



## EDITORIAL

### Are we able to optimize the definition and diagnosis of severe acute respiratory distress syndrome? ☆

### ¿Somos capaces de optimizar la definición y el diagnóstico del síndrome de distrés respiratorio agudo severo?

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Acute respiratory distress syndrome (ARDS) was first described in 1967.<sup>1</sup> However, it was not until 1994 that an international consensus conference established the definition of ARDS that is used today,<sup>2</sup> i.e. recent symptoms onset with severe hypoxemia requiring mechanical ventilation with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of <200 mmHg, radiologically manifest bilateral and diffuse infiltrates, and the absence of cardiogenic lung edema. The criteria defining acute lung injury (ALI) are the same as those applicable to ARDS, though in this case the PaO<sub>2</sub>/FiO<sub>2</sub> ratio is between 200 and 300 mmHg.

ARDS is not a disease but a syndrome. In fact, it is caused by a very heterogeneous group of disorders. In effect, ARDS can be caused by direct lung damage, as in the course of pneumonia, bronchial aspiration or lung contusion. Likewise, it can result from extrapulmonary damage, as during septic shock (in most cases of abdominal origin), pancreatitis, or hemorrhagic shock and consequent polytransfusion.<sup>3</sup> Despite the diversity of underlying causes, the distinction between ARDS of pulmonary or extrapulmonary origin has not been shown to exert an influence upon mortality,<sup>4</sup> in the same way as positive end-expiratory pressure (PEEP) adjustment for the correction of hypoxemia.<sup>5</sup> Nevertheless, mortality is lower in the case of ALI than in genuine

ARDS.<sup>6</sup> Accordingly, the three large studies that have evaluated the impact of PEEP level have indistinctly included patients with ALI and with ARDS.<sup>7–9</sup> Treatment then could differ according to the severity of ARDS. One of the aforementioned studies found that the association of a tidal volume of 6 ml/kg to high PEEP (the latter being increased until reaching a plateau pressure of 28–30 cm H<sub>2</sub>O) allowed significant shortening of the duration of mechanical ventilation, thereby giving rise to a near-significant reduction in mortality.<sup>9</sup> Likewise, this strategy only benefited those patients diagnosed with ARDS, but not those presenting criteria of ALI.<sup>9</sup> The meta-analysis of these three studies has shown elevated PEEP to lessen mortality, though significance was only reached in the group of patients with ARDS.<sup>10</sup> Likewise, prone decubitus only appeared effective in those patients with particularly severe ARDS, defined as PaO<sub>2</sub>/FiO<sub>2</sub> < 100 mmHg.<sup>11</sup> The radiologically identified lesions could also intervene in the prognosis, with higher mortality among patients with infiltration of all four quadrants (diffuse ARDS) than in those with only bibasal lesions (lobar ARDS).<sup>12</sup> The current definition of ARDS does not take into account the severity of lung injury, and the PaO<sub>2</sub>/FiO<sub>2</sub> ratio does not take into consideration the protocolized PEEP. Some authors have suggested that an urgent revision of this definition is needed in order to conduct multicenter studies and determine treatment on the basis of more homogeneous populations.<sup>13</sup>

In this issue of the journal, Sánchez Casado et al.<sup>14</sup> have evaluated the impact of PEEP upon the alveolo-arterial gradient in over 600 patients subjected to mechanical ventilation in the Intensive Care Unit (ICU). The alveolo-arterial

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gradient is directly influenced by the  $\text{PaO}_2/\text{FiO}_2$  ratio and patient severity. In fact, the gradient was higher in the more hypoxemic individuals, evidencing severe lung injury. Likewise, the observed relationship between the alveolo-arterial gradient and the  $\text{PaO}_2/\text{FiO}_2$  ratio was better correlated on taking the protocolized PEEP into account. This finding suggests that the  $\text{PaO}_2/\text{FiO}_2$  ratio is not sufficient as a parameter for evaluating the severity of lung injury, and that the intensity of treatment must be taken into account when assessing the severity of ARDS. The PEEP and  $\text{FiO}_2$  "dosage" exerts a greater influence upon oxygenation and could directly evidence the severity of ARDS. Calculation of the alveolo-arterial ratio at the patient bedside is complex and not ideal, as underscored by the authors of the study, and the gradient is directly influenced by  $\text{FiO}_2$ . Accordingly, for one same  $\text{PaO}_2/\text{FiO}_2$  ratio, the gradient clearly increases if  $\text{FiO}_2$  increases. In fact,  $\text{FiO}_2$  has been shown to be an independent predictor of mortality, despite the presence of a similar  $\text{PaO}_2/\text{FiO}_2$  ratio.<sup>15</sup> The same applies to the PEEP level, since many factors influence oxygenation during the development of ARDS. Hypoxemia can not only worsen secondary to a decrease in cardiac output<sup>16</sup> or the presence of a permeable foramen oval, as found in 20% of the patients,<sup>17</sup> but also to  $\text{FiO}_2$  with a generally higher  $\text{PaO}_2/\text{FiO}_2$  ratio for  $\text{FiO}_2$  100% than for  $\text{FiO}_2$  60%.<sup>18</sup> This means that for one same  $\text{PaO}_2/\text{FiO}_2$  ratio, those patients with a higher  $\text{FiO}_2$  are in more serious condition as regards oxygenation.

As shown by the authors, not only the PEEP dose, but also the  $\text{FiO}_2$  dose, could be a good marker of the severity of lung injury. Villar et al. identified a population with particularly severe ARDS according to the adjusted PEEP level.<sup>19</sup> The patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio of <200 mmHg remained in this condition 24 h after admission, and despite a PEEP of at least 10 cm  $\text{H}_2\text{O}$ , the mortality rate was 45%, versus only 20% in the other cases.<sup>19</sup> It is therefore essential to distinguish the more severe cases, and the definition of ARDS should take not only the  $\text{PaO}_2/\text{FiO}_2$  ratio into account, but also the intensity of treatment as refers to the PEEP level and  $\text{FiO}_2$ .

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