EDITORIAL

Time to Rethink the Approach to Treating Acute Respiratory Distress Syndrome

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In this issue of *JAMA*, Fan et al[1] review the treatment of acute respiratory distress syndrome (ARDS), focusing on recent randomized clinical trials (RCTs). Most of these RCTs failed to show that the interventions that were tested offered significant benefit. These predominantly negative results may prompt the question of whether other rational and more-effective ways are available to increase knowledge and improve treatment of a syndrome that is common, deadly, and arguably emblematic of modern intensive care. Although many of these trials were admirably executed, their failure to demonstrate benefit may often have been due to uncertainties regarding enrollment criteria and imprecise deployment of the interventions that were being tested.

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Critical care physicians and others have learned from laboratory experimentation and clinical observation that the pathobiology of ARDS changes rapidly over hours and days, is highly variable from patient to patient, and is influenced by important co-factors. Thus, wise selection of treatment requires consideration of the timing and intensity of any proposed intervention. Furthermore, patients with ARDS often have multiple concomitant medically and surgically related problems, which can confound interpretation of the effects of ARDS-specific interventions. Perhaps, in rethinking the approach to ARDS, it is valuable to revisit the often-missed link between diagnosis and treatment, with more in-depth understanding of the underlying mechanisms responsible for the clinical manifestations of the syndrome.

Diagnosis

Diagnosis literally means "knowing through" (ie, *through* the symptoms it should be possible to *know* the core of the syndrome, which, since the original description of ARDS, has been recognized to originate in widespread inflammatory lung edema [heavy lung]).[2] However, lung edema cannot be directly assessed at the bedside. The simplest indicators through which the presence of inflammatory edema and its severity may be inferred are hypoxemia normalized to inspired oxygen fraction (Pao_2/Fio_2 ratio) and widespread bilateral x-ray densities. These signature findings are associated with low respiratory system compliance and increased alveolar dead space, which, in turn, obligate high tidal driving pressures and increased ventilation requirements. Not surprisingly, adding compliance and dead space measurement to a quantitative assessment of hypoxemia does not reliably increase diagnostic power, because these covariates reflect the same phenomenon.

The advantage of the recent Berlin definition was the introduction of the "severe ARDS" category, assigned to a Pao_2/Fio_2 ratio lower than 100 mm Hg.[3] This value represents what was called "refractory hypoxemia" because it corresponds to a fraction of right-to-left shunt of about 30%, a value that prevents restoring Pao_2 to 100 mm Hg even when ventilating with pure oxygen. However, the problems with the Berlin definition relate to the imprecision of the Pao_2/Fio_2 ratio in "quantifying edema" if measured at unspecified positive end-expiratory pressure (PEEP) higher than 5 cm H_2O. Indeed, PEEP may mask hypoxemia and the relationship between Pao_2/Fio_2 ratio and the amount of edema, measured by computed tomography scan.[4] In addition, x-ray densities fail to reliably indicate the spread of edema and, depending on their specific features, may reflect different underlying pathologies (consolidation, edema, or collapse) with differing responses to airway pressure.[5] In other words, the current diagnostic criteria do not reflect crucial domains of the disease. Yet, does this underrecognition have clinical consequences?

Therapy

Fan et al[1] classified current ARDS therapies as preventive, pharmacological, adjunctive, and ventilatory. An alternative approach could be to classify therapies based on the ARDS disease mechanism that they target. Furthermore, a rational management approach should consist of 3 contemporaneous actions. First, etiological therapy is intended to cure the disease that causes ARDS. As an example, antibiotics might be considered "etiological therapy" for sepsis-induced ARDS. Second, pathogenic therapy is directed at the process that leads to the clinical manifestations of ARDS. For example, therapies that reduce vascular leak could be tested to modify the deleterious alterations in pulmonary capillary permeability. Third, symptomatic therapy is used to address the symptoms or consequences of ARDS, which may be lethal (such as severe compromise to gas exchange). Such therapies (eg, mechanical ventilation or extracorporeal membrane oxygenation) "buy time" to allow recovery and healing of the lung.

The cure of the disease leading to ARDS is of paramount importance. The underlying etiologic disease likely accounts for the major fraction of ARDS mortality. Comorbidities and age also are important factors. These realities should be considered when interpreting the results of RCTs. Therefore, trials investigating the possible advantages of pathogenic or symptomatic treatments should be large enough to ensure an equal distribution of such nontargeted variables within treatment and control groups or should consider alternative end points that more selectively reflect ARDS disease modification, with the caveat that such end points may be less patient-centered.

As ARDS originates in inflammatory edema, pathogenic therapy includes all the interventions aimed at preventing the formation and spreading of inflammatory edema and promoting its clearance. In this framework, knowledge of the underlying mechanism is of paramount importance, such as understanding why a pneumonic focus remains compartmentalized in one patient but disseminates to cause the typical widespread lung edema of ARDS in another. Anti-inflammatory therapy aims at reducing inflammation and controlling its spread, but patient selection and intervention timing may be crucial. For example, the statins simvastatin[6] and rosuvastatin[7] were proposed as a means to control the spread of inflammatory edema throughout the lung, but were then tested among patients in whom such spread was already evident. Not surprisingly, no benefit was observed. Similarly, to be efficacious, it is likely that therapy aimed at promoting alveolar repair (eg, keratinocyte recombinant factor[8]) or increasing alveolar edema clearance (eg, salbutamol[9]) must be initiated at the appropriate stage of illness. Without such targeting, the most likely outcome will be predictable demonstration of the known adverse effects of these drugs but no demonstration of any putative benefit.

Symptomatic therapy, in the ARDS context, primarily addresses the effects of edema on gas exchange, providing vital assistance until the underlying condition begins to resolve. Consequently, when comparing different symptomatic treatments (eg, ventilatory support), individual risks of lung damage are weighed against the common objective of assuring adequate gas exchange. This damage is collectively referred to as ventilator-induced lung injury and primarily consists of (1) excessive inflation or ventilation (volutrauma)[10]; (2) cyclic opening and closing of pulmonary units (atelectrauma)[11]; (3) maldistribution of stress and strain with stress focusing at the interface within pulmonary units of different elasticity (lung inhomogeneity)[12]; and (4) intensity, frequency, and duration of tidal cycling (mechanical power).[13]

The recent RCTs,[14,15] in addition to previous evidence,[16-18] strongly suggest that avoiding volutrauma and ventilating a patient in the prone position may provide significant survival benefit. Lower tidal volumes applied with PEEP values ranging from 7 cm H_2O to 15 cm H_2O appear advantageous compared with higher tidal volumes and higher PEEP values associated with recruitment maneuvers. Along the same line, high-frequency oscillatory ventilation applied at lung volumes approaching total lung capacity may be of no benefit[19] or actually harmful.[20] Not to be forgotten is the possibly devastating role of hyperinflation on local and general hemodynamics. Reported benefits from prone positioning and neuromuscular blockade[21] are currently debated, but their potential value could relate in part to reduced stress focusing.

Interpreting the Results of ARDS RCTs

A randomized trial may have "null" results for several reasons. First, the underlying hypothesis is based on incorrect or insufficient premises.[22] This may be the case for the studies of anti-inflammatory drugs, for which the premises were too generic and the tested population too diverse. A consistent and plausible, biological hypothesis is necessary before undertaking a randomized trial.

Second, the trial may be underpowered to prove benefit or damage. It is important to understand the mortality potentially attributable to the therapeutic strategy (eg, mechanical ventilation) among the different classes of patients with different severities. Without this knowledge, some studies may appear to have null results, whereas the therapy is actually effective. An example may be extracorporeal carbon dioxide removal for ARDS, a promising intervention currently under investigation.[23] However, ongoing studies such as the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial require an absolute mortality rate difference approaching 20% to establish statistical significance, which seems an unrealistic effect size. Failure of these studies may risk discarding a potentially useful intervention, which already happened with extracorporeal membrane oxygenation almost 4 decades ago.[24]

Third, when the results of RCTs are null (which are deductive studies), the investigations are logically interpreted to be questionable and not definitive; in contrast, when the results of RCTs are positive (for benefit or harm), the evidence is interpreted as extremely strong and must be taken into consideration. In this light, the greater risk of volutrauma compared with repeated tidal opening and closure (atelectrauma) is clearly demonstrated.

In conclusion, considering the entire picture of ARDS, it is important to sharpen the definition to better address the underlying anatomic (eg, capacity and recruitability) and physiologic (eg, gas exchanging) properties of the lung tissue exposed to treatment. Lacking that, it seems logical to select treatments based on the likelihood of positive or adverse response, adjusting empirically and keeping in mind that, in such a diverse patient cohort, aggressive interventions carry innate hazards. Classifying the severity of ARDS requires more accurate determination of the extent of underlying edema. Perhaps splitting moderate ARDS into categories of mild-moderate and moderate-severe at a threshold of 150 mm Hg Pao_2/Fio_2 ratio using a standardized PEEP of 5 cm H_2O may be a useful approach.[25] Matching intervention to pathophysiology is essential. Physiological studies that better characterize the factors causing ventilator-induced lung injury are indicated prior to undertaking an RCT aimed at avoiding it. When a damaging threshold is determined, the indication for the most adequate therapy will immediately follow.

ARTICLE INFORMATION

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