Intensive Care Med (2013) 39:775–778
DOI 10.1007/s00134-013-2834-y

EDITORIAL

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Defining ARDS: do we need a mandatory waiting period?

Received: 18 December 2012
Accepted: 19 December 2012
Published online: 31 January 2013

This editorial refers to the article available at doi:10.1007/s00134-012-2803-x.

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Acute respiratory distress syndrome (ARDS) is a devastating clinical picture known to all clinicians that deal with critically ill patients. We all have in mind the clinical hallmarks that identified the ARDS patients treated in our clinical practice: severe respiratory distress; hypoxemic respiratory failure refractory to O_2 administration; standard chest X-ray showing pulmonary edema that is not the result of congestive heart failure or fluid overload; a silent clinical history for chronic respiratory disease [1]. The need for admitting these patients in an ICU for mechanical ventilation with positive end-expiratory pressure (PEEP) and high inspiratory O_2 fraction (FiO_2) are the unquestionable therapeutic guidelines we all have clear in mind when dealing with these patients [1].

The process required to organize the clinical and pathophysiological knowledge of ARDS in a formal framework (i.e., the process of defining ARDS) has always been controversial. In this context, ARDS is not unique. For example, the definition of AIDS changed rapidly as more of the underlying pathogenesis became understood [2]; the definitions of chronic fatigue syndrome [3] and of chronic migraine [4] are controversial. Nevertheless, it is unquestionable that effective and shared definitions are needed by clinicians to guide selection of the most appropriate treatment for the patients that are expected to benefit the most and to optimize use of resources and communication to the relatives by predicting outcome and by clinical scientist to generate consistent and reproducible clinical studies by including patients with a consistent phenotype [5].

In 1994, the first broad consensus was achieved for a definition of ARDS by the American–European Consensus Conference Committee (AECC). Under the auspices of the American Thoracic Society (ATS) and of the European Society of Intensive Care Medicine (ESICM), Gordon Bernard and Antonio Artigas chaired a consensus group that included around 50 experts in the field from North America and Europe. Experts were grouped in subcommittees that met in occasion of the annual meetings of both societies from 1992 (Miami) to 1996 (Glasgow). Bernard, Artigas, and coworkers defined ARDS as the acute onset of hypoxemia (PaO_2/FiO_2 $\leq$200 mmHg) with bilateral infiltrates on frontal chest x-ray consistent with edema in the absence of left atrial hypertension. They also defined a new, broader term, Acute Lung Injury (ALI), defined using the same criteria but with a less stringent criterion for hypoxemia (PaO_2/FiO_2 $\leq$300 mmHg). Thus, ALI included ARDS, but it also included a subset with relatively mild hypoxemia (i.e., PaO_2/FiO_2 201–300). The panel paid particular

attention to the implication of the definition of ARDS for design and coordination of clinical trials [6–9]. The two major advantages of this consensus definition are: (a) including patients with less severe hypoxemia (200< PaO_2/FiO_2 ≤300 mmHg) may facilitate enrollment in clinical trials and ultimately demonstrate benefit in both the severe and less severe subsets (b) the definition is simple to apply in the clinical setting thus enabling large scale epidemiologic studies [10]. The AECC therefore allowed generation of a large amount of data advancing our knowledge on the incidence and outcomes and improving our ability to better care for patients with ARDS [11, 12].

Despite this unquestionable success, a number of issues regarding the AECC definition have emerged [13, 14]. First, the AECC demanded the "acute onset" but does not explicitly define the time window (e.g., hours, days, or weeks), nor from when to judge the onset of the syndrome. Second, the chest X-ray criterion has been shown to have poor to moderate inter-observer reliability. Third, although the definition requires a pulmonary artery wedge pressure (PAWP) ≤18 mm Hg (when measured), patients with ARDS frequently have elevated PAWPs often because of transmitted airway pressures and/or vigorous fluid resuscitation. Forth, there is evidence that ALI and ARDS as defined using the AECC criteria is under-recognized by clinicians, particularly the subgroup of patients with milder hypoxemia (i.e., those with PaO_2/FiO_2 201–300) [15]. Fifth, PaO_2/FiO_2 is not constant across a range of both FiO_2 and PEEP in individual patients. In an elegant study of four combinations of FiO_2 and PEEP with standardized tidal volumes applied 24 h after ARDS onset, Villar and coworkers determined that the combination of PEEP >10 cm H_2O and FIO_2 >0.5 with a tidal volume of 7 ml/kg PBW demonstrated substantial reclassification of high- and low-mortality groups in comparison to PaO_2/FiO_2 ratios determined on usual care ventilator settings at the time of diagnosis [16]. They proposed that standardized ventilator settings after a 24 h waiting period should be used to define ARDS [16].

To address these limitations of the AECC definition, the European Society of Intensive Care Medicine, with the endorsement of the American Thoracic Society and of the Society of Critical Care Medicine, convened an international expert panel to revise and adjust the AECC definition of ARDS. Feasibility, reliability, face validity and predictive validity were important considerations in developing the new definition. An empiric evaluation of the preliminary draft using data from more than 4,000 patients with presumed ARDS recruited from several clinical trials and observational cohorts from North America, Europe, and Australia was done to assess predictive validity. A requirement for standardized ventilator settings was considered but not thought to be feasible as this practice is not generally part of contemporary usual care. The essential aspects of the new definition (the "Berlin definition") are as follows. First, acute was defined as 1 week or less. Second, chest radiograph criteria were clarified to improve inter-reliability and example radiographs provided. Third, the wedge pressure criterion was removed and clinical vignettes added in an effort to improve the ability to exclude cardiac causes of bilateral infiltrates. Fourth, the term acute lung injury was abandoned. Fifth, measurement of the PaO_2/FIO_2 ratio was changed to require a specific minimum amount of PEEP; three categories of ARDS were proposed (mild, moderate, and severe) based on the PaO_2/FIO_2 ratio cut-offs of 300 and below [17, 18]. In addition, minute ventilation (as a surrogate for dead space), and compliance of the respiratory system were initially proposed by the consensus panel. Empiric evaluation revealed that inclusion of these variables did not improve the predictive validity and they were therefore removed saving clinicians and clinical scientists from an otherwise much more complicated definition [19, 20].

In this issue of the journal, Villar and coworkers expand on their prior work by demonstrating in a prospective observational cohort ($n = 282$) that the PaO_2/FIO_2 ratio obtained on ventilator settings where the FiO2 was at least 0.5 with a PEEP of at least 10 cm H_2O 24 h of ARDS onset may allow a better risk classification. The PaO_2/FiO_2 determined on these settings no later than 24 h after ARDS onset, stratified patients into mild (PaO_2/FiO_2 >200; $n = 47$, mortality 17 %), moderate ARDS (PaO_2/FiO_2 100–200; $n = 149$, mortality 40.9 %), and severe ARDS (PaO_2/FiO_2 <100 ($n = 86$, mortality 58.1 %) ($p = 0.00001$). They concluded that this definition will allow enrollment of appropriate patients (e.g., higher risk) in therapeutic clinical trials and called this a "universal definition of ARDS" [21]. Unfortunately, a direct statistical comparison of the definitions was not performed.

The standardization of both FiO_2 and PEEP when using PaO_2/FiO_2 to estimate the severity of venous admixture is physiologically sound. However, the prognostic value of the PaO_2/FiO_2 ratio on standardized settings 24 h after ARDS onset will reflect the combined effects of disease progression and the standardized settings. As the authors themselves note, "it appears that patients who are getting better early in the course do better, and those that decline over the first 24 h do worse." We agree and propose that it is better to identify all patients with the syndrome as early as possible. Moreover, as secular trends in ventilator management continue toward the use of lower tidal volumes and higher PEEP, the gap between proposed standardized settings and usual care ventilator practices narrows and the value of standardization diminishes. In a recent evaluation of this issue using a much larger cohort, Britos and colleagues found no change in the predictive validity of PaO_2/FiO_2 when PEEP was added [22]. The receiver operator characteristic curve for PaO_2/FiO_2 and oxygenation index were surprisingly similar. Greater

standardization of ventilator management in usual care may explain the different observations [22].

The approach advocated by Villar and colleagues would certainly be appropriate for studies of high-risk interventions where the risk to benefit profile may be more acceptable and the anticipated benefits could be expected after a 24-h waiting period. However, most successful interventions in experimental lung injury must be given before or shortly after the insult, and nearly all have failed in clinical trials of established ARDS. Thus, the focus in increasingly on earlier intervention and prevention of ARDS, would not be possible with a 24 h waiting period [23]. Changing the ventilator to standardized settings to determine eligibility for a clinical trial is a research procedure and requires informed consent if such a practice is not part of usual care. This will make large scale epidemiologic studies impossible and biased [24]. This requirement would also make it impossible to study the clinical recognition of ARDS as clinicians would first have to recognize these patients to place them on the standardized ventilator settings to make the diagnosis. These major limitations make the standardized settings and the mandatory waiting period unsuitable requirements for a "universal" definition, much less a feasible one.

Syndrome definitions should be in a constant state of evolution and debate. Until we have, and to allow us to find, the perfect biomarker for lung injury, investigators must apply standardized definitions using training materials [25]. Investigators are encouraged to apply refinements to the "Berlin Definition" for specific studies that enrich the patient population. In a clinical trial where a 24-h delay in randomization and consent are outweighed by the value of assessing PEEP responsiveness on standardized ventilator settings, the modifications to the Berlin Definitions as proposed by Villar, et al. [21], would be extremely valuable.

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