Editorial

Evolving definition of acute respiratory distress syndrome

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Acute respiratory distress syndrome (ARDS) accounts for more than 10% of ICU admissions and involves almost a quarter of patients requiring mechanical ventilation (1). Despite several decades of research and progress, particularly regarding mechanical ventilation, ARDS remains associated with high mortality. In the absence of gold standard for its diagnosis, ARDS recognition depends on the use of a reliable definition. Definition of ARDS evolved step by step by improving understanding pathophysiology (2) and ventilator management (3).

ARDS was described for the first time in 1967 by Ashbaugh *et al.* (4). They reported a series of 12 patients under mechanical ventilation who required a positive end-expiratory pressure (PEEP) from 5 to 10 cmH2O to maintain arterial oxygenation. ARDS was defined as a clinico-radiological syndrome associating tachypnea, cyanosis refractory to oxygen therapy, decreased pulmonary compliance and diffuse alveolar infiltration on chest radiographs. The radiological signs did not allow to distinguish an ARDS from a cardiogenic pulmonary edema.

In 1988, Murray and colleagues (5) defined ARDS in a 3-part definition, which marked the beginning of standardization of the diagnostic process. First, the acute character of the disease was taken into account. Then, the etiology (community-acquired pneumonia, inhalation pneumonia, septic shock, severe traumatism) was underlined. And finally, the severity of pulmonary involvement was specified by the lung injury score (LIS) which associates the degree of hypoxemia, the PEEP level, the radiological abnormalities and the pulmonary compliance. Despite these precisions, there was still some doubt about the mechanism of edema. There was no consideration in this definition of the left ventricular systolic function. Moreover, the LIS was not assessed prospectively and validated.

In 1994, a consensus definition of ARDS was proposed by an American-European expert conference (6). ARDS was defined by the association of a PaO_2/FiO_2 ratio lower than 200 mmHg, bilateral interstitial alveolar syndrome on chest X-rays and a non-cardiogenic pulmonary edema (defined by a Pulmonary Artery Occlusion Pressure <18 mmHg). A less severe presentation with a PaO_2/FiO_2 ratio between 200 and 300 mmHg was named acute lung injury. This clinico-radiological definition had some limits. In a large autopsy study done in deceased ARDS patients (defined by the consensus conference of 1994), Esteban *et al.* (7), reported that the observed pulmonary histology was compatible with the diagnosis of ARDS in only 29% of cases. In the 382 patients with ARDS, the sensitivity of the clinical definition was 75% (95% CI, 66–82%) and the specificity was 84% (95% CI, 79–88%). In another study, a sensitivity of 85% and a specificity of only 51% have been reported (8).

Finally, the so-called Berlin definition was established in 2012 (9,10). This international consensus conference removed the notion of acute lung injury, adds to the clinical criteria of the 1994 definition the acute character of the syndrome and the need to objectively evaluate cardiac function by echography or Swan-Ganz catheter. This definition allows to individualize three groups of severity

according to the PaO_2/FiO_2 ratio evaluated in the presence of a PEEP of at least 5 cmH2O. Therefore, ARDS patients were classified as mild (200 mmHg < PaO_2/FiO_2 ratio ≤300 mmHg), moderate (200 mmHg < PaO_2/FiO_2 ratio ≤300 mmHg) or severe (PaO_2/FiO_2 ratio ≤100 mmHg). This new definition should lead to a better distinction from hydrostatic edema and takes into account ventilator settings. However, the Berlin definition has also some limitation. In their retrospective series of 712 autopsies, Thille *et al.* studied a series of patients with clinical criteria of ARDS according to the new definition (11). A total of 356 patients had clinical criteria of ARDS at the time of death. They reported a sensitivity of 89% and a specificity of 63% to identify ARDS using the Berlin definition. Diffuse alveolar damage was found in 45% of patients with clinical criteria for ARDS. Maybe other indicators, such as FiO_2 (12), should be included to improve the specificity of this definition. In the years to come, biological markers could also help us to improve ARDS diagnosis. The soluble receptor for advanced glycation end-products (sRAGE) is a marker of lung epithelial injury and alveolar fluid clearance, with promising values for assessing prognosis and lung injury severity in ARDS. In a recent meta-analysis including 746 ventilated ARDS, Jabaudon *et al.* (13) reported higher baseline levels of sRAGE in non survivors compared with survivors.

The symptomatic treatments of ARDS also need to improve their indications through a better definition and identification of strong prognostic markers in the very heterogeneous "ARDS population".

Neuromuscular blocker agents (NMBAs) were the first adjunctive treatment to demonstrate a reduction of mortality in ARDS (14). In a multicenter, double-blind trial, 339 patients with moderate to severe ARDS for less than 48 hours (i.e., with a PaO_2/FiO_2 ratio <150 mmHg and PEEP ≥5 cmH_2O) were randomized into 2 groups, a group receiving a continuous infusion of cisatracurium besylate (177 patients) and a placebo group (162 patients). This study showed an improvement in the adjusted 90-day survival rate in the interventional group compared to the placebo group. After adjusting for the baseline PaO_2/FiO_2 ratio, plateau pressure, and the Simplified Acute Physiology Score II (SAPS2), the hazard ratio (HR) of day 90 mortality in the NMBA group compared to the placebo group was 0.68 (95% confidence interval, 0.48 to 0.98, P=0.04). Patients in the NMBA group had a shorter duration of mechanical ventilation than those in the placebo group. Clinical practice guidelines (15) for the use of NMBAs in critical ill recommended a continuous NMBAs in ARDS with a PaO_2/FiO_2 ratio inferior to 150 in ARDS ventilated with a PEEP higher to 5 cmH_2O.

Prone position (PP) is a simple and inexpensive technique used early in management of ARDS. This is the second adjunctive measure which has an effect on the reduction of mortality in ARDS, despite the disappointing results of the first four randomized controlled trials (16-19). One major problem of these four trials was the inclusion of mild and moderate ARDS patients. Guérin *et al.* (20) conduced a multicenter, prospective, randomized controlled study on the use of PP in ARDS patients with a PaO_2/FiO_2 ratio lower than 150 mmHg, ventilated according to a lung-protective strategy, with a PEEP of at least 5 cm of water. A total of 466 patients were randomly assigned to two groups. In the interventional group, 237 patients have undergone prone positioning sessions of at least 16 hours. The 28-day mortality was 16% in the prone group versus 32.8% in the supine group (P<0.001). According to international guidelines, only patients with a PaO_2/FiO_2 ratio of less than 150 are candidates to a continuous neuromuscular blockade and could beneficiate from prone positioning.

In clinical trials, patients with moderate ARDS seemed to separate in two populations: patients with a mild-moderate ARDS (PaO_2/FiO_2 ratio between 150 and 200) versus patients with a moderate-severe ARDS (PaO_2/FiO_2 ratio between 101 and 149). These were the only ones to benefit from neuromuscular blockade and prone positioning. Mortality is influenced by the PaO_2/FiO_2 ratio, Villar and colleagues (21) found in 300 patients with ARDS ventilated patients with PaO_2/FiO_2 less than 150 had a higher mortality than patients with a PaO_2/FiO_2 greater than or equal to 150. In this latter study, classification of patients in each group changed significantly after 24 hours of protective ventilation. The persistence of a PaO_2/FiO_2 ratio less than 150 at 24 hours in ARDS patients ventilated provided a strong association with in-hospital mortality.

Maiolo and colleagues (22) published the results of a retrospective study which included, between 2003 and 2016 in three ICU, patients with moderate and severe ARDS requiring mechanical ventilation. Clinical characteristics and ventilatory settings of 227 patients were recorded. All the patients had pulmonary CT-scans at 5 and 45 cmH_2O of airway pressure in the first 72 h of care, to calculate lungs weight, to identify non-aerated tissues—poorly aerated tissues—normally inflated tissues—hyper-inflated tissues and to characterize lung inhomogeneity and recruitability.

First, they considered patients with moderate ARDS (PaO_2/FiO_2 ratio from 101 to 200) and tried to characterize the differences between two groups: patients with mild-moderate ARDS (PaO_2/FiO_2 ratio between 150 and 200) versus patients with moderate-severe ARDS (PaO_2/FiO_2 ratio between 101 and 149). Patients with moderate-severe ARDS were more severe considering gas exchange: greater FiO_2, greater $PaCO_2$ and lower pH. Ventilator settings (tidal volumes, minute ventilation and PEEP) were comparable. Analysis of respiratory system mechanics showed greater peak pressures in moderate-severe ARDS without any differences between plateau pressure, driving pressure and compliance. However, the mechanical power (stress), normalized to the total lung capacity (TLC), was higher in these patients. Looking at CT-scans, patients with moderate-severe ARDS had heavier lungs, greater inhomogeneity, more non-inflated tissues and higher lung recruitability. Despite these differences, suggesting a more severe pattern for "moderate-severe ARDS" than "mild-moderate ARDS", mortality was slightly higher in this second subset of patients, without any statistical difference (38% versus 27%, P=0.25).

This study confirms the heterogeneity of patients with moderate and severe ARDS. Patients with moderate-severe ARDS (PaO_2/FiO_2 <150) had different characteristics regarding gas exchanges, ventilator mechanics and CT anatomical findings. These characteristics may explain the effectiveness of symptomatic and specific treatments in this population such as continuous neuromuscular blockade or prone positioning.

Conclusions

Although the Berlin definition improves the identification and the classification of ARDS, we need more information to direct the symptomatic treatment. Maiolo *et al.* showed that moderate ARDS patients are really different and identify two different subgroups. Using a PaO2/FiO2 ratio threshold of 150 (measured at 5 cmH2O PEEP), and identified two populations that differed in their anatomical and physiological characteristics. This classification may provide a more homogeneous distribution of ARDS patients across the severity subgroups.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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