NMBA and diaphragmatic atrophy, or because of the development of critical illness paresis/palsy consequent weaning difficulties.
- VILI (ventilator-induced lung injury); mainly volutrauma/barotrauma, atelectrauma and/or biotrauma.
- Lung injury caused by production of scars, necrotic areas, pneumatoceles, bronchopulmonary fistulae and even brain air embolia, related to cycled ventilation of lung segments with recruitment and unrecruitment, followed by regional hypoxia, cell injury, alveolocytes type II destruction with poor surfactant production and more loss of compliance
- These mechanical and biochemical factors develop together with inflammatory mediators free lose, superoxide radicals generation, neutrophilic infiltration and immune cell activation, and finally alveolocapillary membrane injury, bacterial translocation, with toxins and cytokines liberation, inflammatory cells activation, multiorgan dysfunction and risk of death.

Two different adult distress types are distinguished: the primary ARDS, caused by direct lung injury, mainly secondary to pneumonia, and the secondary ARDS, as a response to a distanced focus of injury, over all the most frequently seen, an abdominal diffuse (peritonitis) or focal inflammatory origin (like necrotizing pancreatitis). Nevertheless, neither the diagnostic accuracy nor the treatment strategy seems to be different enough to justify this different subdivision and it seems rather to be an academic difference

Pathology: During the first 48 h of the beginning of ARDS a first edema phase is produced, followed by a 4 to 6 days of proteins exudation by permeability increase of alveolar capillaries, that translates through the presence of hyaline membranes (HM), which constitutes the hallmark of ARDS. Although the presence of HM confirms the diagnosis of ARDS, the absence of HM does not exclude this diagnosis, because it is still based on clinical criteria, but ARDS should be put on doubt, It has been already been confirmed in some papers both in primary as well as in secondary ARDS cases. It could be observed in this phase by the microscopical study of the fluid obtained at this time by bronchoscopic alveolar lavage or in the biopsy specimens obtained through opened minithoracostomy or by bronchoscopic biopsy, together with the presence of macrophage cells which ar responsible for the increase of inflammatory mediators in the alveoli.

#### Treatment strategies:

- Non-invasive mechanical ventilation (NIMV) has stated its usefulness and prognostic improvement in patients with COPD acute crisis, in cardiac failure, and in post-extubation, but with the mentioned difficulties regarding mix-max heterogeneity and diagnosis of ARDS, we can only say that NIMV can be intended in the beginning phase, but the experiences among distress patients are limited. And if oxygenation does not improve, intubation should not be delayed.
- Invasive Ventilation: The current criteria are the use of mechanical ventilation (MV) with low volumes and low Plateau Pressures (Pplat) and PEEP levels over the occlusion pressure; from efficacy reasons muscle relaxants are usually needed to avoid the fighting of patients against the respirator. The gas exchange and oxygenation should be repeatedly evaluated. In order to normalize the PaCO<sub>2</sub>, the corrected MV should be calculated to avoid dead space.
- The oesophagic pressure could be measured as surrogated expression of the pleural space in order to evaluate the lung mechanics and to separate it from the effect of the thoracic wall
- The factors that are currently accepted regarding the use of MV on ARDS are: normalized tidal volume (Vt) depending of real compliance (C) and it is named "driving pressure", which is calculated as the pressure increase (incrPr):  $\text{incrPr} = Vt/C$ . This driving pressure is the major mortality predictor, much more than Pplat over 39 or the simple Vt.
- Optimal PEEP should be calculated through the transpulmonary pressure (Ptp) using an oesophageal balloon to measure the Poes as a surrogate of pleural pressure (Ppl):  $Ptp = P_{alv} - Ppl$ . As the pressure to open the the lungs has to overcome the thoracic (Ptx), abdominal (Pabd) and alveolar (Palv), the driving pressure (Pdrive) represents the distention and collapsing force. Adjusting PEEP to driving pressure and maintaining the teleinspiratory pressure under 25 cm H<sub>2</sub>O the cycling atelectasis and overdistention is reduced,
- Permissive Hypercapnia, alveolar recruitment and low airway pressure are also admitted and recommended additional criteria for ventilation of patients with ARDS;

- A new concept introduced for identification of ARDS subgroups is the subphenotypes, attributing less importance to  $\text{PaO}_2/\text{FiO}_2$  or to the Berlin definition on ARDS. It seems that some subgroups of patients identified using statistical methods among large ARDS populations, will have more benefit using some therapeutic strategies. Following these techniques, the subphenotype 2 has been identified, that is associated to higher levels of inflammatory markers, needed more vasoactive amines, or had higher plasma bicarbonates, and had more mortality. Using higher levels of PEEP in these patients, mortality could be significantly reduced.
- Prone position (PP), reduces atelectasis, helps drainage of secretions, optimizes pulmonary circulatory flow to the dependant lung and helps to reduce Pplat. This PP strategy is used in about one third of severe ARDS patients and it was associated to improved oxygenation rates, lower ventilation pressures less complications and improved survival.
- Extracorporeal membrane oxygenation (ECMO): in critically ill patients with multiorgan failure or among those where prone position or the ventilation strategies have failed, it seems that application of decarboxylation and membrane oxygenation, still with prudence, plays an increasing roll. The survival (that during the past years was not higher than 60%) has improved gradually along the last 20 years.

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