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EDITORIAL

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Clinical trials in patients with the acute respiratory distress syndrome: Burn after reading

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Burn After Reading is a film written and directed by the Coen brothers which was released in 2008 (http://en.wikipedia.org/wiki/Burn_After_Reading). The plot is seemingly without direction and is based upon computer files, medical records, numerical data, money, exchange of information, and erratic behaviors. Everything ends badly. Analysts of the Central Intelligence Agency made attempts to understand what really happened in the film and concluded that although individually everything sounded important, as a whole everything was meaningless. This is exactly how we feel after reading the review by Tonelli et al. [1] of 159 randomized controlled trials (RCTs) and 29 meta-analyses of trials in patients with acute respiratory distress syndrome (ARDS). On first glance this review appeared to be an excellent summary of ARDS research which we, as clinicians involved in the field, were very keen to read, but which ultimately left us still looking for more. After 25 years and hundreds of millions of euros/dollars of clinical research funding, only three specific interventions have been found that can decrease ARDS mortality, namely, the use of low tidal volumes, prone positioning, and neuromuscular blockade early in the course of severe ARDS. According to Tonelli et al., the survival benefit of these specific interventions has only been demonstrated in a single RCT for each intervention [2–4], without any further validation or confirmatory trial.

We acknowledge the impressive quantity of data summarized by Tonelli et al. [1] Several key issues emerge from this immense academic undertaking. First, they outline why their review is important for clinicians and scientists and secondly, they suggest what must be done differently to improve future study designs in ARDS. The two major factors which could explain the long list of negative RCTs in ARDS are (1) excessive heterogeneity in study populations and (2) a lack of standardization of outcome measures.

Since the diagnosis of ARDS is based on a combination of clinical, oxygenation, hemodynamic, and radiographic criteria, patient groups are highly heterogeneous. Given that severe hypoxemia is the hallmark of ARDS, it is crucial to assess the severity of hypoxemia and hence the severity of ARDS in order to predict the

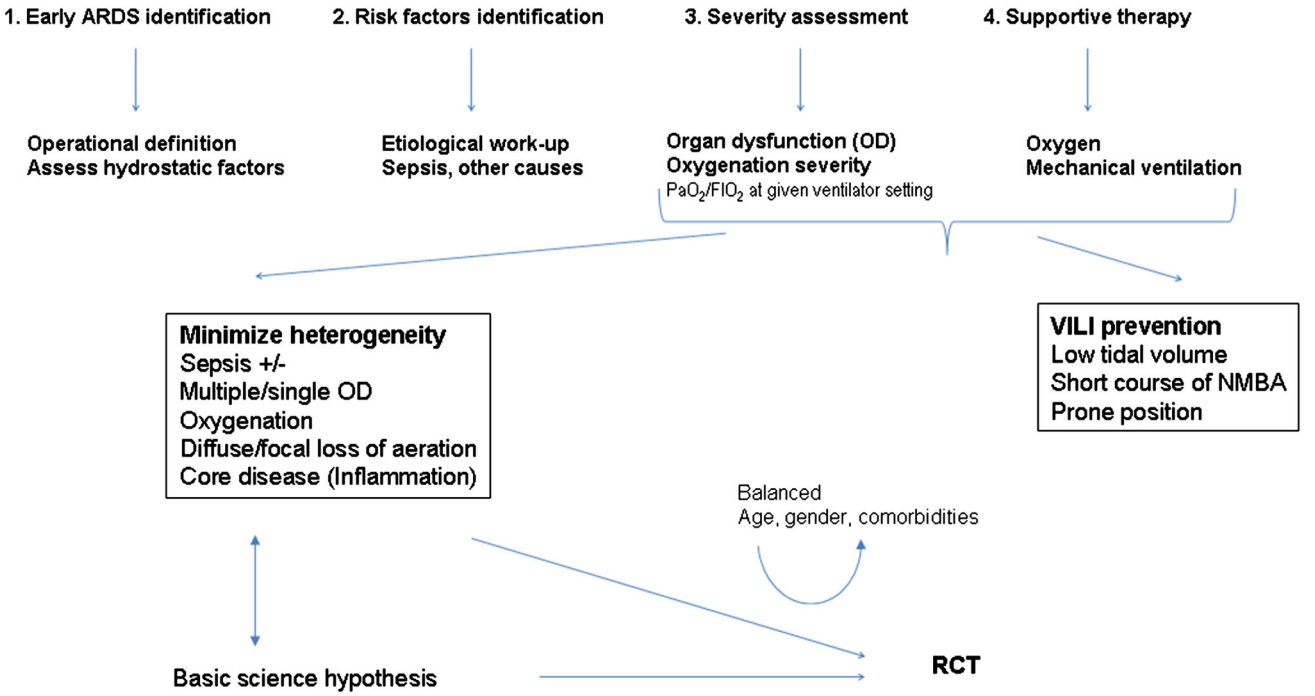

Fig. 1 Suggested steps of a standardized method for assessing lung severity and to identify homogeneous group of acute respiratory distress syndrome (*ARDS*) patients for enrolment into future clinical trials. *1* The operational definition of ARDS, though largely imperfect, should allow an early identification of patients at risk for ARDS. At this step, eliminating a patient with cardiogenic pulmonary edema or identifying the hydrostatic component of the respiratory failure is important. *2* At the same time, cause or risk factor for ARDS must be quickly identified. Sepsis, from a pulmonary or extra-pulmonary source, is the primary cause of ARDS. *3* The severity of ARDS results from the intensity of the lung failure, as assessed by the partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FIO_2) ratio under standard ventilator settings, and the number of distant organs involved. *4* Management will modify the lung response to the precipitating cause. In particular, mechanical ventilation can promote further damage to the lung if not performed in a lung protective manner. Basic science should be in continuous interaction with this model and provide insights into the pathogenesis of the acute lung injury to be tested. *NMBA* Neuromuscular blocking agents, *OD* organ dysfunction, *VILI* ventilator-induced lung injury, *RCT* Randomized Controlled Trial

development and progression of the syndrome in any given patient, and to guide and assess the response to treatment. The PaO_2/FiO_2 ratio (partial pressure of oxygen in arterial blood/fraction of inspired oxygen) is the hallmark for assessing hypoxemia in ARDS patients. However, current ARDS definitions do not mandate a standardized procedure for its measurement although changes in positive end-expiratory pressure (PEEP) and FiO_2 alter the PaO_2/FiO_2 [5, 6]. Most RCTs have enrolled patients with a wide range of lung injury without acknowledging that some patients evolve with standard care to less severe forms of lung injury within 24 h of diagnosis, while others evolve into more severe forms. This concern is highlighted in two recent observational reports where the PaO_2/FiO_2 at ARDS onset was incapable of separating patients into distinct categories of severity associated with significantly different mortalities [7, 8]. However, a persistently low PaO_2/FiO_2 is associated with a poor outcome and may be a marker of failure to respond to conventional therapy [5, 6]. If patients in a trial with a low risk of death are not excluded or stratified, the trial will not demonstrate the efficacy of the intervention, regardless of the sample size. This may explain why in the last 14 years since the publication of the ARDSnet trial, only two RCTs have had positive results [3, 4]. In both trials, only patients with a PaO_2/FiO_2 threshold under a specific level of PEEP and FiO_2 that persisted 18–36 h were enrolled. Thus, a standardized method for assessing lung severity must be mandatory to identify a homogeneous group of ARDS patients for enrolment into future trials (Fig. 1).

Many clinicians have criticized the results of RCTs in ARDS since the inclusion/exclusion criteria exclude the very patients they treat [9]. In addition, the number of patients provided by participating centers has been unacceptably unbalanced. Statistical significance is not an indicator of practical relevance. Although the *p* values reported in some trials are impressive, the clinical effects may be small. In other words, it is difficult to generalize the results of these studies since many have excluded commonly encountered patients, are uncontrolled for multiple variables, enrolled patients at different time-

periods of their disease process, had an unequal contribution of patients by center, and general care was not protocolized.

As stated by Tonelli et al. [1], another key issue is the lack of standardization in reporting mortality. It is difficult to compare studies for extracting definitive and applicable conclusions when outcome is reported using different time-periods that include the intensive care unit (ICU), hospital, or 28-day up to 6-month mortality. In more than 80 RCTs, ICU and hospital mortalities were not reported. If researchers/clinicians cannot agree on standard outcome time-periods, then it will not be possible to create an ARDS database to evaluate progress over time.

Finally, pathophysiologically oriented investigations and evidence-based medicine are tightly linked with RCTs, the ultimate method for hypothesis testing. An RCT should be supported by a strong pathophysiological rationale. In the three positive RCTs mentioned earlier, such a background (i.e., prevention of ventilator-induced lung injury) does exist. In this respect, the story of prone ventilation is illustrative as there has been a continuous refinement in the design of RCTs fed by evolving concepts regarding the pathophysiology of ARDS specifically and mechanical ventilation in general. For the Nobel Laureate Christian de Duve, the RCT has the ultimate goal of not to prove the working hypothesis but to demonstrate that it is false [10]. In a sense, a negative RCT is not bad news as it refutes a hypothesis and engages the researcher to move ahead—either to refine the hypothesis or move in another direction.

The statistician Richard Royall said there are three questions a scientist should ask after a study [11]: "What is the evidence?", "What should I believe?", and "What should I do?" It is unfortunate that after 25 years of clinical research in ARDS, only three trials can answer these questions. Let us start a new era of clinical research by setting new standards for identifying subsets of ARDS patients with similar severity of illness, and let us standardize clinically relevant outcomes. If we do not learn from the past, we will continue performing negative RCTs that should be burned after being read.

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